UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PAR PHARMACEUTICAL, INC.

Petitioner

v.

NOVARTIS AG.

Patent Owner

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U.S. Patent No. 9,006,224

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DECLARATION OF SCOTT BENNETT, Ph.D.

15 July 2016

I, Scott Bennet, Ph.D., resident of Urbana, Illinois, hereby declare as follows:

Introduction and Qualifications

1. I have been retained by Latham & Watkins LLP to provide my opinions concerning the public availability of certain documents at issue in *inter partes* review proceedings for U.S. Patent Nos. 9,006,224.

2. My curriculum vitae is appended to this document as Appendix A. From 1956 to 1960, I attended Oberlin College, where I received an A.B. in English. I then attended Indiana University, where I received an M.A. in 1966 and a Ph.D. in 1967, both in English. In 1976, I received a M.S. in Library Science from the University of Illinois. I also served at the University of Illinois at Urbana-Champaign in two capacities. First, from 1967 to 1974, I was an Assistant Professor of English; then from 1974 to 1981, I was an Instructor, Assistant Professor, and Associate Professor of Library Science.

3. From 1981 to 1989, I served as the Assistant University Librarian for Collection Management, Northwestern University. From 1989 to 1994, I served as the Director of The Milton S. Eisenhower Library at The Johns Hopkins University. From 1994 to 2001, I served as the University Librarian at Yale University. In 2001, I retired from Yale University.

4. Since then, I have served in multiple capacities for various organizations, including as a consultant on library space planning from 2004 to the present, as a Senior Advisor for the library program of the Council of Independent Colleges from 2001 to 2009, as a member of the Wartburg College Library Advisory Board from 2004 to the present, and as a Visiting Professor at the Graduate School of Library and Information Science, University of Illinois at Urbana-Champaign, in the Fall of 2003. I was a founding partner of Prior Art Documentation Services, LLC, in 2015.

5. Over the course of my work as a librarian, professor, researcher, and author of numerous publications, I have had extensive experience with cataloging and online library management systems built around Machine-Readable Cataloging (MARC) standards. As a consultant, I have substantial experience in authenticating documents and establishing the date when they were available to persons exercising reasonable diligence.

6. In the course of more than fifty years of academic life, I have myself been an active researcher. I have collaborated with many individual researchers and, as a librarian, worked in the services of thousands of researchers at four prominent research universities. Members of my family are university researchers. Over the years, I have read some of the voluminous professional literature on the information seeking behaviors of academic researchers. And as an educator, I

have a broad knowledge of the ways in which students in a variety of disciplines learn to master the bibliographic resources used in their disciplines. In all of these ways, I have a general knowledge of the how researchers work.

7. My work in this matter is being billed at my standard consulting rate of $88 per hour. My compensation is not in any way contingent upon the outcome of this or any other *inter partes* review. I have no financial or personal interest in the outcome of this proceeding or any related litigation.

Scope of this Declaration

8. I am not a lawyer and I am not rendering an opinion on the legal question that any particular document is, or is not, a "printed publication" under the law.

9. I am, however, rendering my expert opinion on when and how each of the documents addressed herein was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents before November 2004 or November 2005.

10. I reserve the right to supplement my opinion in the future to respond to any arguments that the parties to this case raise and to take into account new information as it becomes available.

Materials Considered in Forming My Opinion

11. In forming the opinions expressed in this declaration, I have relied on the Documents and the Attachments created for this declaration, as listed below.

Document 1 (Exhibit 1027). Öberg, K. "Treatment of neuroendocrine tumours of the gastrointestinal tract." Oncologia, 27,4 (2004): 57-61.

Document 2 (Exhibit 1005). Boulay, Anne, et al. "Antitumor Efficacy of Intermittent Treatment Schedules with the Rapamycin Derivative RAD001 Correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells." Cancer Research, 65, 1 (January 2004): 252-261.

Document 3 (Exhibit 1029). O'Donnell, S. et al. "A phase 1 study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamics (PD) endpoints in patients with solid tumors." Abstract 803 of a poster discussion. Meeting Proceedings. American Society of Clinical Oncology. Thirty-Ninth Annual Meeting, May 31 – June 3, 2003, Chicago, Illinois, 22 (2003): 200.

Document 4 (Exhibit 1038). Tabernero, J., et al. "A phase 1 study with tumor molecular pharmacodynamics (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patents (pts) with solid

tumors." Abstract 3007 of an oral presentation. Journal of Clinical Oncology. Supplement. 2005 ASCO Annual Meeting Proceedings. 41st Annual Meeting, May 13-17, 2005. Orlando, FL. 23, 16, Supplement (1 June 2005): 193s.

Document 5 (Exhibit 1011). Duran, I., et al. "A phase II trial of temsirolimus in metastatic neuroendocrine carcinomas (NECs)." Publication only abstract 3097. Journal of Clinical Oncology. Supplement. 2005 ASCO Annual Meeting Proceedings. 41st Annual Meeting, May 13-17, 2005. Orlando, FL. 23, 16, Supplement (1 June 2005): 215s.

12. The following Attachments are true and accurate representations of library material and online documents and records, as they are identified below. Unless otherwise indicated, all Attachments are records made in the regular course of business and available to the public. All attachments were created on 26 June – 14 June 2016, and all URLs referenced in this declaration were available on 15 July 2016.

Attachment 1a: Illinois Statewide Library Catalog record for Oncologia

Attachment 1b: Copy of Öberg from the SciELO Web site

Attachment 1c: British Library catalog record for Oncologia

Attachment 1d: British Library holdings record for Oncologia

Attachment 1e: Copy of the table of contents for Oncologia, volume 27, issue 4, from the British Library

Attachment 1f: Copy of Öberg from the British Library

Attachment 1g: Web of Science index record for Öberg

Attachment 2a: Statewide Illinois Library Catalog record for Cancer Research

Attachment 2b: University of Illinois at Urbana-Champaign Library catalog record for Cancer Research

Attachment 2c: Copy of Boulay from the University of Illinois at Urbana-Champaign Library

Attachment 2d: Copy of Boulay from the University of Wisconsin Library

Attachment 2e: PubMed record for Boulay

Attachment 2f: Copy of Boulay from the AACR Publications Web site

Attachment 3a: Program for the 2003 ASCO Annual Meeting

Attachment 3b: Copy of O'Donnell from the University of Minnesota Library

Attachment 3c: University of Minnesota Library monograph catalog record for the 2003 ASCO Annual Meeting proceedings

Attachment 3d: Statewide Illinois Library Catalog record for the 2003 ASCO Annual Meeting proceedings

Attachment 3e: Google Scholar list of documents citing O'Donnell

Attachment 3f: Index record for a documenting citing O'Donnell

Attachment 4a: Copy of Tabernero from the University of Illinois at Urbana-Champaign Library

Attachment 4b: Copy of Tabernero from the University of Minnesota Library

Attachment 4c: University of Illinois at Urbana-Champaign Library catalog record for the Journal of Clinical Oncology

Attachment 4d: Statewide Illinois Library Catalog record for the Journal of Clinical Oncology

Attachment 4e: Google Scholar list of documents citing Tabernero

Attachment 4f: Index record for a documenting citing Tabernero

Attachment 5a: Copy of Duran from the University of Illinois at Urbana-Champaign Library

Attachment 5b: Copy of Duran from the University of Minnesota Library

Attachment 5c: Google Scholar list of documents citing Duran

Attachment 5d: Copy of document citing Duran

Background Information

13. *Persons of ordinary skill in the art*. I am told by counsel that the subject matter of this proceeding relates to oncology and the treatment of specific tumors.

14. I am told by counsel that persons of ordinary skill in this subject matter or art have an understanding of cancer and the medical treatment of tumors.

I am told by counsel that such a person typically has, at the minimum, a Ph.D. in cancer biology, molecular biology, medicinal chemistry, or a related field with several years of experience in chemotherapeutic drug development, including evaluating cancer therapeutics in *in vitro* and/or *in vivo* assays; or an MD with several years of specific experience in oncology and clinical pharmacology.

15. It is my opinion that such a person would have been engaged in advanced research starting at least in graduate or medical school, learning though study and practice in the field and possibly through formal instruction the bibliographic resources relevant to his or her research. In the mid-2000s, such a person would have had access to a vast array of long-established print resources in chemistry, biology, and the health sciences as well as to a rich set of online resources providing indexing information, abstracts, and full text services for those disciplines.

16. *Conference papers*. Conference papers are typically presented at a conference. The circumstances of such presentation may vary, especially as regards the prominence of the conference, the number of conference participants, and the organization and conduct of the conference. Sometimes, only posters of research findings are presented. Formal publication of papers presented at conferences also varies. Sometimes, the papers are published before the conference so as to be available to conference participants. Sometimes, papers are

published only after the conference, and in some cases only abstracts of the papers are published.

17. Because of this variability, detailed information about the conference may often be used to establish the public accessibility of conference papers. The availability of such information, especially for long past conferences, varies.

18. *Library catalog records*. Some background on MARC formatted records, OCLC, WorldCat, and OCLC's Connexion is needed to understand the library catalog records used in this declaration.

19. Libraries world-wide use the MARC format for catalog records; this machine readable format was developed at the Library of Congress in the 1960s.

20. MARC formatted records use numerous tags and codes. For instance, they provide a variety of subject access points based on the content of the document being cataloged. All may be found in the MARC Fields 6XX. MARC Field 600, for instance, identifies personal names used as subjects, and the MARC Field 650 identifies topical terms. An ordinarily skilled researcher might discover material relevant to his or her topic by a search using the terms employed in the MARC Fields 6XX.

21. The MARC Field 040, subfield a, identifies the library or other entity that created the original catalog record for a given document and transcribed it into machine readable form. The MARC Field 008 identifies the date when this first

catalog record was entered on the file. This date persists in all subsequent uses of the first catalog record, although newly created records for the same document, separate from the original record, will show a new date.

22. WorldCat is the world's largest public online catalog, maintained by the Online Computer Library Center, Inc., or OCLC, and built with the records created by the thousands of libraries that are members of OCLC. WorldCat provides a user-friendly interface for the public to use MARC records; it requires no knowledge of MARC tags and codes. WorldCat records appear in many different catalogs, including the Statewide Illinois Library Catalog. The date a given catalog record was created (corresponding to the MARC Field 008) appears in some detailed WorldCat records as the Date of Entry.

23. When an OCLC participating institution acquires a document for which it finds no previously created record in OCLC, or when the institution chooses not to use an existing record, it creates a record for the document using OCLC's Connexion, the bibliographic system used by catalogers to create MARC records. Connexion automatically supplies the date of record creation in the MARC Field 008.

24. Once the MARC record is created by a cataloger at an OCLC participating member institution, it becomes available to other OCLC participating members in Connexion and to the public in WorldCat.

25. The public availability of MARC formatted catalog records and detailed WorldCat records showing the Date of Entry varies.

26. When a book has been cataloged, it will normally be made available to readers soon thereafter—normally within a few days or (at most) within a few weeks of cataloging.

27. *Publications in series*. A library typically creates a MARC catalog record for a series of publications, such as the proceedings of an annual conference, when the library receives its first issue. When the institution receives subsequent issues/volumes of the series, the issues/volumes are checked in (sometimes using a date stamp), added to the institution's holdings records, and made available very soon thereafter—normally within a few days of receipt or (at most) within a few weeks of receipt.

28. The initial serials record will often not reflect all of the subsequent changes in publication details (including minor variations in title, etc.).

29. When a library does not intend systematically to acquire a series, but adds individual volumes of a series to its collections, the library will typically treat each such volume as an individual book, or monograph. In this case, the MARC Field 008 will record the date when the record for that individual volume, not the series, was created.

30. It is sometimes possible to find both a series and a monograph library catalog record for the same publication.

31. *Periodical publications*. A library typically creates a MARC catalog record for a periodical publication when the library receives its first issue; subsequent issues will be entered under the same record and therefore do not receive a new date in MARC field 008. When the institution receives subsequent issues/volumes of the periodical, the issues/volumes are checked in (often using a date stamp), added to the institution's holdings records, and made available very soon thereafter—normally within a few days of receipt or (at most) within a few weeks of receipt.

32. The initial periodicals record will sometimes not reflect all of the subsequent changes in publication details (including minor variations in title, etc.).

33. *Internet Archive.* The Internet Archive is a non-profit digital library founded in 1996.

34. The Internet Archive maintains an archive of Web pages collected from the Internet using software called a crawler. Crawlers automatically create a snapshot of Web pages as they existed at a certain point in time. The WayBack Machine is an application created by the Internet Archive to search its archive of Web pages and to represent, graphically, the date of each crawler capture. The Internet Archive, now with about 50 petabytes of data, collects only Web material

that is publicly available. Some sites are "not archived because they were password protected, blocked by robots.txt, or otherwise inaccessible to our automated systems. Site owners might have also requested that their sites be excluded from the WayBack Machine" (see the WayBack Machine FAQ, https://archive.org/about/faqs.php#The_Wayback_Machine).

35. *Indexing*. An ordinarily skilled researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodical and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery service, or other provider.

36. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The formats in which these access terms are presented vary from service to service.

37. Indexing services commonly provide bibliographic information, abstracts, and access to full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document is evidence that the document was publicly available and in use by researchers no later than the publication date of the citing document.

38. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. Date information for indexing entries is, however, often unavailable, especially for online indexes. Nonetheless, indexing services enhance their value to researchers by reporting on publications as promptly as possible. Generally, one may reasonably assume that index entries—especially those in online services—become available to researchers in reasonably near proximity to the listed publication date of the documents indexed.

39. Prominent indexing services include:

40. Web of Science. Like its print predecessors Science Citation Index, Social Science Citation Index, and Arts and Humanities Citation Index, Web of Science provides thorough coverage of a broad set of disciplines. A Thomson Reuters product, Web of Science indexes 1,700 arts and humanities journals from 1975 to the present, 8,500 scientific journals from 1900 to the present, and some 300 social science journals from 1900 to the present.

41. Scopus. Produced by Elsevier, a major publisher, Scopus is the largest database of abstracts and citations of peer-reviewed literature. Its scope includes the social sciences, science, technology, medicine, and the arts. It includes 60 million records from more than 21,500 titles from some 5,000 international publishers. Coverage includes 360 trade publications, over 530 book

series, more than 7.2 million conference papers, and 116,000 books. Records date from 1823.

42. Google Scholar. Google Scholar indexes the texts and metadata of scholarly publications across a wide range of disciplines. It includes most peer-reviewed online academic journals, conference papers, theses, technical reports, and other material. Google does not publish the size of the Google Scholar database, but researchers have estimated that it contained approximately 160 million items in 2014 (Enrique Oduna-Malea, et al., "About the size of Google Scholar: playing the numbers," Scientometrics, 104,3 (September 2015): 931-949, available at https://arxiv.org/ftp/arxiv/papers/1407/1407.6239.pdf).

43. MEDLINE/PubMed. Produced by the National Library of Medicine, MEDLINE provides access to journal articles in the life sciences and biomedicine. The NLM Medical Subject Headings (MeSH®) are used to provide subject access. More than 22 million records are included in the database from some 5,600 publications issued from 1950 to the present. The database is freely available via the PubMed interface and is one of the most heavily used medical databases.

Consideration of individual documents

Document 1 (Exhibit 1027). Öberg, K. "Treatment of neuroendocrine tumours of the gastrointestinal tract." Oncologia, 27,4 (2004): 57-61.

Hereafter referred to as Öberg.

44. Document 1 is a research paper by K. Öberg published in 2004 in Volume 27, Issue 3 of the journal Oncologia.

45. Based on the evidence presented below—print and online publication, library date stamp, and indexing—it is my opinion that Öberg was available to researchers no later than June 2004.

46. Attachment 1a is a true and accurate copy of the Illinois Statewide Library Catalog for Oncologia, showing that the periodical began publication in 1976 and that 44 libraries world-wide hold the title. Most of these libraries hold the online version of Oncologia, available through SciELO, the Scientific Electronic Library Online.

47. Attachment 1b is a true and accurate copy of Öberg in the online version available from a search for Öberg at the SciELO Web site (http://scielo.isciii.es/scielo.php?script=sci_home&lng=en&nrm=iso),

48. Öberg is available in print as well, although relatively few libraries hold print copies of Oncologia. The British Library is one of these libraries. Attachment 1c is a true and accurate copy of the British Library catalog record for

Oncologia. Attachment 1d is a true and accurate copy of the British Library holdings record for Oncologia, showing volume 27, issue 4 as available.

49. Attachments 1e and 1f are true and accurate copies of material relating to Öberg obtained from the British Library. These materials are in a condition that creates no suspicion about their authenticity. They were found within the custody of a library – a place where if authentic they would likely be.

50. Attachment 1e is a true and accurate copy of the table of contents for volume 27, issue 4 of Oncologia obtained from the British Library. The Table of Contents is in Spanish, but Öberg is listed in English and shown to begin on p. 57.

51. Attachment 1f is a true and accurate copy of the print version of Öberg obtained from the British Library. It includes the cover for this issue of Oncologia and some preliminary matter. Attachment 1f bears a British Library (Boston Spa) date stamp of 24 May 2004. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp.

52. I infer from this 24 May 2004 date stamp that this issue of Oncologia had been cataloged and was made accessible to readers at the British Library shortly after it was processed, no later than June 2004.

53. An ordinarily skilled researcher could also have discovered Öberg through the Web of Science. Attachment 1g is a true and accurate copy of that service's index record for Öberg, drawn from the BIOSIS database. BIOSIS is a major indexing and abstracting service founded in 1926 and now, since its purchase by Thompson Reuters, part of the Web of Science. Attachment 1g shows the bibliographic details for Öberg and the variety of search terms by which the paper might be found. The Web of Science is a reliable indexing service, listing articles such as Öberg soon after their listed publication date.

Document 2 (Exhibit 1005). Boulay, Anne, et al. "Antitumor Efficacy of Intermittent Treatment Schedules with the Rapamycin Derivative RAD001 Correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells." Cancer Research, 65, 1 (January 2004): 252-261. Hereafter referred to as Boulay.

54. Document 2 is a research paper by Anne Bouley and others and published in the January 2004 issue of the Cancer Research, Volume 65, Number 1, pages 252-261. This paper is herein referred to as Boulay.

55. Based on the evidence presented below—publication in a widely held periodical, library processing, and indexing—it is my opinion that Boulay was publicly accessible to an ordinarily skilled researcher by mid-February 2004.

56. Attachment 2a is a true and accurate copy of the Statewide Illinois Library Catalog showing that Cancer Research began publication in 1941 and is held by 694 libraries world-wide. An ordinarily skilled researcher would have had no difficulty locating copies of this periodical.

57. The University of Illinois at Urbana-Champaign is one library where an ordinarily skilled researcher could have found Boulay in 2004. Attachment 2b is a true and accurate copy of that library's catalog record for Cancer Research, showing its holdings of volume 65. Attachment 2c is a true and accurate copy of Boulay from the University of Illinois at Urbana-Champaign Library's copy of Cancer Research. This attachment shows the periodical cover, preliminary matter, the table of contents showing Boulay, and Boulay. This copy of Boulay is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be.

58. The cover shown in Attachment 2c includes a date stamp indicating that the January 2004 issue of Cancer Research was processed at the University of Illinois at Urbana-Champaign Library on 30 January 2004. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp.

59. I infer from this 30 January 2004 date stamp that this issue of Cancer Research had been cataloged and was made accessible to readers at the University of Illinois at Urbana-Champaign Library shortly after it was processed, no later than mid-February 2004.

60. This date stamp indicates the January 2004 issue of the Cancer Research had been mailed to this library and to other subscribers (including other library subscribers) sometime before 30 January 2004, because it takes some time for the item to arrive at and to be processed by the library. I therefore conclude that the January 2004 issue of Cancer Research would have been received by other subscribers, and that other subscribing libraries would have processed and made this issue available to their readers at about the same time.

61. As an example, Attachment 2d is a true and accurate copy of Boulay from the University of Wisconsin Library, with a date stamp of 23 January 2004 indicating that it was processed by this library on that date. This copy of Boulay is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be. Based on my experience, I affirm the date stamp in Attachment 2d has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date

indicated by the stamp. One may reasonably infer from this 23 January 2004 date stamp that this issue of Cancer Research had been catalogued and was made accessible to readers at the University of Wisconsin Library shortly after processing, no later than mid-February 2004. This is within the general time frame of access documented in Attachment 2c.

62. An ordinarily skilled researcher could also have discovered Boulay through MEDLINE/PubMed. Attachment 2e is a true and accurate copy of the MEDLINE/PubMed item record for Boulay, showing the MeSH terms that an ordinarily skilled researcher could have used to discover Boulay. MEDLINE/PubMed is a reliable indexing service, listing articles such as Boulay soon after their publication. Attachment 2f is a true and accurate copy of Boulay, available from a link in the MEDLINE/PubMed record to the American Association for Cancer Research (AACR) Publications Web site. This online copy bears, on the first page, information about the journal title and the publication date of 1 January 2004.

Document 3 (Exhibit 1029). O'Donnell, A. et al. "A phase 1 study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamics (PD) endpoints in patients with solid tumors." Abstract 803 of a poster discussion. Meeting Proceedings. American Society of

Clinical Oncology. Thirty-Ninth Annual Meeting, May 31 – June 3, 2003, Chicago, Illinois, 22 (2003): 200. Hereafter referred to as O'Donnell.

63. Document 3 is an abstract of a research paper by A. O'Donnell and others presented as a poster discussion at the 2003 annual meeting of the American Society of Clinical Oncology (ASCO) and published in the ASCO meeting proceedings in 2003. This abstract is herein referred to as O'Donnell.

64. Based on the evidence presented below—poster presentation at a prominent conference, publication in a widely held periodical, library cataloging, and citation—it is my opinion that O'Donnell was publicly accessible to an ordinarily skilled researcher by no later than mid-August 2003 and was in actual use by researchers by November 2003.

65. O'Donnell was presented at the ASCO meeting on Tuesday, 3 June 2003. Attachment 3a is a true and accurate copy of the meeting's program (available at https://web.archive.org/web/20050113192755/http:/www.asco.org/asco/downloads/asco_final_program.pdf). It describes the broad scope of the meeting and reports that "nearly 2,100 abstracts, representing the latest advances in cancer research, will be presented in oral and poster sessions" and that "one hundred sessions in the 2003 ASCO Annual Meeting program are certified for pharmacy and/or nursing continuing education credit."

66. Attachment 3b is a true and accurate copy of O'Donnell from the University of Minnesota Library. This copy of O'Donnell is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be. Attachment 3b shows that O'Donnell was presented as a poster discussion on Tuesday [3 June 2003]. Attachment 3b has a library processing date stamp of 29 July 2004. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and this date represents a common interval between a conference presentation and the publication of the conference proceedings. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp.

67. I infer from this date stamp that the 2003 ASCO Annual Meeting proceedings were catalogued and made accessible to readers at the University of Minnesota shortly after processing, no later than mid-August 2004.

68. This stamp also indicates that the conference proceedings were mailed to this library and to other subscribers (including other libraries) sometime before 29 July 2004, because it takes some time for the item to arrive at and to be processed by the library. I therefore conclude that these conference proceedings would have been received by other subscribers shortly thereafter, and that other

subscribing libraries would have processed and made this issue available to their readers at about the same time.

69. Attachment 3c is a true and accurate copy of the University of Minnesota Library monograph catalog record, in MARC format, for the 2003 ASCO Annual Meeting proceedings. As explained in the Background Information section, above, MARC Field 040, subfield a, indicates the meeting proceedings were first cataloged by the University of Missouri, Columbia, Health Sciences Library (OCLC code = MMU). The MARC Field 008 MARC indicates this catalog record was entered on 4 August 2003.

70. Attachment 3d is a true and accurate copy of the Statewide Illinois Library Catalog showing that the ASCO Annual Meeting proceedings are held by 71 libraries world-wide. An ordinarily skilled researcher would have had no difficulty locating copies of these conference proceedings.

71. An ordinarily skilled researcher could also have discovered O'Donnell through citations to it in other, related publications. Attachment 3e is a true and accurate copy of a list of 75 publications citing Stone identified by Google Scholar. One of these papers was by Charles Sawyers, "Will mTOR inhibitors make it as cancer drugs?," Cancer Cell, 4,5 (November 2003): 343-348. Attachment 3f is a true and accurate copy of the index record for the Sawyers paper from the Scopus, with O'Donnell appearing as the 31st reference.

Document 4 (Exhibit 1038). Tabernero, J., et al. "A phase 1 study with tumor molecular pharmacodynamics (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patents (pts) with solid tumors." Abstract 3007 of an oral presentation. Journal of Clinical Oncology. Supplement. 2005 ASCO Annual Meeting Proceedings. 41st Annual Meeting, May 13-17, 2005. Orlando, FL. 23, 16, Supplement (1 June 2005): 193s. Hereafter referred to as Tabernero.

72. Document 4 is an oral abstract of a research paper by J. Tabernero and others presented at a 2005 meeting of the American Society of Clinical Oncology (ASCO) and published in the ASCO annual meeting proceedings in 2005. This oral abstract is herein referred to as Tabernero.

73. Based on the evidence presented below—presentation at a prominent conference, publication in a widely held periodical, library date stamps, and citation—it is my opinion that Tabernero was publicly accessible to an ordinarily skilled researcher by late June 2005 and in actual use by researchers by October 2005.

74. Tabernero was presented as an oral abstract at the ASCO meeting on Sunday, 15 May 2005. Attachment 4a is a true and accurate copy of Tabernero from the University of Illinois at Urbana-Champaign Library. This copy of Tabernero is in a condition that creates no suspicion about its authenticity. It was

found within the custody of a library – a place where if authentic it would likely be. The preliminary matter in Attachment 4a describes oral abstract presentations as "didactic presentations . . . determined by the Scientific Program Committee to be of the highest scientific merit." The "Letter from the Editor" indicates the broad scope of the meeting by reporting that the proceedings contain more than 2,000 abstracts.

75. Attachment 4a shows a library processing date stamp of 13 June 2005. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and this date represents a common interval between a conference presentation and publication of the conference proceedings. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp.

76. I infer from this date stamp that this issue of the Journal of Clinical Oncology had been catalogued and was made accessible to readers at the University of Illinois at Urbana-Champaign Library shortly after processing, and no later than late June 2005.

77. This date stamp indicates the 1 June 2005 Supplement to the Journal of Clinical Oncology had been mailed to this library and to other subscribers (including other library subscribers) sometime before 13 June 2005, because it

takes some time for the item to arrive at and to be processed by the library. I therefore conclude that the 1 June 2005 Supplement to the Journal of Clinical Oncology would have been received by other subscribers, and that other subscribing libraries would have processed and made this issue available to their readers at about the same time.

78. As an example, Attachment 4b is a true and accurate copy of Tabernero from the University of Minnesota Library, with a date stamp of 9 June 2005. This copy of Tabernero is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be. Based on my experience, I affirm the date stamp on Attachment 4b has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp. One may reasonably infer from this date stamp that the 1 June 2005 Supplement to the Journal of Clinical Oncology was accessible to readers at the University of Minnesota Library by late June 2005. This is within the general time frame of access documented in Attachment 4a.

79. Attachment 4c is a true and accurate copy of the University of University of Illinois at Urbana-Champaign Library catalog record for the Journal

of Clinical Oncology, showing the holdings for the June supplements to volume 23, number 16.

80. Attachment 4d is a true and accurate copy of the Statewide Illinois Library Catalog record showing that the Journal of Clinical Oncology began publication in 1983 and is held by 788 libraries world-wide. An ordinarily skilled researcher would have had no difficulty locating copies of these widely-held conference proceedings.

81. An ordinarily skilled researcher could also have discovered Tabernero through citations to it in other, related publications. Attachment 4e is a true and accurate copy of the first page of a list of 73 publications citing Tabernero identified by Google Scholar. One of these papers was written by F. Meric-Bernstein and F. J. Esteva, "Potential role of mammalian target of rapamycin inhibitors in breast cancer therapy," Clinical Breast Cancer, 6,4 (October 2005): 357-360. Attachment 4f is a true and accurate copy of the Scopus index record for the Meric-Bernstein and Esteva paper, with the citation of Tabernero being the 36th reference.

Document 5 (Exhibit 1011). Duran, I., et al. "A phase II trial of temsirolimus in metastatic neuroendocrine carcinomas (NECs)." Publication only abstract 3097. Journal of Clinical Oncology. Supplement. 2005 ASCO Annual Meeting Proceedings. 41st Annual Meeting, May 13-17, 2005.

Orlando, FL. 23, 16, Supplement (1 June 2005): 215s. Hereafter referred to as Duran.

82. Document 5 is an abstract of a research paper by I. Duran and others published in the proceedings of the 2005 annual meeting of American Society of Clinical Oncology (ASCO. This abstract is herein referred to as Duran.

83. Based on the evidence presented below—publication in a widely held periodical, library date stamps, and citation—it is my opinion that Duran was publicly accessible to an ordinarily skilled researcher by late June 2005 and in actual use by researchers by December 2005.

84. Attachment 5a is a true and accurate copy of the cover, table of contents, preliminary matter, and of Duran from the University of Illinois at Urbana-Champaign Library. This copy of Duran is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be. As explained in the preliminary matter to Attachment 5a, Duran—as a publication only abstract—was not presented at the 2005 ASCO annual meeting but it was published in the proceedings of the 2005 meeting.

85. Attachment 5a shows a library processing date stamp of 13 June 2005. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do

not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp, and this date represents a common interval between a conference presentation and publication of the conference proceedings.

86. I infer from this date stamp that this issue of the journal had been catalogued and was made accessible to readers at the University of Illinois at Urbana-Champaign Library shortly after processing, no later than late June 2005.

87. This date stamp indicates the 1 June 2005 Supplement to the Journal of Clinical Oncology had been mailed to this library and to other subscribers (including other library subscribers) sometime before 13 June 2005, because it takes some time for the item to arrive at and to be processed by the library. I therefore conclude that the 1 June 2005 Supplement to the Journal of Clinical Oncology would have been received by other subscribers, and that other subscribing libraries would have processed and made this issue available to their readers at about the same time.

88. As an example, Attachment 5b is a true and accurate copy of Duran from the University of Minnesota Library, with a date stamp of 9 June 2005. This copy of Duran is in a condition that creates no suspicion about its authenticity. It was found within the custody of a library – a place where if authentic it would likely be. Based on my experience, I affirm the date stamp in Attachment 5b has

the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp. One may reasonably infer from this date stamp that the 1 June 2005 Supplement to the Journal of Clinical Oncology was accessible to readers at the University of Minnesota Library by late June 2005. This is within the general time frame of access documented in Attachment 4a.

89. Attachment 4c is a true and accurate copy of the University of University of Illinois at Urbana-Champaign Library catalog record for the Journal of Clinical Oncology, showing the holdings for the June supplements to volume 23, number 16.

90. Attachment 4d is a true and accurate copy of the Statewide Illinois Library Catalog record showing that the Journal of Clinical Oncology began publication in 1983 and is held by 788 libraries world-wide. An ordinarily skilled researcher would have had no difficulty locating copies of these widely-held conference proceedings.

91. An ordinarily skilled researcher could also have discovered Duran through citations to it in other, related publications. Attachment 5c is a true and accurate copy of the first page of a list of 14 publications citing Duran identified by Google Scholar. One of these papers was written by R. V. Orlova and A. V Novik,

"Modern approaches to drug treatment of generalized forms of neuroendocrine tumors, symptomatic therapy syndrome in neuroendocrine neoplasmas," Prakticheskaia Onkologia, 6,4 (December 2005): 240-246, with the citation of Duran being the 5th reference. Attachment 5d is a true and accurate copy of this paper, in Russian, available at http://practical-oncology.ru/arh024/08.pdf. There follows a transliteration of the bibliographic information provided on the first page of Attachment 5g, whereas the bibliographic citation given above is a translation of that bibliographic information: *Transliteration*: Orlova, R. V., Novik A. V. "Sovremennye podkhody lekarstvennogo lecheniia generalizovannykh form neiroendokrinykh opukholei, simptomaticheskaia terapiia sindromov pri neiroendo kninnykh neoplaziiakh" in Prakticheskaia Onkologiia, V. 6, No. 4, 2005 (December 2005).

Attestation

92. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code

and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

14 July 2015

_____ _____

Scott Bennett, Ph.D.
Managing Partner
Prior Art Documentation Services LLC

Date

EXHIBIT A: RESUME

SCOTT BENNETT
Yale University Librarian Emeritus

711 South Race
Urbana, Illinois 61801-4132
2scottb@prairienet.org
217-367-9896

EMPLOYMENT

Retired, 2001. Retirement activities include:

- Managing Partner in Prior Art Documentation Services, LLC, 2015-. This firm provides documentation services to patent attorneys; more information is available at http://www.priorartdocumentation.com
- Consultant on library space design, 2004- . This consulting practice is rooted in a research, publication, and public speaking program conducted since I retired from Yale University in 2001. I have served more than 50 colleges and universities in the United States and abroad with projects ranging in likely cost from under $50,000 to over $100 million. More information is available at http://www.libraryspaceplanning.com/
- Senior Advisor for the library program of the **Council of Independent Colleges**, 2001-2009
- Member of the Wartburg College Library Advisory Board, 2004-
- Visiting Professor, Graduate School of Library and Information Science, **University of Illinois at Urbana-Champaign**, Fall 2003

University Librarian, **Yale University**, 1994-2001

Director, The Milton S. Eisenhower Library, **The Johns Hopkins University**, Baltimore, Maryland, 1989-1994

Assistant University Librarian for Collection Management, **Northwestern University**, Evanston, Illinois, 1981-1989

Instructor, Assistant and Associate Professor of Library Administration**, University of Illinois at Urbana-Champaign**, 1974-1981

Assistant Professor of English, **University of Illinois at Urbana-Champaign**, 1967-1974

Woodrow Wilson Teaching Intern, **St. Paul's College**, Lawrenceville, Virginia, 1964-1965

EDUCATION

University of Illinois, M.S., 1976 (Library Science)
Indiana University, M.A., 1966; Ph.D., 1967 (English)
Oberlin College, A.B. magna cum laude, 1960 (English)

HONORS AND AWARDS

Morningside College (Sioux City, IA) Doctor of Humane Letters, 2010

American Council of Learned Societies Fellowship, 1978-1979; Honorary Visiting Research Fellow, Victorian Studies Centre**, University of Leicester**, 1979; **University of Illinois** Summer Faculty Fellowship, 1969

Indiana University Dissertation Year Fellowship and an **Oberlin College** Haskell Fellowship, 1966-1967; **Woodrow Wilson** National Fellow, 1960-1961

PROFESSIONAL ACTIVITIES

American Association for the Advancement of Science: Project on Intellectual Property and Electronic Publishing in Science, 1999-2001

American Association of University Professors: University of Illinois at Urbana-Champaign Chapter Secretary and President, 1975-1978; Illinois Conference Vice President and President, 1978-1984; national Council, 1982-1985, Committee F, 1982-1986, Assembly of State Conferences Executive Committee, 1983-1986, and Committee H, 1997-2001 ; Northwestern University Chapter Secretary/Treasurer, 1985-1986

Association of American Universities: Member of the Research Libraries Task Force on Intellectual Property Rights in an Electronic Environment, 1993-1994, 1995-1996

Association of Research Libraries: Member of the Preservation Committee, 1990-1993; member of the Information Policy Committee, 1993-1995; member of the Working Group on Copyright, 1994-2001; member of the Research Library Leadership and Management Committee, 1999-2001; member of the Board of Directors, 1998-2000

Carnegie Mellon University: Member of the University Libraries Advisory Board, 1994

Center for Research Libraries: Program Committee, 1998-2000

Johns Hopkins University Press: Ex-officio member of the Editorial Board, 1990-1994; Co-director of Project Muse, 1994

Library Administration and Management Association, Public Relations Section, Friends of the Library Committee, 1977-1978

Oberlin College: Member of the Library Visiting Committee, 1990, and of the Steering Committee for the library's capital campaign, 1992-1993; President of the Library Friends, 1992-1993, 2004-2005; member, Friends of the Library Council, 2003-

Research Society for Victorian Periodicals: Executive Board, 1971-1983; Co-chairperson of the Executive Committee on Serials Bibliography, 1976-1982; President, 1977-1982

A Selected Edition of W.D. Howells (one of several editions sponsored by the MLA Center for Editions of American Authors): Associate Textual Editor, 1965-1970; Center for Editions of American Authors panel of textual experts, 1968-1970

Victorian Studies: Editorial Assistant and Managing Editor, 1962-1964

Wartburg College: member, National Advisory Board for the Vogel Library, 2004-

Some other activities: Member of the **Illinois State Library** Statewide Library and Archival Preservation Advisory Panel; member of the **Illinois State Archives** Advisory Board; member of a committee advising the **Illinois Board of Higher Education** on the cooperative management of research collections; chair of a major collaborative research project conducted by the **Research Libraries Group** with support from Conoco, Inc.; active advisor on behalf of the **Illinois Conference AAUP** to faculty and administrators on academic freedom and tenure matters in northern Illinois.

Delegate to **Maryland Governor's Conference on Libraries and Information Service**; principal in initiating state-wide preservation planning in Maryland; principal in an effort to widen the use of mass deacidification for the preservation of library materials through cooperative action by the **Association of Research Libraries** and the **Committee on Institutional Cooperation**; co-instigator of a campus-wide information service for **Johns Hopkins University**; initiated efforts with the **Enoch Pratt Free Library** to provide information services to Baltimore's Empowerment Zones; speaker or panelist on academic publishing, copyright, scholarly communication, national and regional preservation planning, mass deacidification.

Consultant for the **University of British Columbia** (1995), **Princeton University** (1996), **Modern Language Association**, (1995, 1996), **Library of Congress** (1997), **Center for Jewish History** (1998, 2000-), **National Research Council** (1998); Board of Directors for the **Digital Library Federation**, 1996-2001; accreditation visiting team at **Brandeis University** (1997); mentor for **Northern Exposure to Leadership** (1997); instructor and mentor for ARL's **Leadership and Career Development Program** (1999-2000)

At the **Northwestern University Library**, led in the creation of a preservation department and in the renovation of the renovation, for preservation purposes, of the Deering Library book stacks.

At the **Milton S. Eisenhower Library**, led the refocusing and vitalization of client-centered services; strategic planning and organizational restructuring for the library; building renovation planning. Successfully completed a $5 million endowment campaign for the humanities collections and launched a $27 million capital campaign for the library.

At the **Yale University Library**, participated widely in campus-space planning, university budget planning, information technology development, and the promotion of effective teaching and learning; for the library has exercised leadership in space planning and renovation, retrospective conversion of the card catalog, preservation, organizational development, recruitment of minority librarians, intellectual property and copyright issues, scholarly communication, document delivery services among libraries, and instruction in the use of information resources. Oversaw approximately $70 million of library space renovation and construction. Was co-principal investigator for a grant to plan a digital archive for Elsevier Science.

Numerous to invitations speak at regional, national, and other professional meetings and at alumni meetings. Lectured and presented a series of seminars on library management at the **Yunnan University Library**, 2002. Participated in the 2005 International Roundtable for Library and Information Science sponsored by the **Kanazawa Institute of Technology** Library Center and the Council on Library and Information Resources.

PUBLICATIONS

"Putting Learning into Library Planning," *portal: Libraries and the Academy*, 15, 2 (April 2015), 215-231.

"How librarians (and others!) love silos: Three stories from the field " available at the Learning Spaces Collaborary Web site, http://www.pkallsc.org/

"Learning Behaviors and Learning Spaces," *portal: Libraries and the Academy,* 11, 3 (July 2011), 765-789.

"Libraries and Learning: A History of Paradigm Change," *portal: Libraries and the Academy,* 9, 2 (April 2009), 181-197. Judged as the best article published in the 2009 volume of *portal*.

"The Information or the Learning Commons: Which Will We Have?" *Journal of Academic Librarianship*, 34 (May 2008), 183-185. One of the ten most-cited articles published in JAL, 2007-2011.

"Designing for Uncertainty: Three Approaches," *Journal of Academic Librarianship*, 33 (2007), 165–179.

"Campus Cultures Fostering Information Literacy," *portal: Libraries and the Academy*, 7 (2007), 147-167. Included in Library Instruction Round Table Top Twenty library instruction articles published in 2007

"Designing for Uncertainty: Three Approaches," *Journal of Academic Librarianship*, 33 (2007), 165–179.

"First Questions for Designing Higher Education Learning Spaces," *Journal of Academic Librarianship*, 33 (2007), 14-26.

"The Choice for Learning," *Journal of Academic Librarianship*, 32 (2006), 3-13.

With Richard A. O'Connor, "The Power of Place in Learning," *Planning for Higher Education*, 33 (June-August 2005), 28-30

"Righting the Balance," in *Library as Place: Rethinking Roles, Rethinking Space* (Washington, DC: Council on Library and Information Resources, 2005), pp. 10-24

Libraries Designed for Learning (Washington, DC: Council on Library and Information Resources, 2003)

"The Golden Age of Libraries," in *Proceedings of the International Conference on Academic Librarianship in the New Millennium: Roles, Trends, and Global Collaboration*, ed. Haipeng Li (Kunming: Yunnan University Press, 2002), pp. 13-21. This is a slightly different version of the following item.

"The Golden Age of Libraries," *Journal of Academic Librarianship*, 24 (2001), 256-258

"Second Chances. An address . . . at the annual dinner of the Friends of the Oberlin College Library November 13 1999," Friends of the Oberlin College Library, February 2000

"Authors' Rights," *The Journal of Electronic Publishing* (December 1999), http://www.press.umich.edu/jep/05-02/bennett.html

"Information-Based Productivity," in *Technology and Scholarly Communication*, ed. Richard Ekman and Richard E. Quandt (Berkeley, 1999), pp. 73-94

"Just-In-Time Scholarly Monographs: or, Is There a Cavalry Bugle Call for Beleaguered Authors and Publishers?" *The Journal of Electronic Publishing* (September 1998), http://www.press.umich.edu/jep/04-01/bennett.html

"Re-engineering Scholarly Communication: Thoughts Addressed to Authors," *Scholarly Publishing*, 27 (1996), 185-196

"The Copyright Challenge: Strengthening the Public Interest in the Digital Age," *Library Journal*, 15 November 1994, pp. 34-37

"The Management of Intellectual Property," *Computers in Libraries*, 14 (May 1994), 18-20

"Repositioning University Presses in Scholarly Communication," *Journal of Scholarly Publishing*, 25 (1994), 243-248. Reprinted in *The Essential JSP. Critical Insights into the World of Scholarly Publishing. Volume 1: University Presses* (Toronto: University of Toronto Press, 2011), pp. 147-153

"Preservation and the Economic Investment Model," in *Preservation Research and Development. Round Table Proceedings, September 28-29, 1992*, ed. Carrie Beyer (Washington, D.C.: Library of Congress, 1993), pp. 17-18

"Copyright and Innovation in Electronic Publishing: A Commentary," *Journal of Academic Librarianship*, 19 (1993), 87-91; reprinted in condensed form in *Library Issues: Briefings for Faculty and Administrators*, 14 (September 1993)

with Nina Matheson, "Scholarly Articles: Valuable Commodities for Universities," *Chronicle of Higher Education*, 27 May 1992, pp. B1-B3

"Strategies for Increasing [Preservation] Productivity*," Minutes of the [119th] Meeting [of the Association of Research Libraries]* (Washington, D.C., 1992), pp. 39-40

"Management Issues: The Director's Perspective," and "Cooperative Approaches to Mass Deacidification: Mid-Atlantic Region," in *A Roundtable on Mass Deacidification*, ed. Peter G. Sparks (Washington, D.C.: Association of Research Libraries, 1992), pp. 15-18, 54-55

"The Boat that Must Stay Afloat: Academic Libraries in Hard Times," *Scholarly Publishing*, 23 (1992), 131-137

"Buying Time: An Alternative for the Preservation of Library Material," ACLS *Newsletter*, Second Series 3 (Summer, 1991), 10-11

"The Golden Stain of Time: Preserving Victorian Periodicals" in *Investigating Victorian Journalism*, ed. Laurel Brake, Alex Jones, and Lionel Madden (London: Macmillan, 1990), pp. 166-183

"Commentary on the Stephens and Haley Papers" in *Coordinating Cooperative Collection Development: A National Perspective*, an issue of *Resource Sharing and Information Networks*, 2 (1985), 199-201

"The Editorial Character and Readership of *The Penny Magazine*: An Analysis," *Victorian Periodicals Review*, 17 (1984), 127-141

"Current Initiatives and Issues in Collection Management," *Journal of Academic Librarianship*, 10 (1984), 257-261; reprinted in *Library Lit: The Best of 85*

"Revolutions in Thought: Serial Publication and the Mass Market for Reading" in *The Victorian Periodical Press: Samplings and Soundings*, ed. Joanne Shattock and Michael Wolff (Leicester: Leicester University Press, 1982), pp. 225-257

"Victorian Newspaper Advertising: Counting What Counts," *Publishing History*, 8 (1980), 5-18

"Library Friends: A Theoretical History" in *Organizing the Library's Support: Donors, Volunteers, Friends*, ed. D.W. Krummel, Allerton Park Institute Number 25 (Urbana: University of Illinois Graduate School of Library Science, 1980), pp. 23-32

"The Learned Professor: being a brief account of a scholar [Harris Francis Fletcher] who asked for the Moon, and got it," *Non Solus*, 7 (1980), 5-12

"Prolegomenon to Serials Bibliography: A Report to the [Research] Society [for Victorian Periodicals]," *Victorian Periodicals Review*, 12 (1979), 3-15

"The Bibliographic Control of Victorian Periodicals" in *Victorian Periodicals: A Guide to Research*, ed. J. Don Vann and Rosemary T. VanArsdel (New York: Modern Language Association, 1978), pp. 21-51

"John Murray's Family Library and the Cheapening of Books in Early Nineteenth Century Britain," *Studies in Bibliography*, 29 (1976), 139-166. Reprinted in Stephen Colclough and Alexis Weedon, eds., *The History of the Book in the West: 1800-1914*, Vol. 4 (Farnham, Surrey: Ashgate, 2010), pp. 307-334.

with Robert Carringer, "Dreiser to Sandburg: Three Unpublished Letters," *Library Chronicle*, 40 (1976), 252-256

"David Douglas and the British Publication of W. D. Howells' Works," *Studies in Bibliography*, 25 (1972), 107-124

as primary editor, W. D. Howells, *Indian Summer* (Bloomington: Indiana University Press, 1971)

"The Profession of Authorship: Some Problems for Descriptive Bibliography" in *Research Methods in Librarianship: Historical and Bibliographic Methods in Library Research*, ed. Rolland E. Stevens (Urbana: University of Illinois Graduate School of Library Science, 1971), pp. 74-85

edited with Ronald Gottesman, *Art and Error: Modern Textual Editing* (Bloomington: Indiana University Press, 1970)--also published in London by Methuen, 1970

"Catholic Emancipation, the *Quarterly Review*, and Britain's Constitutional Revolution," *Victorian Studies*, 12 (1969), 283-304

as textual editor, W. D. Howells, *The Altrurian Romances* (Bloomington: Indiana University Press, 1968); introduction and annotation by Clara and Rudolf Kirk

as associate textual editor, W. D. Howells, *Their Wedding Journey* (Bloomington: Indiana University Press, 1968); introduction by John Reeves

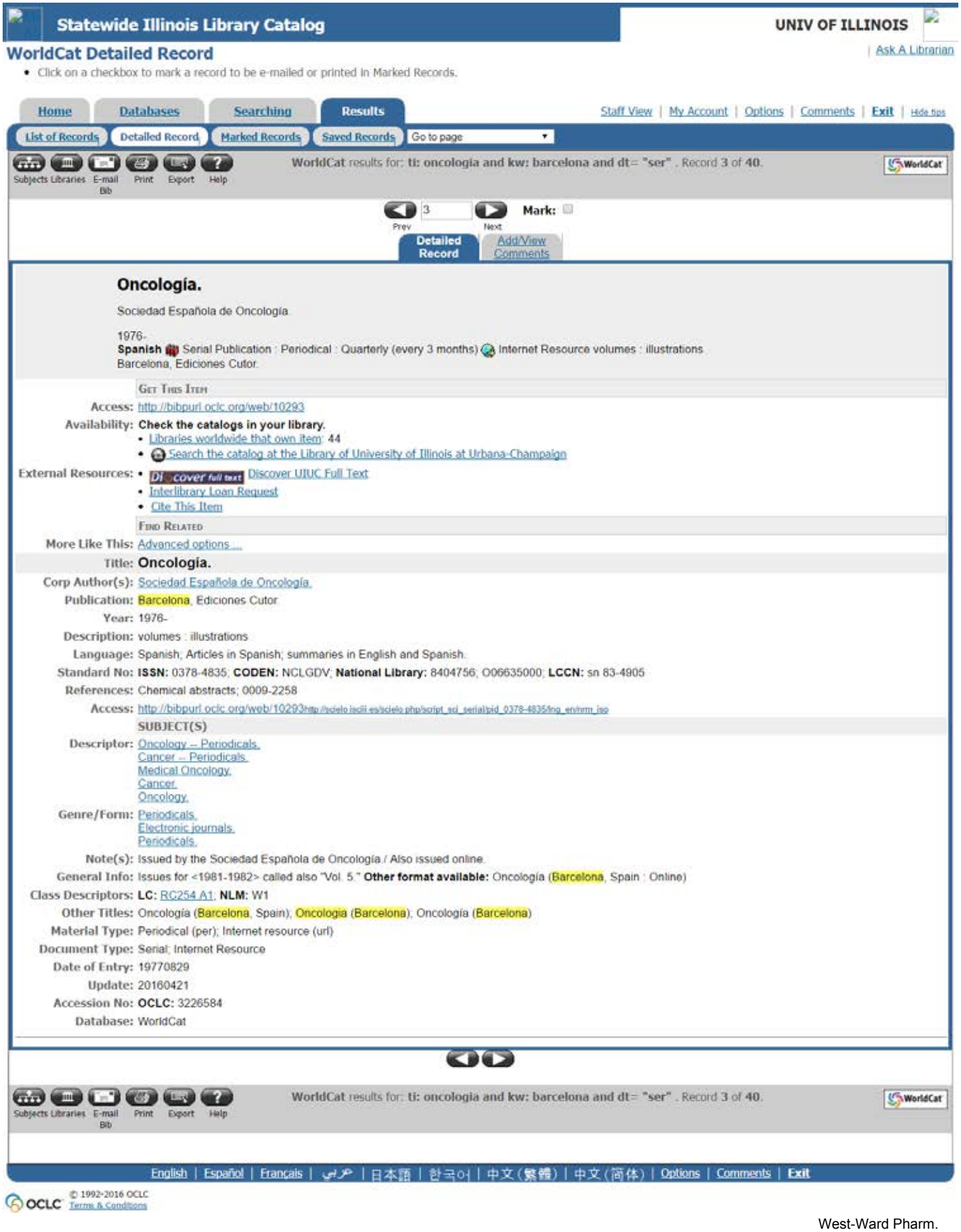
"A Concealed Printing in W. D. Howells," *Papers of the Bibliographic Society of America*, 61 (1967), 56-60

editor, *Non Solus*, A Publication of the University of Illinois Library Friends, 1974-1981

editor, Robert B. Downs Publication Fund, University of Illinois Library, 1975-1981

reviews, short articles, etc. in *Victorian Studies*, *Journal of English and German Philology*, *Victorian Periodicals Newsletter*, *Collection Management*, *Nineteenth-Century Literature*, *College & Research Libraries*, *Scholarly Publishing Today*, *ARL Newsletter*, *Serials Review*, *Library Issues*, *S[ociety for] S[cholarly] P[ublishing] Newsletter*, and *Victorian Britain: An Encyclopedia*

Attachment 1a: Illinois Statewide Library Catalog record for Oncologia



Statewide Illinois Library Catalog

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- Click on a checkbox to mark a record to be e-mailed or printed in Marked Records.

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WorldCat results for: ti: oncologia and kw: barcelona and dt= "ser" . Record 3 of 40.

Prev 3 Next Mark:

Detailed Record | Add/View Comments

Oncología.

Sociedad Española de Oncología

1976-
Spanish Serial Publication : Periodical : Quarterly (every 3 months) Internet Resource volumes : illustrations
Barcelona, Ediciones Cutor.

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Title: **Oncología.**

Corp Author(s): Sociedad Española de Oncología.

Publication: Barcelona, Ediciones Cutor

Year: 1976-

Description: volumes : illustrations

Language: Spanish; Articles in Spanish; summaries in English and Spanish.

Standard No: **ISSN:** 0378-4835; **CODEN:** NCLGDV; **National Library:** 8404756; 006635000; **LCCN:** sn 83-4905

References: Chemical abstracts; 0009-2258

Access: http://bibpurl.oclc.org/web/10293http://scielo.isciii.es/scielo.php/script_sci_serial/pid_0378-4835/lng_en/nrm_iso

SUBJECT(S)

Descriptor: Oncology -- Periodicals.
Cancer -- Periodicals.
Medical Oncology.
Cancer.
Oncology.

Genre/Form: Periodicals.
Electronic journals.
Periodicals.

Note(s): Issued by the Sociedad Española de Oncología / Also issued online.

General Info: Issues for <1981-1982> called also "Vol. 5." **Other format available:** Oncología (Barcelona, Spain : Online)

Class Descriptors: **LC:** RC254.A1; **NLM:** W1

Other Titles: Oncología (Barcelona, Spain); Oncologia (Barcelona); Oncología (Barcelona)

Material Type: Periodical (per); Internet resource (url)

Document Type: Serial; Internet Resource

Date of Entry: 19770829

Update: 20160421

Accession No: **OCLC:** 3226584

Database: WorldCat

Subjects Libraries E-mail Bib Print Export Help

WorldCat results for: ti: oncologia and kw: barcelona and dt= "ser" . Record 3 of 40.

English | Español | Français | عربي | 日本語 | 한국어 | 中文(繁體) | 中文(简体) | Options | Comments | Exit

Attachment 1a: Illinois Statewide Library Catalog record for Oncologia

Treatment of neuroendocrine tumours of the gastrointestinal tract

K. Öberg

Introduction

Neuroendocrine tumours (NE) of the gastrointestinal tract and pancreas constitute about 2% of all malignant tumours. They include a number of different tumours, derived from cells of the diffuse neuroendocrine cell-system[1]. The largest group of NE tumours are the so called carcinoids, with an incidence of about 2.5/100.000[2], which by tradition have been divided into foregut, midgut and hindgut tumours. Endocrine pancreatic tumours has an incidence of 0.4-0.8/100.000. This old classification is based on the embryonic origin of the different tumours, where the foregut carcinoid primaries has been located in the lung, thymus, gastric mucosa and the midgut carcinoids with primary tumours in the ileum, caecum and proximal colon and the hindgut carcinoids with the primaries in the distal colon and rectum. This old classification is now about to be abandoned, and more tumour-biology-based classification has emerged. The new WHO-classification is now indicating five subtypes[3].

1. Well-differentiated endocrine tumour
2. Well-differentiated endocrine carcinoma
3. Poorly-differentiated endocrine carcinoma
4. Mixed exocrine and endocrine carcinomas
5. Tumour-like lesions

This classification can be used for all types of NE tumours, not only for carcinoids. A classical midgut carcinoid will be called with the new terminology A well-differentiated endocrine carcinomas of the ileum, whereas a benign insulin producing tumour of the pancreas will be A well-differentiated endocrine tumour of the pancreas. The differentiation between different tumours types is based on histomorphology, tumour-size and presence or absence of local invasion and/or metastases. This new classification of NE tumours is a step forward, although the former classification of carcinoid tumours into foregut, midgut and hindgut, remains clinically available and is still used in many clinical studies. It will take some time for the new classification to receive general acceptance.

NE tumours exhibit substantial differences in terms of genotype and phenotype. Foregut carcinoids mainly pulmonary, but also endocrine pancreatic tumours, frequently show losses of 11q, which represent a characteristic genetic alteration in these tumours. Both typical and atypical carcinoids of the lung show loss of heterozygosity at 11q13, harboring the multiple endocrine neoplasia Type 1 (MEN-1) gene. Atypical carcinoids also show loss of heterozygosity at 3p14-p21.3. Recent studies have shown that carcinoid tumours of the lung and the GI tract may develop via different molecular pathways. Inactivation of one of several tumours suppressor genes on chromosome 18 may be important for the biological behaviour of GI tumours. Familiar midgut carcinoids are rare but bronchial carcinoids as well as endocrine pancreatic tumours and gastric carcinoids may be part of a MEN-1 syndrome[4, 5].

Such differences in molecular genetics and tumour biology play a role for the diagnosis and treatment of neuroendocrine gastrointestinal tumours.

Treatment of NE tumours

Surgery

The clinical management of metastatic NE tumours requires a multimodal approach including surgery and other means of cytoreductive treatment, radiotherapy and medical treatment. Surgery remains the treatment of choice and is the only approach that can achieve a complete cure in patients with NE tumours. In cases of metastases, surgery has been used to improve hormone-mediated symptoms, quality of life and survival in certain groups of patients, as well as to reduce tumours bulk and prevent further local and systemic effects. Surgical resection of primary tumours as well as lymph nodes and liver involvement can improve survival. In addition, surgery can also be employed after medical treatment to achieve substantial tumour reduction in an attempt to maxi-

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University Hospital
Uppsala (Sweden)

TABLE IA

Cytotoxic therapy for carcinoid tumours

Drug	Regimen	Number of patients	Overall response (%)	Median duration (months)
Single agents				
Doxorubicin	60 mg/m^2 every 3-4 weeks	81	21	6
5-Fluorouracil	500 mg/m^2/day x 5 every 5 weeks	30	17-26	3
Streptozotocin	500-1500 mg/m^2/day x 5 every 3-5 weeks	14	0-17	2
Dacarbazine	250 mg/m^2/day x 5 every 4-5 weeks	15	13	4.5
Cisplatin	45-90 mg/m^2 every 3-4 weeks	16	6	4.5
Combinations				
Streptozotocin + 5-fluorouracil	500 mg/m^2/day x 5 every 3-6 weeks 400 mg/m^2/day x 5 every 3-6 weeks	175	7-33	3-7
Streptozotocin + doxorubicin	1000 mg/m^2/week x 4 25 mg/m^2/week then every 2 weeks	10	40	5
Streptozotocin + cyclophosphamide	500 mg/m^2/day every 6 weeks 100 mg/m^2 once every 3 weeks	24	39	6.5
Etoposide + cisplatin	130 mg/m^2/day x 3 45 mg/m^2/day on day 2 and 3, repeat cycle every 4 weeks	13	0	-

mize the disease-free interval[6, 7]. Surgery and thermal ablation (radiofrequency treatment) are new promising methods for treatment of liver metastases. Significant clinical improvement and reduction in tumour size has been reported[8, 9].

Liver transplantation has been suggested in selected patients without residual extrahepatic manifestations. However, long-term results are not that encouraging at the moment and the liver transplantation should only be reserved for a very few patients, where other means of therapy cannot control the disease[9].

Enbolization/chemoenbolization

A significant number of patients carry liver metastases at diagnosis, therefore treatment aimed at reducing the tumour bulk in the liver may significantly improve quality of life and survival. Such procedures include embolization of liver metastasis with or without concomitant cytotoxic agents (chemoembolization). Objective symptomatic and hormonal responses are ranging from 65% to 80%, but the method must be repeated to achieve long-lasting responses.

Radiotherapy

External radiotherapy has demonstrated limited value. Today this kind of therapy is mainly reserved for treatment of brain metastases and pain related to bone metastases. Tumour-targeted radioactive treatment using radiolabeled somatostatin analogues have been applied during the last years with some encouraging results. The different compounds have been 111Indium-DTPA-octreotide, 90Y-DOTA-octreotide, 90Y-DOTATOC and MAURITIUS giving about the same results with symptomatic improvement in 40% of the patients, biochemical responses in 24% to 30% and significant tumour reduction in a small number, 5% to 10%. In order to overcome the limitation of administrating doses of radiotherapy to non octreotide avid lesions and the lack of uptake due to tumour heterogeneity in addition to Ytrium 90 several other isotopes such as Lutetium 177 and Rhenium-186 are being considered. 177Lu-DOTA-octreotate shows high tumours uptake with a very good ratio of tumour to kidney uptake and is suggested to be an ideal compound for radionuclear treatment. Radiotherapy with this compound has recently been administered to 80 patients with a variety of progressive NE tumours and 49% showed partial remission[10, 11].

TABLE IB

Cytotoxic Therapy - Endocrine pancreatic tumours

Regimen	No of patients	Over all response rate (%)	Median duration
Streptozotocin	52	42	NA
Streptozotocin +5-FU	106	31-63	14-23 mo
Streptozotocin + Doxorubicin	36	69	18 mo
Streptozotocin + Doxorubicin +5-FU	11	54,5	15 mo

Medical treatment

Medical treatment of NE tumours includes treatment with both chemotherapy and biological agents, such as somatostatin analogues and interferon-alfa.

Chemotherapy (Table Ia, Ib)

Chemotherapy has been considered the gold standard for treatment of most NE tumours, however, it is usually reported for only a limited number of patients and with variable crite-

TABLE II

Neuroendocrine tumours: somatostatin analogue therapy (summary of several trials)

Response	Standard dose (100-1500 µg/day)	High dose (>3000 µg/day)	*Slow release (20-30 mg/day every 2-4 weeks)*
Symptomatic (%)	64 (146/228)	42 (11/26)	63 (76/119)
Biochemical (%)			
-complete response	11 (6/54)	3 (1/33)	3 (3/119)
-partial response	55 (116/211)	72 (24/83)	64 (76/119)
-stable disease	34 (72/211)	21 (7/33)	18 (21/119)
-progressive disease	11 (23/211)	3 (1/33)	15 (19/119)
Tumour (%)			
-complete response	-	2 (1/53)	-
-partial response	5 (7/131)	11 (6/53)	3 (4/119)
-stable disease	38 (50/131)	47 (25/53)	79 (94/119)
-progressive disease	56 (74/131)	39 (21/51)	18 (21/119)

TABLE III

Therapy with interferon-α in patients with midgut carcinoids

Number of patients	Biochemical response (%)	Subjective response (%)	Tumour value response (%)
29§	PR 53 (13/25)	72 (32/29)	PR 10 (3/29)
	SD 36 (9/25)		SD 86 (25/29)
27§§	PR 39 (9/23)	65	PR 20 (4/20)
16	PR 16 (1/6)		PR 0 (0/16)
	SD 50 (3/6)	80 (4/5)	SD 66 (10/15)
14	PR 44 (4/9)	55	PR 0 (0/16)
13	PR 8 (1/13)		PR 8 (1/13)
	SD 31 (4/13)	50	SD 77 (10/13)

§ Natural leukocyte interferon-α, 6 MU subcutaneously x 8 weeks
§§ High-dose interferon-$\alpha_{,2a}$ 24 MU/m² subcutaneously x 8 weeks
PR: Partial response; SD: Stable disease

ria for assessing antitumour responses. Cytotoxic treatment is predominantly used in patients with tumours that show high proliferative capacity and large tumour burden; a proliferation index analyzed by the antibody Ki67 should be above 10% to 15%. Classical midgut carcinoids with low proliferating capacity (Ki67) usually <2%) have not benefited from regular cytotoxic treatment. The most common chemotherapy in endocrine pancreatic tumour is a combination of Streptozotocin plus 5-fluorouracil or doxorubicin. Reported objective response-rates has been between 40% and 70%, whereas in classical midgut carcinoids the same combination has only generated responses of <10% with short duration. For anaplastic tumours and high proliferative capacity (Ki67 above 15%) combination with cisplatinum and etoposide has been particularly useful with a response-rate up to 67% with a tendency to more prolonged survival[12].

Somatostatin analogues (Table II)

The rationale for the clinical use of somatostatin analogues is based on the identification of high-affinity somatostatin receptors in 80% to 90% of NE tumours. Regular octreotide at a subcutaneous daily dose of 200-450 _g is associated with a median 60% symptomatic, 70% biochemical and 8% tumour response. A limited number of patients have been reported with partial tumour regression during treatment with somatostatin analogues, and very few cases have shown complete tumour regression. However, a high number of patients reached disease stabilization. Today slow-release formulations of octreotide Sandostatin LAR® and Somatuline Autogel® have been effective with a monthly dosage of 20-30 mg Sandostatin LAR® or 60-120 mg Somatuline Autogel®. SOM230 is a new somatostatin analogue which has a prolonged half-live, (approximately 24h) and exerts a more potent inhibitory effect than currently available compounds as it binds with much higher affinity to somatostatin receptors 1, 2, 3 and 5. The introduction of SOM230 into clinical practice will address a long-standing question as to whether somatostatin receptor subtypes 1 and 3, which mediate antitumour effects (cell cycle inhibition and induction of apoptosis) will be clinically beneficial in NE tumours[13, 14].

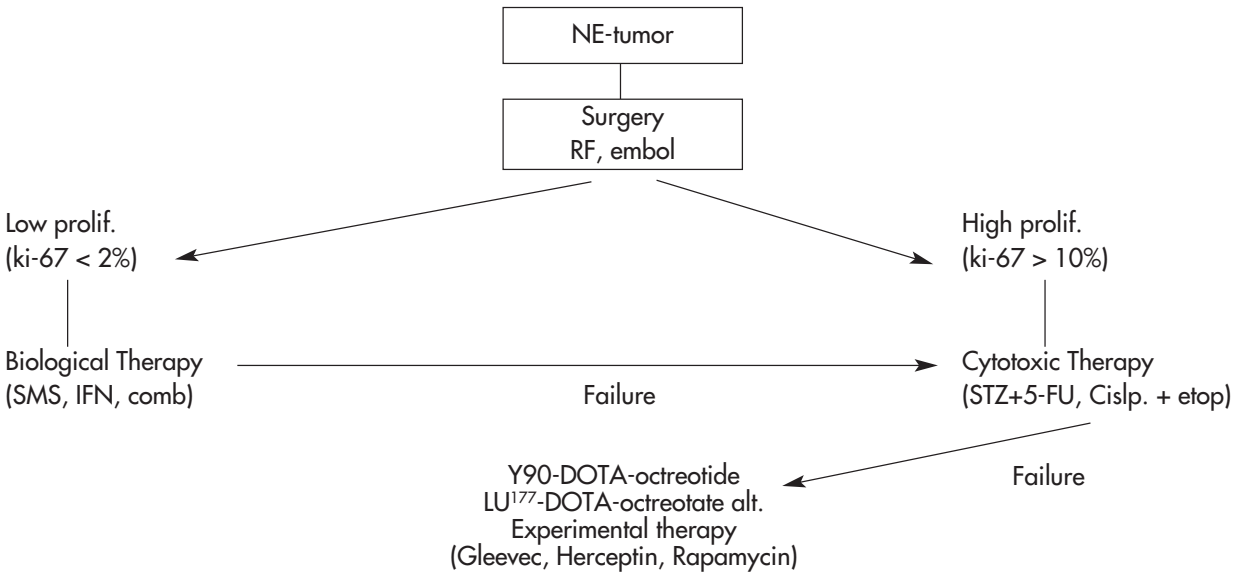

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Interferons (Table III)

Interferons are compounds known to exert a combination of effects directed to several groups of tumours and are considered as biological response modifiers as they interact with other soluble or cell-associated regulatory factors. The recommended dose of interferon-alfa is 3-9 MU every other day, subcutaneously or slow release formulation pegylated interferon alfa 80-100 μg once a week, subcutaneously. Data derived from several studies of carcinoid tumours have reported a median symptomatic and biochemical response rate of 40% to 70% and biochemical response in 40% to 60% and a significant tumour reduction in 10% to 12% of patients. Disease stabilization is noted in a further 35% of the patients. Flu-like symptoms are almost universal with interferon treatment but are usually short lasting. Chronic fatigue and mild depression may develop in approximately 50% of patients. Autoimmune reactions appear in approximately 15% of patients[15, 16].

Combination therapy with IFNα and somatostatin analogue

Patients for whom mono-therapy with interferon alone or octreotide alone could not control the disease have received the combination. Both hormone levels and clinical symptoms were controlled in 40%-70% of the patients but also tumour growth in one third[16].

The therapy of Neuroendocrine Tumours is summarized in an algorithm (Fig. 1).

New compounds

Inhibition of the intracellular signal transduction from tyrosine kinase receptors may be new targets in the treatment of NE tumours. Many NE tumours express platelet-derived growth factor alfa- and beta-receptor subtypes and ligands and also EGF-receptor. Another interesting new compound is Rapamycin, which may block signal transduction through the m-TOR pathway. Clinical trials with this compound as a single agent or in combination with cytotoxic agents are planned. Over the next five years the precise role of tumour-targeted radioactive treatment with somatostatin analogue-based compounds will be defined. New somatostatin analogues, such as SOM230 and somatostatin receptor subtype-specific analogues will also be developed. The tumour biology for different subtypes of NE tumours will be defined and thus new treatments including tyrosine kinase inhibitors, antiangiogenic compounds as well as combinations of these, will be applied in clinical trials.

References

1. Kimura W, Kuroda, A, Morioka, Y. Clinical pathology of endocrine tumors of the pancreas. Dig Dis Sci 1991; 36:933-42.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97:934-59.
3. Solcia E, Kloppel, G, Sobin, LH. Histological Typing of Endocrine Tumours. In: New York USA: Springer 2000; 38-74.
4. Rindi G, Villanacci V, Ubiali A. Biological and molecular aspects of gastroenteropancreatic neuroendocrine tumors. Digestion 2000; 62 Suppl 1:19-26.
5. Oberg K. Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. Curr Opin Oncol 2002; 14:38-45.
6. Thompson GB, van Heerden JA, Grant CS et al. Islet cell carcinomas of the pancreas: a twenty-year experience. Surgery 1988; 104:1011-7.
7. Hellman P, Lundstrom T, Ohrvall U et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002; 26:991-7.

8. Ruszniewski P, Malka D. Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. Digestion 2000; 62 Suppl 1:79-83.
9. Le Treut YP, Delpero JR, Dousset B et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. Ann Surg 1997; 225:355-64.
10. De Jong M BW, Bernard HF et al. Response to radionuclide therapy using 90Y and 111In-labeled somatostatin analogs in dependent on tumor size. J Nucl Med 2000; 41:147.
11. Kwekkeboom DJ, Bakker WH, Kooij PP et al. (177Lu-DOTA-OTyr3)octreotate: comparison with (111In-DTPAo)octreotide in patients. Eur J Nucl Med 2001; 28: 1319-25.
12. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 2001; 12 Suppl 2:S111-4.
13. Eriksson B, Oberg K. Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. Ann Oncol 1999; 10 Suppl 2:S31-8.
14. Weckbecker G, Briner U, Lewis I, Bruns C. SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. Endocrinology 2002; 143:4123-30.
15. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumors. Acta Oncol 1991; 30: 519-22.
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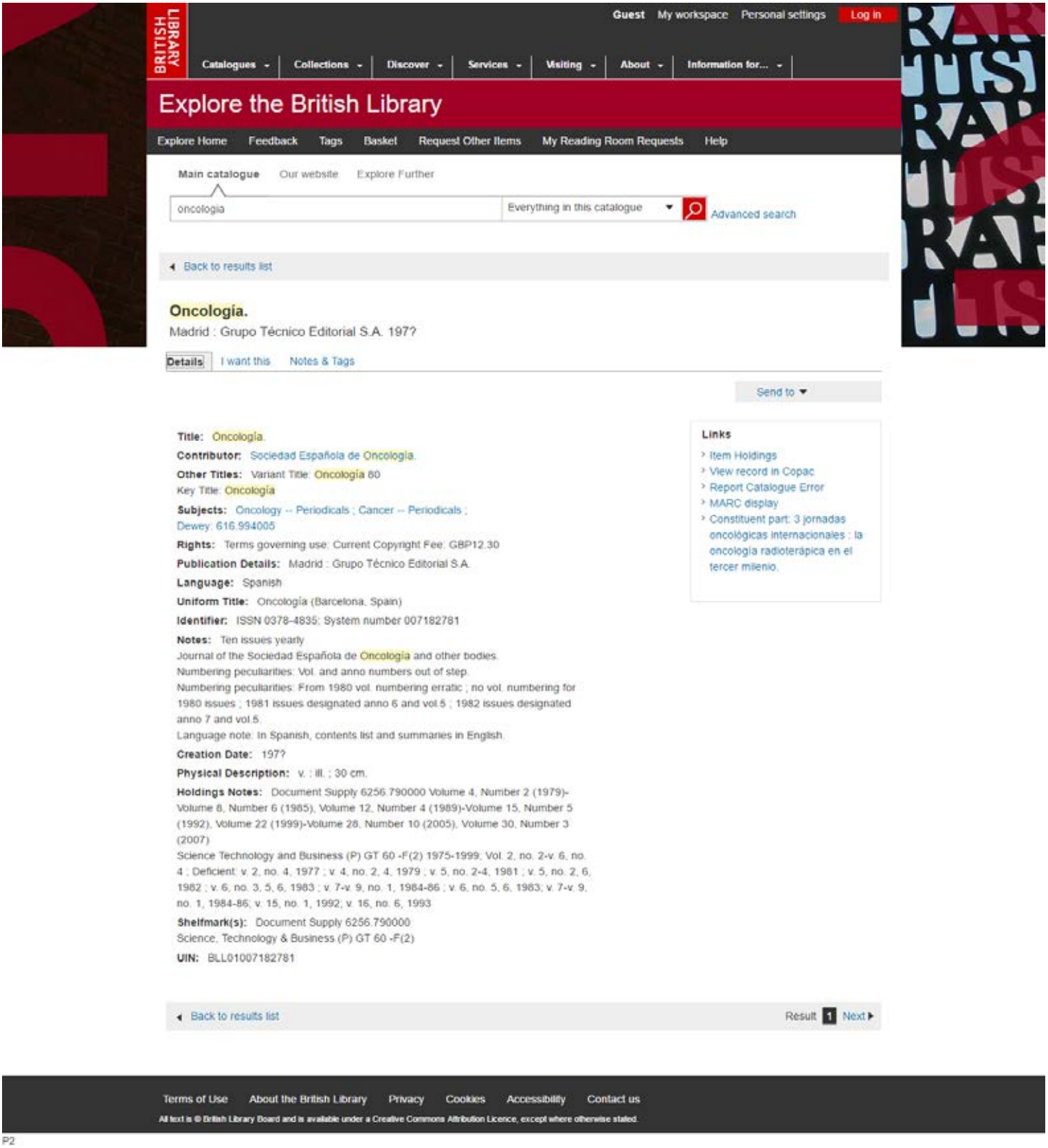

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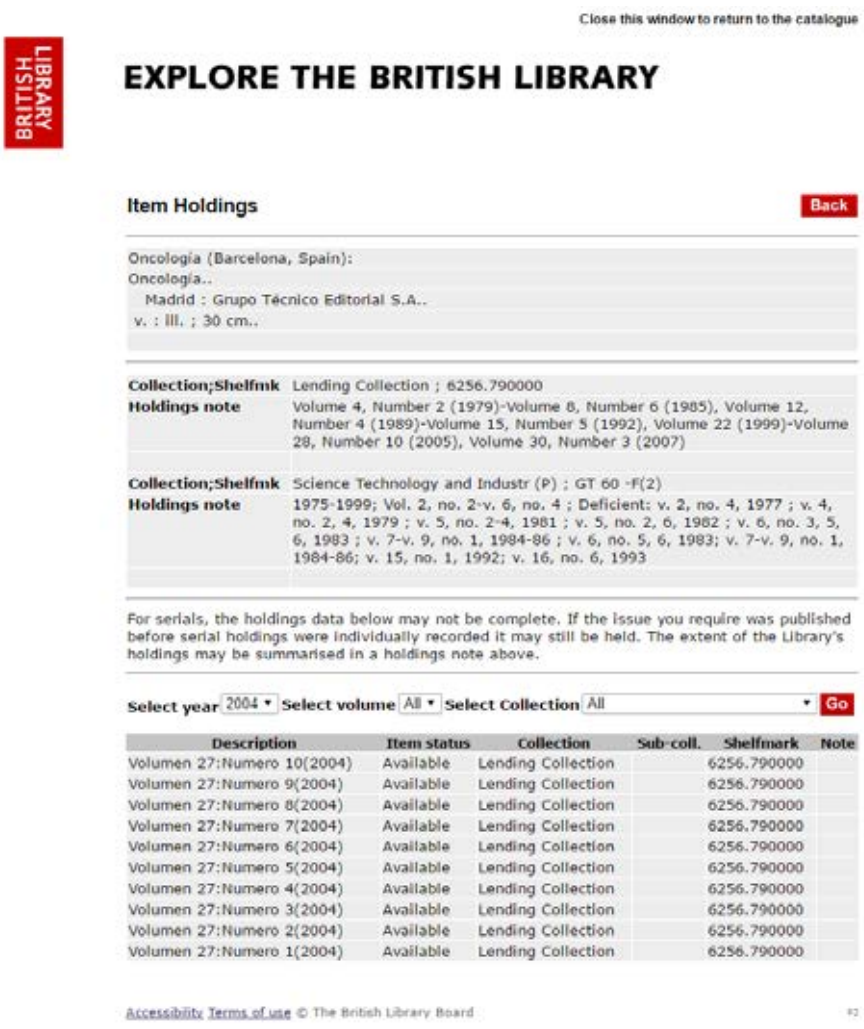

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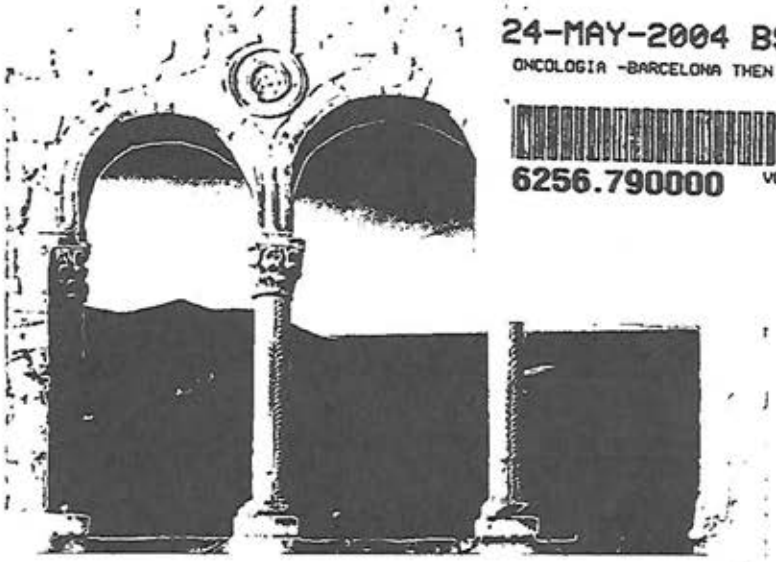

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Treatment of neuroendocrine tumours of the gastrointestinal tract

K. Öberg

Introduction

Neuroendocrine tumours (NE) of the gastrointestinal tract and pancreas constitute about 2% of all malignant tumours. They include a number of different tumours, derived from cells of the diffuse neuroendocrine cell-system[1]. The largest group of NE tumours are the so called carcinoids, with an incidence of about 2.5/100.000[2], which by tradition have been divided into foregut, midgut and hindgut tumours. Endocrine pancreatic tumours has an incidence of 0.4-0.8/100.000. This old classification is based on the embryonic origin of the different tumours, where the foregut carcinoid primaries has been located in the lung, thymus, gastric mucosa and the midgut carcinoids with primary tumours in the ileum, caecum and proximal colon and the hindgut carcinoids with the primaries in the distal colon and rectum. This old classification is now about to be abandoned, and more tumour-biology-based classification has emerged. The new WHO-classification is now indicating five subtypes[3].

1. Well-differentiated endocrine tumour
2. Well-differentiated endocrine carcinoma
3. Poorly-differentiated endocrine carcinoma
4. Mixed exocrine and endocrine carcinomas
5. Tumour-like lesions

This classification can be used for all types of NE tumours, not only for carcinoids. A classical midgut carcinoid will be called with the new terminology A well-differentiated endocrine carcinomas of the ileum, whereas a benign insulin producing tumour of the pancreas will be A well-differentiated endocrine tumour of the pancreas. The differentiation between different tumours types is based on histomorphology, tumour-size and presence or absence of local invasion and/or metastases. This new classification of NE tumours is a step forward, although the former classification of carcinoid tumours into foregut, midgut and hindgut, remains clinically available and is still used in many clinical studies. It will take some time for the new classification to receive general acceptance.

NE tumours exhibit substantial differences in terms of genotype and phenotype. Foregut carcinoids mainly pulmonary, but also endocrine pancreatic tumours, frequently show losses of 11q, which represent a characteristic genetic alteration in these tumours. Both typical and atypical carcinoids of the lung show loss of heterozygosity at 11q13, harboring the multiple endocrine neoplasia Type 1 (MEN-1) gene. Atypical carcinoids also show loss of heterozygosity at 3p14-p21.3. Recent studies have shown that carcinoid tumours of the lung and the GI tract may develop via different molecular pathways. Inactivation of one of several tumours suppressor genes on chromosome 18 may be important for the biological behaviour of GI tumours. Familiar midgut carcinoids are rare but bronchial carcinoids as well as endocrine pancreatic tumours and gastric carcinoids may be part of a MEN-1 syndrome[4,5].

Such differences in molecular genetics and tumour biology play a role for the diagnosis and treatment of neuroendocrine gastrointestinal tumours.

Treatment of NE tumours

Surgery

The clinical management of metastatic NE tumours requires a multimodal approach including surgery and other means of cytoreductive treatment, radiotherapy and medical treatment. Surgery remains the treatment of choice and is the only approach that can achieve a complete cure in patients with NE tumours. In cases of metastases, surgery has been used to improve hormone-mediated symptoms, quality of life and survival in certain groups of patients, as well as to reduce tumours bulk and prevent further local and systemic effects. Surgical resection of primary tumours as well as lymph nodes and liver involvement can improve survival. In addition, surgery can also be employed after medical treatment to achieve substantial tumour reduction in an attempt to maxi-

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TABLE IA

Cytotoxic therapy for carcinoid tumours

Drug	Regimen	Number of patients	Overall response (%)	Median duration (months)
Single agents				
Doxorubicin	60 mg/m² every 3-4 weeks	81	21	6
5-Fluorouracil	500 mg/m²/day x 5 every 5 weeks	30	17-26	3
Streptozotocin	500-1500 mg/m²/day x 5 every 3-5 weeks	14	0-17	2
Dacarbazine	250 mg/m²/day x 5 every 4-5 weeks	15	13	4.5
Cisplatin	45-90 mg/m² every 3-4 weeks	16	6	4.5
Combinations				
Streptozotocin + 5-fluorouracil	500 mg/m²/day x 5 every 3-6 weeks 400 mg/m²/day x 5 every 3-6 weeks	175	7-33	3-7
Streptozotocin + doxorubicin	1000 mg/m²/week x 4 25 mg/m²/week then every 2 weeks	10	40	5
Streptozotocin + cyclophosphamide	500 mg/m²/day every 6 weeks 100 mg/m² once every 3 weeks	24	39	6.5
Etoposide + cisplatin	130 mg/m²/day x 3 45 mg/m²/day on day 2 and 3, repeat cycle every 4 weeks	13	0	-

mize the disease-free interval[6, 7]. Surgery and thermal ablation (radiofrequency treatment) are new promising methods for treatment of liver metastases. Significant clinical improvement and reduction in tumour size has been reported[8, 9].

Liver transplantation has been suggested in selected patients without residual extrahepatic manifestations. However, long-term results are not that encouraging at the moment and the liver transplantation should only be reserved for a very few patients, where other means of therapy cannot control the disease[9].

Enbolization/chemoenbolization

A significant number of patients carry liver metastases at diagnosis, therefore treatment aimed at reducing the tumour bulk in the liver may significantly improve quality of life and survival. Such procedures include embolization of liver metastasis with or without concomitant cytotoxic agents (chemoembolization). Objective symptomatic and hormonal responses are ranging from 65% to 80%, but the method must be repeated to achieve long-lasting responses.

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-partial response	55 (116/211)	72 (24/83)	64 (76/119)
-stable disease	34 (72/211)	21 (7/33)	18 (21/119)
-progressive disease	11 (23/211)	3 (1/33)	15 (19/119)
Tumour (%)			
-complete response	-	2 (1/53)	-
-partial response	5 (7/131)	11 (6/53)	3 (4/119)
-stable disease	38 (50/131)	47 (25/53)	79 (94/119)
-progressive disease	56 (74/131)	39 (21/51)	18 (21/119)

TABLE III

Therapy with interferon-α in patients with midgut carcinoids

Number of patients	Biochemical response (%)	Subjective response (%)	Tumour value response (%)
29[§]	PR 53 (13/25)	72 (32/29)	PR 10 (3/29)
	SD 36 (9/25)		SD 86 (25/29)
27[§§]	PR 39 (9/23)	65	PR 20 (4/20)
16	PR 16 (1/6)		PR 0 (0/16)
	SD 50 (3/6)	80 (4/5)	SD 66 (10/15)
14	PR 44 (4/9)	55	PR 0 (0/16)
13	PR 8 (1/13)		PR 8 (1/13)
	SD 31 (4/13)	50	SD 77 (10/13)

§ Natural leukocyte interferon-α, 6 MU subcutaneously x 8 weeks
§§ High-dose interferon-α_{2b} 24 MU/m² subcutaneously x 8 weeks
PR: Partial response; SD: Stable disease

ria for assessing antitumour responses. Cytotoxic treatment is predominantly used in patients with tumours that show high proliferative capacity and large tumour burden; a proliferation index analyzed by the antibody Ki67 should be above 10% to 15%. Classical midgut carcinoids with low proliferating capacity (Ki67) usually <2%) have not benefited from regular cytotoxic treatment. The most common chemotherapy in endocrine pancreatic tumour is a combination of Streptozotocin plus 5-fluorouracil or doxorubicin. Reported objective response-rates has been between 40% and 70%, whereas in classical midgut carcinoids the same combination has only generated responses of <10% with short duration. For anaplastic tumours and high proliferative capacity (Ki67 above 15%) combination with cisplatinum and etoposide has been particularly useful with a response-rate up to 67% with a tendency to more prolonged survival[12].

Somatostatin analogues (Table II)

The rationale for the clinical use of somatostatin analogues is based on the identification of high-affinity somatostatin receptors in 80% to 90% of NE tumours. Regular octreotide at a subcutaneous daily dose of 200-450 _g is associated with a median 60% symptomatic, 70% biochemical and 8% tumour response. A limited number of patients have been reported with partial tumour regression during treatment with somatostatin analogues, and very few cases have shown complete tumour regression. However, a high number of patients reached disease stabilization. Today slow-release formulations of octreatide Sandostatin LAR® and Somatuline Autogel® have been effective with a monthly dosage of 20-30 mg Sandostatin LAR® or 60-120 mg Somatuline Autogel®. SOM230 is a new somatostatin analogue which has a prolonged half-live, (approximately 24h) and exerts a more potent inhibitory effect than currently available compounds as it binds with much higher affinity to somatostatin receptors 1, 2, 3 and 5. The introduction of SOM230 *into clinical practice will address a long-standing* question as to whether somatostatin receptor subtypes 1 and 3, which mediate antitumour effects (cell cycle inhibition and induction of apoptosis) will be clinically beneficial in NE tumours[13, 14].

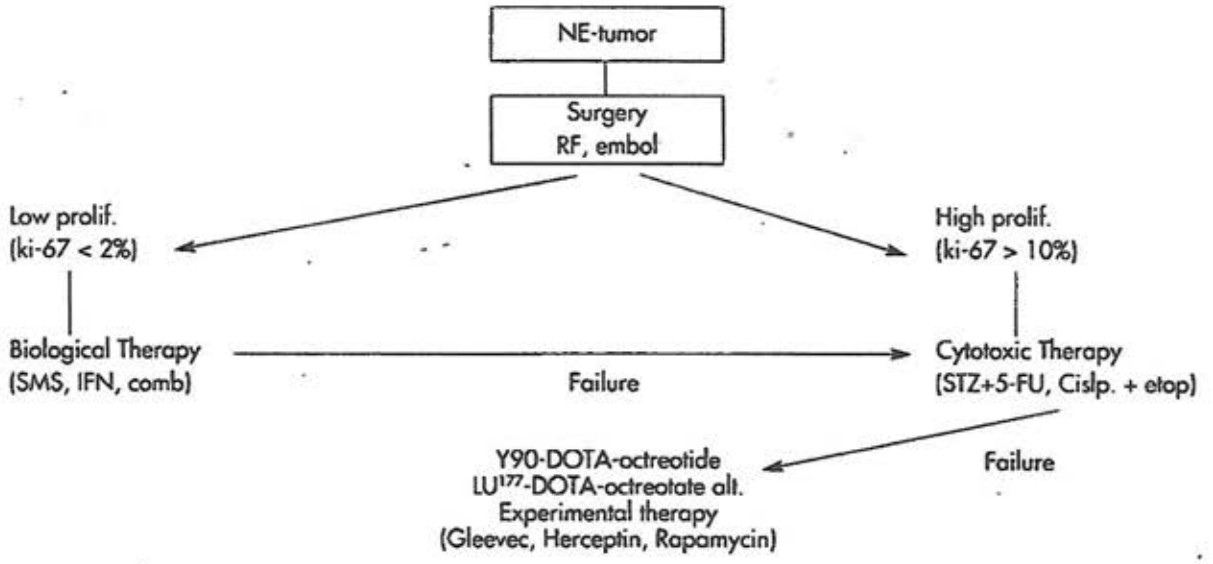


Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Interferons (Table III)

Interferons are compounds known to exert a combination of effects directed to several groups of tumours and are considered as biological response modifiers as they interact with other soluble or cell-associated regulatory factors. The recommended dose of interferon-alfa is 3-9 MU every other day, subcutaneously or slow release formulation pegylated interferon alfa 80-100 µg once a week, subcutaneously. Data derived from several studies of carcinoid tumours have reported a median symptomatic and biochemical response rate of 40% to 70% and biochemical response in 40% to 60% and a significant tumour reduction in 10% to 12% of patients. Disease stabilization is noted in a further 35% of the patients. Flu-like symptoms are almost universal with interferon treatment but are usually short lasting. Chronic fatigue and mild depression may develop in approximately 50% of patients. Autoimmune reactions appear in approximately 15% of patients[15, 16].

Combination therapy with IFNα and somatostatin analogue

Patients for whom mono-therapy with interferon alone or octreotide alone could not control the disease have received the combination. Both hormone levels and clinical symptoms were controlled in 40%-70% of the patients but also tumour growth in one third[16].

The therapy of Neuroendocrine Tumours is summarized in an algorithm (Fig. 1).

New compounds

Inhibition of the intracellular signal transduction from tyrosine kinase receptors may be new targets in the treatment of NE tumours. Many NE tumours express platelet-derived growth factor alfa- and beta-receptor subtypes and ligands and also EGF-receptor. Another interesting new compound is Rapamycin, which may block signal transduction through the m-TOR pathway. Clinical trials with this compound as a single agent or in combination with cytotoxic agents are planned. Over the next five years the precise role of tumour-targeted radioactive treatment with somatostatin analogue-based compounds will be defined. New somatostatin analogues, such as SOM230 and somatostatin receptor subtype-specific analogues will also be developed. The tumour biology for different subtypes of NE tumours will be defined and thus new treatments including tyrosine kinase inhibitors, antiangiogenic compounds as well as combinations of these, will be applied in clinical trials.

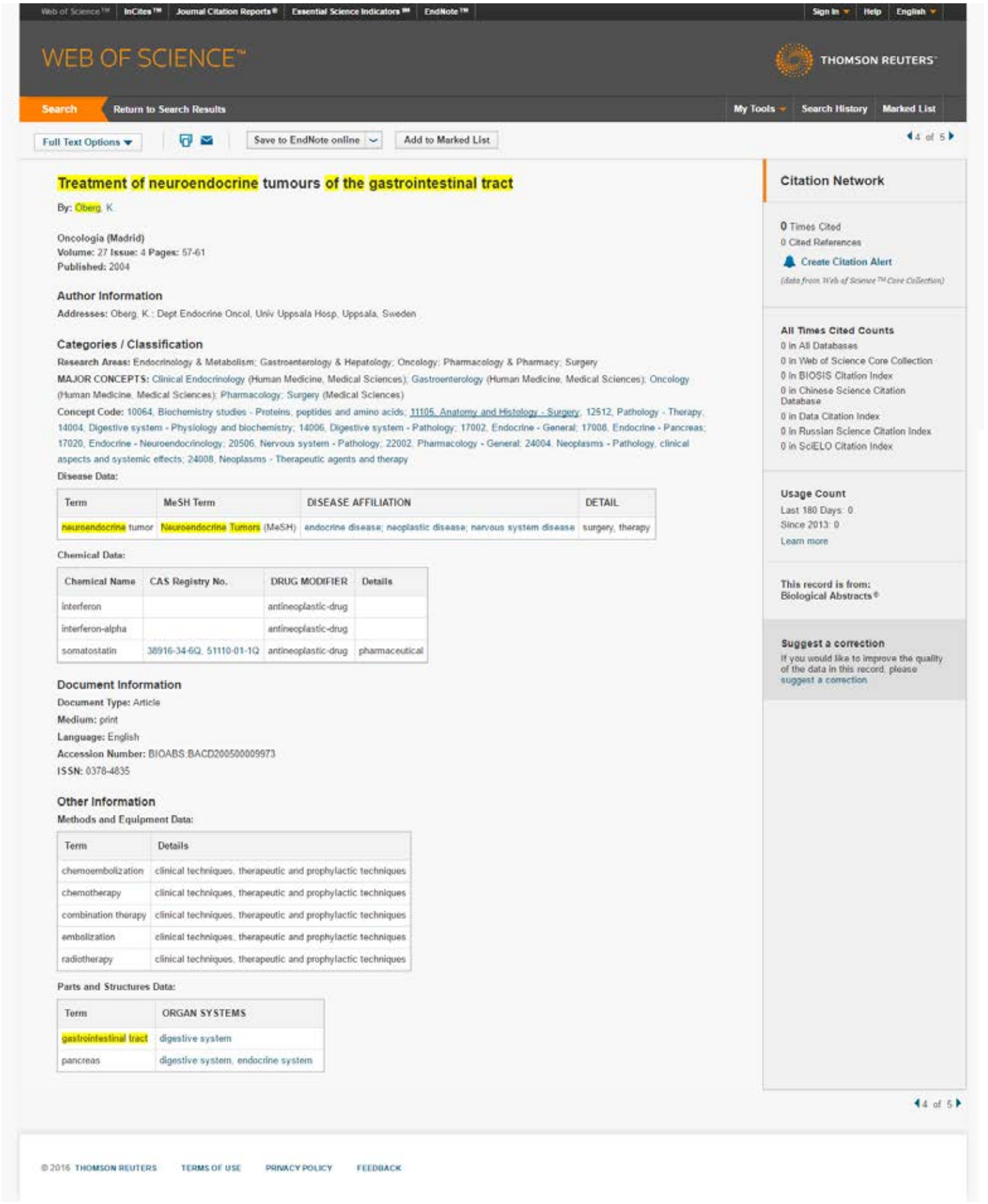
References

1. Kimura W, Kuroda, A, Morioka, Y. Clinical pathology of endocrine tumors of the pancreas. Dig Dis Sci 1991; 36:933-42.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97:934-59.
3. Solcia E, Kloppel, G, Sobin, LH. Histological Typing of Endocrine Tumours. In: New York USA: Springer 2000; 38-74.
4. Rindi G, Villanacci V, Ubiali A. Biological and molecular aspects of gastroenteropancreatic neuroendocrine tumors. Digestion 2000; 62 Suppl 1:19-26.
5. Oberg K. Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. Curr Opin Oncol 2002; 14:38-45.
6. Thompson GB, van Heerden JA, Grant CS et al. Islet cell carcinomas of the pancreas: a twenty-year experience. Surgery 1988; 104:1011-7.
7. Hellman P, Lundstrom T, Ohrvall U et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg 2002; 26:991-7.

Attachment 1f: Copy of Öberg from the British Library

8. Ruszniewski P, Malka D. Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. Digestion 2000; 62 Suppl 1:79-83.
9. Le Treut YP, Delpero JR, Dousset B et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. Ann Surg 1997; 225:355-64.
10. De Jong M BW, Bernard HF et al. Response to radionuclide therapy using 90Y and 111In-labeled somatostatin analogs in dependent on tumor size. J Nucl Med 2000; 41:147.
11. Kwekkeboom DJ, Bakker WH, Kooij PP et al. [177Lu-DOTA-OTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med 2001; 28: 1319-25.
12. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 2001; 12 Suppl 2:S111-4.
13. Eriksson B, Oberg K. Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. Ann Oncol 1999; 10 Suppl 2:S31-8.
14. Weckbecker G, Briner U, Lewis I, Bruns C. SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. Endocrinology 2002; 143:4123-30.
15. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumors. Acta Oncol 1991; 30: 519-22.
16. Fjallskog ML, Sundin A, Westlin JE et al. Treatment of malignant endocrine pancreatic tumors with a combination of alpha-interferon and somatostatin analogs. Med Oncol 2002; 19:35-42.

Attachment 1g: Web of Science index record for Öberg



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Treatment of neuroendocrine tumours of the gastrointestinal tract

By: Oberg, K.

Oncologia (Madrid)
Volume: 27 Issue: 4 Pages: 57-61
Published: 2004

Author Information

Addresses: Oberg, K.: Dept Endocrine Oncol, Univ Uppsala Hosp, Uppsala, Sweden

Categories / Classification

Research Areas: Endocrinology & Metabolism; Gastroenterology & Hepatology; Oncology; Pharmacology & Pharmacy; Surgery

MAJOR CONCEPTS: Clinical Endocrinology (Human Medicine, Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology; Surgery (Medical Sciences)

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Disease Data:

Term	MeSH Term	DISEASE AFFILIATION	DETAIL
neuroendocrine tumor	Neuroendocrine Tumors (MeSH)	endocrine disease; neoplastic disease; nervous system disease	surgery, therapy

Chemical Data:

Chemical Name	CAS Registry No.	DRUG MODIFIER	Details
interferon		antineoplastic-drug	
interferon-alpha		antineoplastic-drug	
somatostatin	38916-34-6Q, 51110-01-1Q	antineoplastic-drug	pharmaceutical

Document Information

Document Type: Article
Medium: print
Language: English
Accession Number: BIOABS:BACD200500009973
ISSN: 0378-4835

Other Information

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Term	Details
chemoembolization	clinical techniques, therapeutic and prophylactic techniques
chemotherapy	clinical techniques, therapeutic and prophylactic techniques
combination therapy	clinical techniques, therapeutic and prophylactic techniques
embolization	clinical techniques, therapeutic and prophylactic techniques
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Parts and Structures Data:

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gastrointestinal tract	digestive system
pancreas	digestive system, endocrine system

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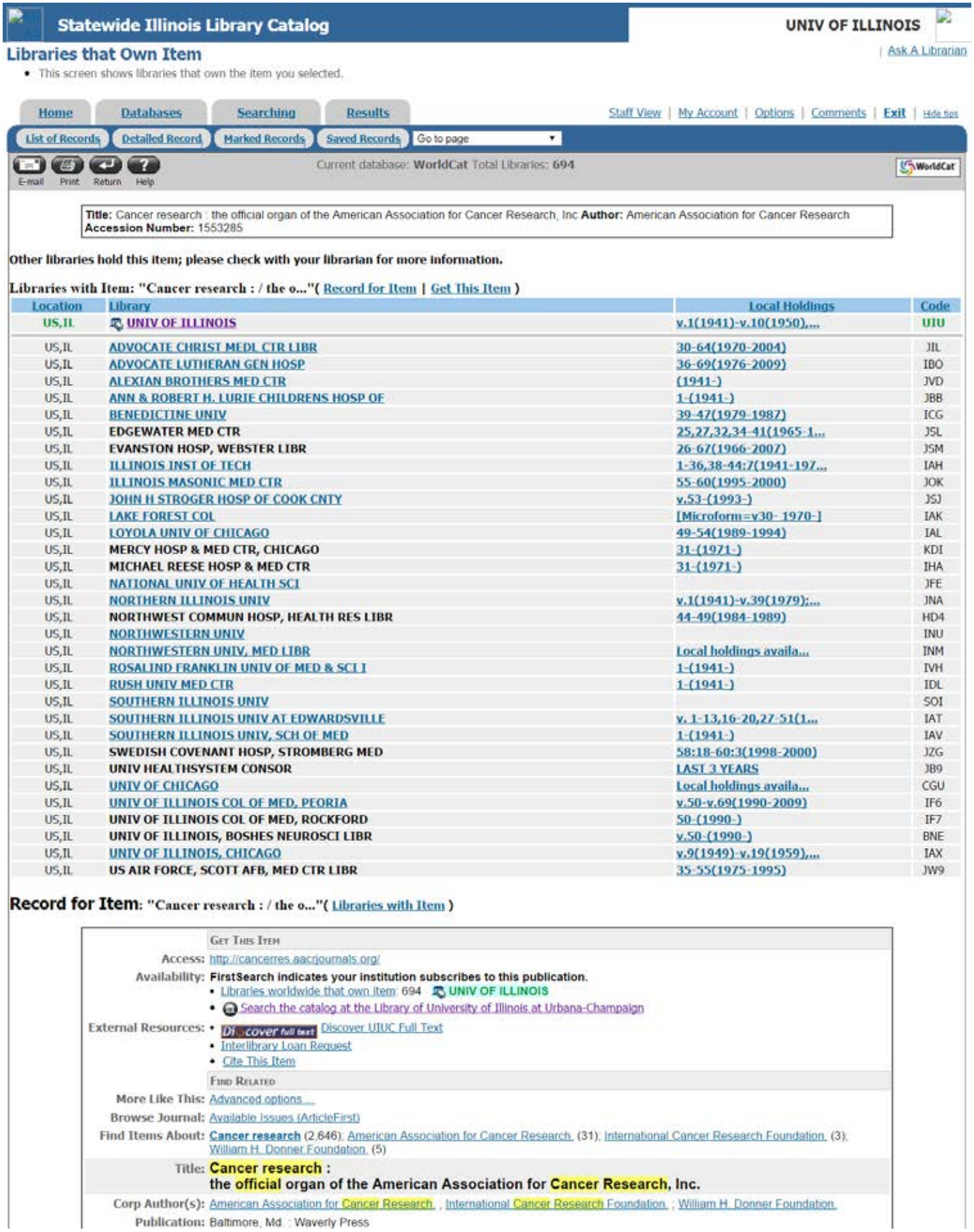

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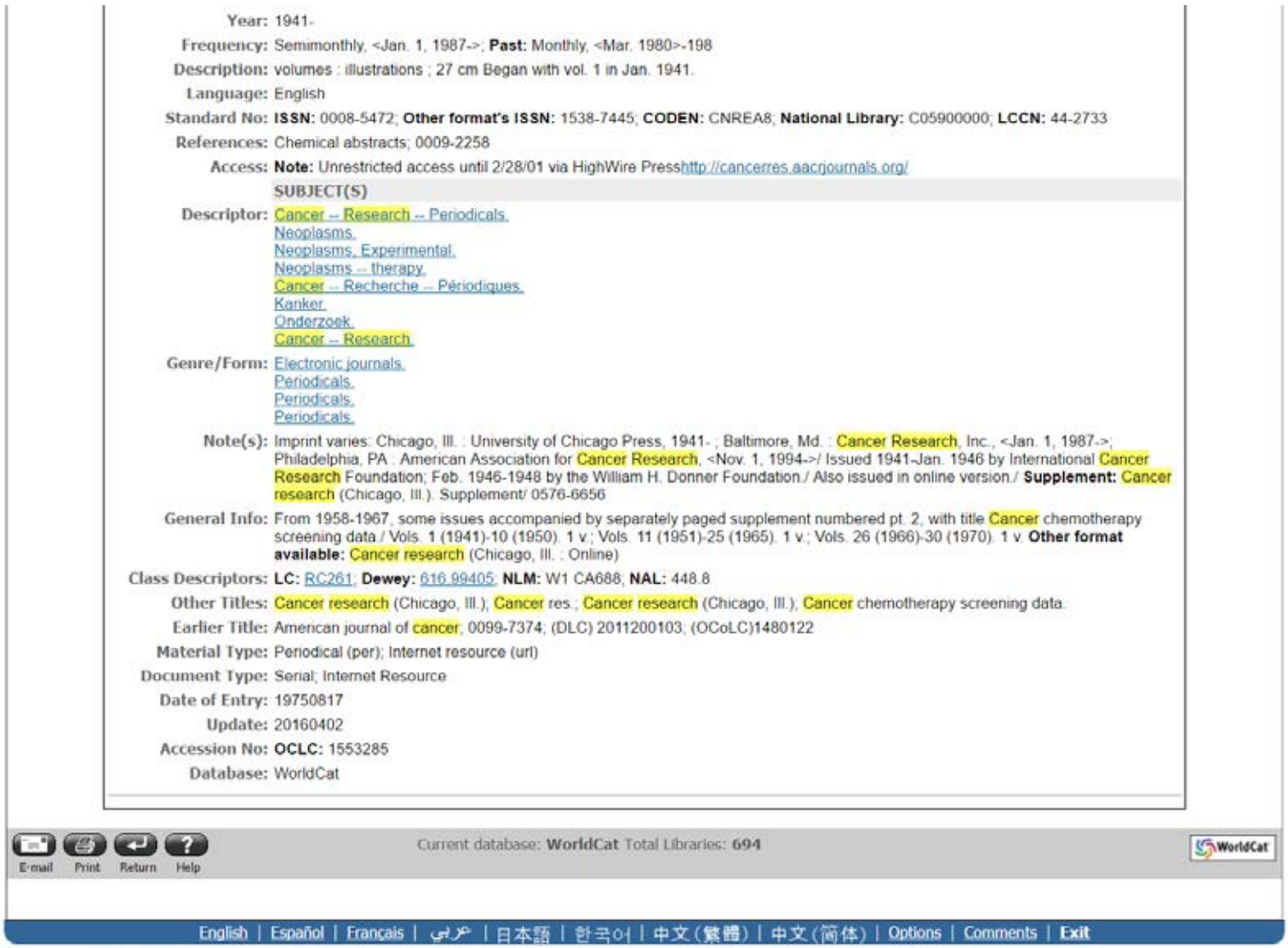

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Other Titles:	Cancer research (Chicago, Ill.), Cancer res., Cancer research (Chicago, Ill.), Cancer chemotherapy screening data.
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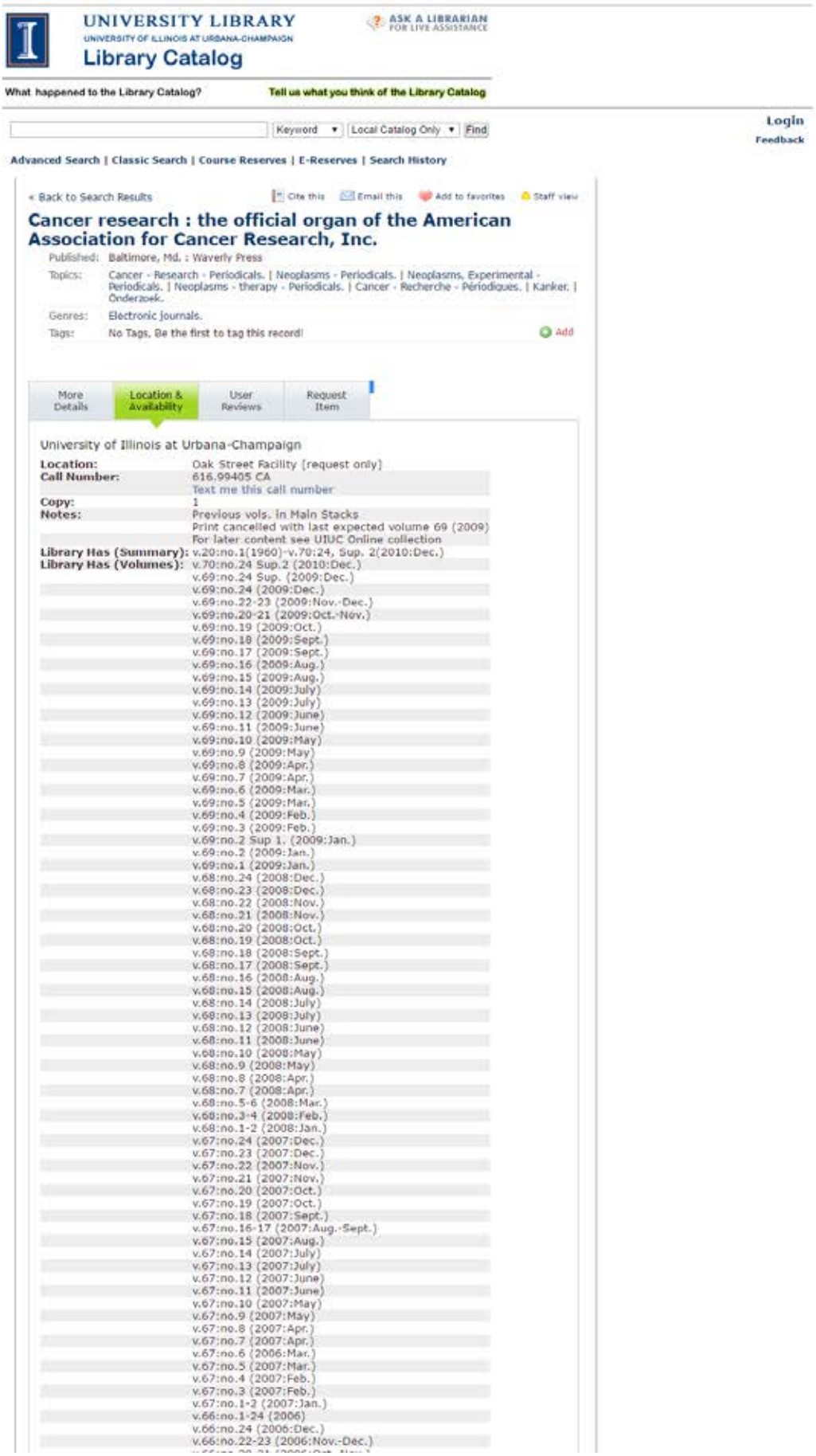

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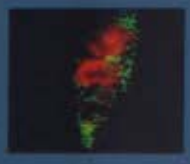

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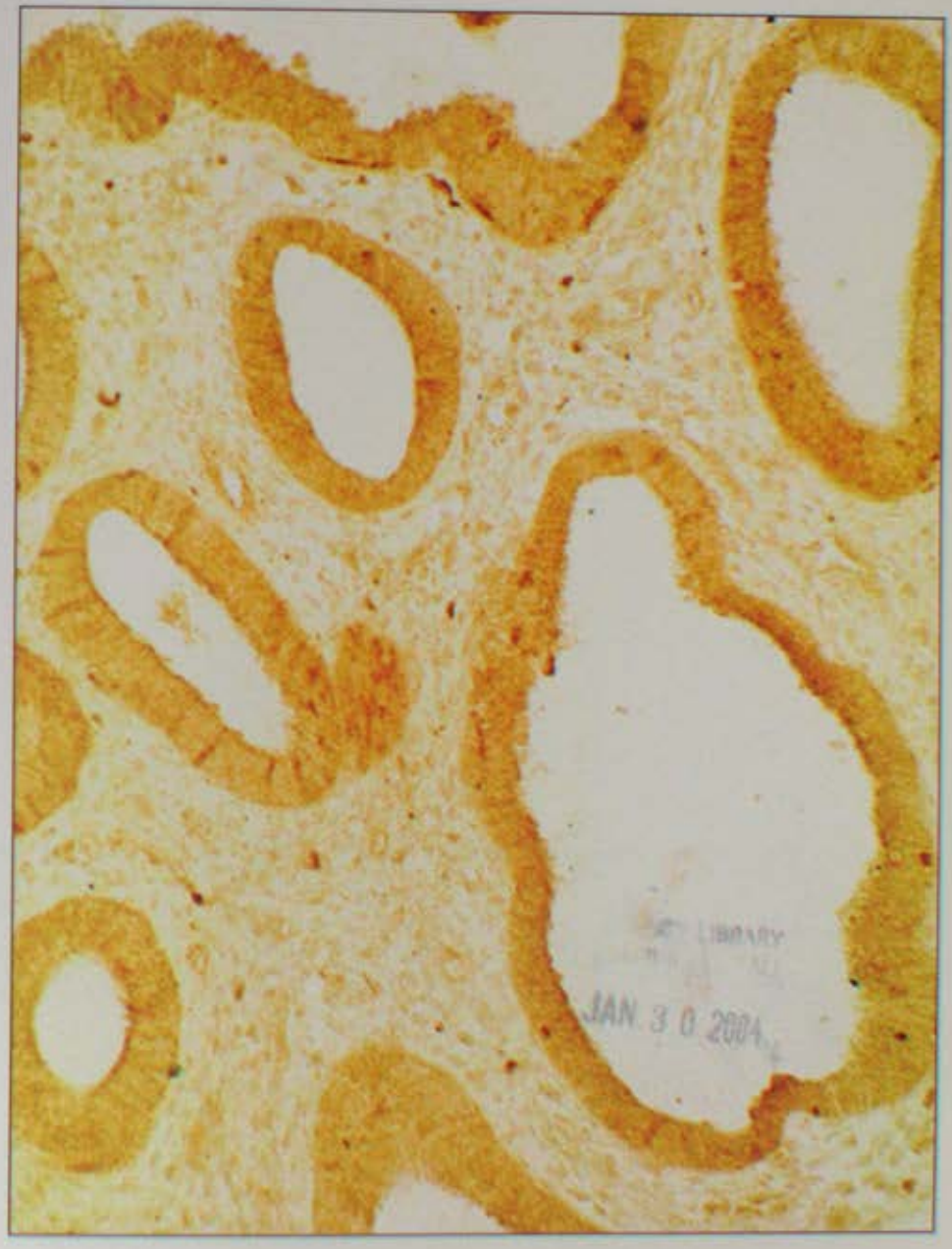

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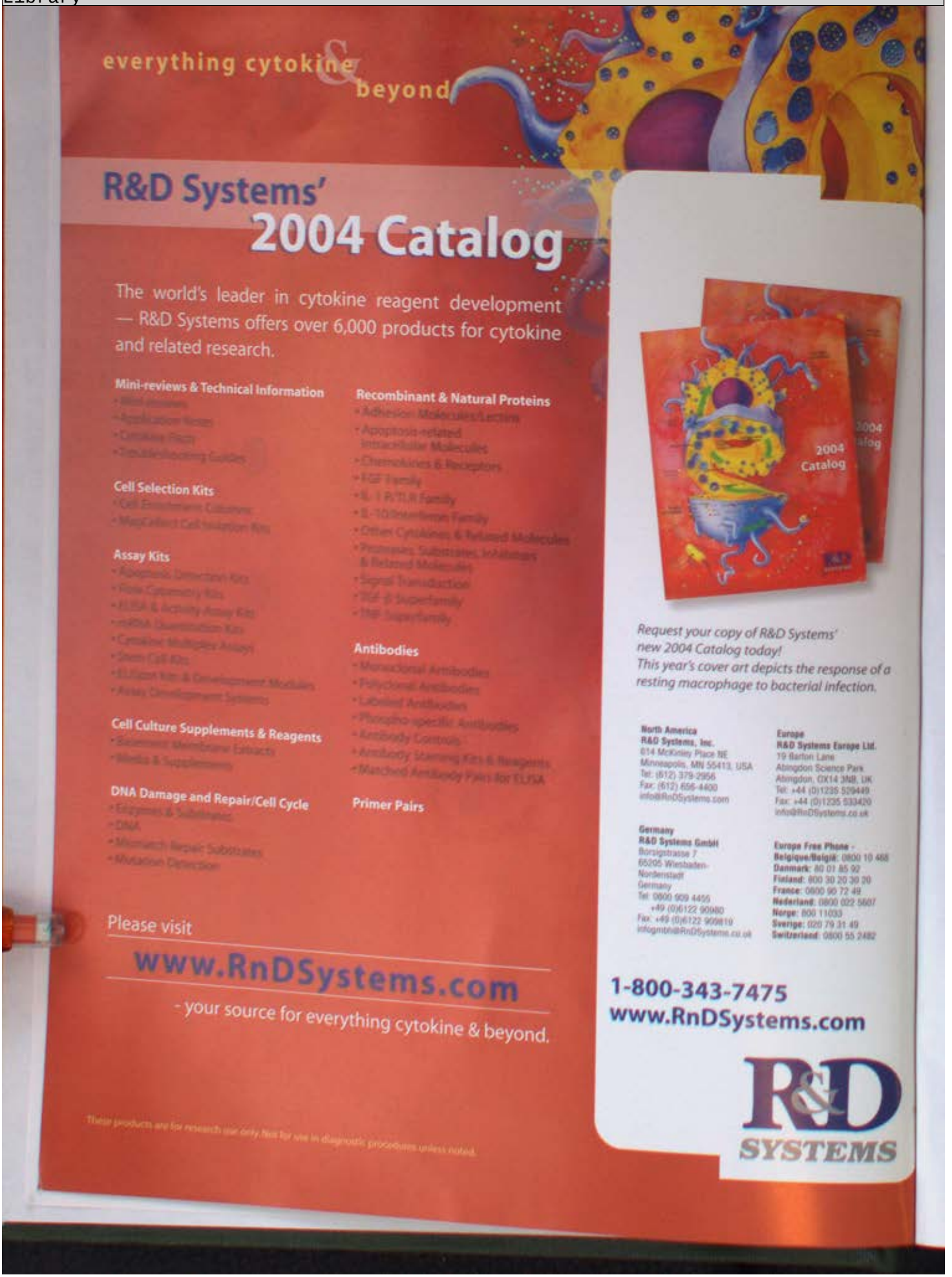

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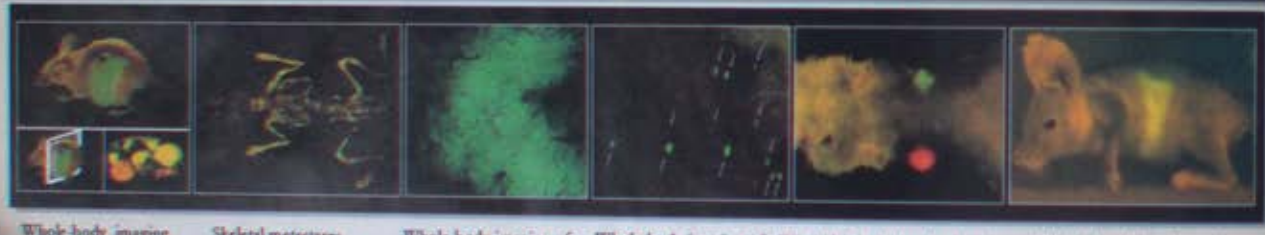

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1. Yang, M., et al. Whole-body optical imaging of green fluorescent protein-expressing tumors and metastases. Proc. Natl. Acad. Sci. USA 97, 1206-1211, 2000.
2. Yang, M., et al. Visualizing gene expression by whole-body fluorescence imaging. Proc. Natl. Acad. Sci. USA 97, 12278-12282, 2000.
3. Yang, M., et al. Whole-body and intravital optical imaging of angiogenesis in orthotopically implanted tumors. Proc. Natl. Acad. Sci. USA 98, 2616-2621, 2001.
4. Hoffman, R.M. Orthotopic metastatic mouse models for anticancer drug discovery and evaluation: a bridge to the clinic. Investig. New Drugs 17, 343-359, 1999.
5. McCann, J. Jellyfish protein gives new glow to tumor imaging. Journal of the National Cancer Institute 93, 976-977, 2001.
6. Yang, M., et al. Direct external imaging of nascent cancer, tumor progression, angiogenesis, and metastasis on internal organs in the fluorescent orthotopic model. Proc. Natl. Acad. Sci. USA 99, 3824-3829, 2002.
7. Schmitt, C.A., et. al. Dissecting p53 tumor suppressor functions in vivo. Cancer Cell 1, 289-298, 2002.
8. Schmitt, C.A., et. al. Senescence program controlled by p53 and $p16^{INK4a}$ contributes to the outcome of cancer therapy. Cell 109, 335–346, 2002.
9. Hoffman, R.M. Green fluorescent protein imaging of tumor growth, metastasis, and angiogenesis in mouse models. Lancet Oncology 3, 546-556, 2002.

MetaMouse US Patents: 5,491,284; 5,569,812; European Patent 0437488; Japanese Patent 2,664,261. GFP US Patents: 6,232,523; 6,251,384; 6,235,968.

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Antitumor Efficacy of Intermittent Treatment Schedules with the Rapamycin Derivative RAD001 Correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells

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ABSTRACT

The orally bioavailable rapamycin derivative RAD001 (everolimus) targets the mammalian target of rapamycin pathway and possesses potent immunosuppressive and anticancer activities. Here, the antitumor activity of RAD001 was evaluated in the CA20948 syngeneic rat pancreatic tumor model. RAD001 demonstrated dose-dependent antitumor activity with daily and weekly administration schedules; statistically significant antitumor effects were observed with 2.5 and 0.5 mg/kg RAD001 administered daily [treated tumor *versus* control tumor size (T/C), 23% and 23–30%, respectively], with 3–5 mg/kg RAD001 administered once weekly (T/C, 14–36%), or with 5 mg/kg RAD001 administered twice weekly (T/C, 36%). These schedules were well tolerated and exhibited antitumor potency similar to that of the cytotoxic agent 5-fluorouracil (T/C, 23%). Moreover, the efficacy of intermittent treatment schedules suggests a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical profiling of mammalian target of rapamycin signaling in tumors, skin, and peripheral blood mononuclear cells (PBMCs), after a single administration of 5 mg/kg RAD001, indicated that RAD001 treatment blocked phosphorylation of the translational repressor eukaryotic initiation factor 4E-binding protein 1 and inactivated the translational activator ribosomal protein S6 kinase 1 (S6K1). The efficacy of intermittent treatment schedules was associated with prolonged inactivation of S6K1 in tumors and surrogate tissues (≥72 h). Furthermore, detailed analysis of the dose dependency of weekly treatment schedules demonstrated a correlation between antitumor efficacy and prolonged effects (≥7 days) on PBMC-derived S6K1 activity. Analysis of human PBMCs revealed that S6K1 also underwent a concentration-dependent inactivation after RAD001 treatment *ex vivo* (>95% inactivation with 20 nM RAD001). In contrast, human PBMC-derived eukaryotic initiation factor 4E-binding protein 1 was present predominantly in the hypophosphorylated form and was unaffected by RAD001 treatment. Taken together, these results demonstrate a correlation between the antitumor efficacy of intermittent RAD001 treatment schedules and prolonged S6K1 inactivation in PBMCs and suggest that long-term monitoring of PBMC-derived S6K1 activity levels could be used for assessing RAD001 treatment schedules in cancer patients.

INTRODUCTION

RAD001 (everolimus), an orally bioavailable derivative of rapamycin, is a macrolide antifungal antibiotic that demonstrates potent antiproliferative effects against a variety of mammalian cell types. Specifically, RAD001 inhibits cytokine-driven lymphocyte proliferation (1), as well as the proliferation of human tumor-derived cells grown either in culture or as tumors in animal models (2, 3). As a result of these properties, RAD001 is being clinically developed both as an immunosuppressant for prevention of allograft rejection (Certican; Ref. 1) and as a novel therapeutic in the fight against human cancer (2–4).

RAD001, like rapamycin, binds with high affinity to a ubiquitous intracellular receptor, the immunophilin FKBP12. This complex specifically interacts with the mammalian target of rapamycin (mTOR) protein kinase; inhibiting downstream signaling events (5). The mTOR kinase is a member of the phosphoinositide kinase-related kinase family, which consists of high molecular weight serine/threonine kinases involved in cell cycle checkpoint control (6). Several lines of evidence suggest that mTOR acts as a sensor for stress (7) and the availability of amino acids (8–10) or intracellular ATP (11). In the presence of mitogens and sufficient nutrients, mTOR relays a signal to translational regulators, specifically enhancing the translation of mRNAs encoding proteins essential for cell growth (12) and progression through the G_1 to S transition (13, 14). Consistent with targeting the mTOR pathway, treatment of mammalian cells with rapamycin has been shown to inhibit these signaling events, mimicking a starvation phenotype (15) and leading to growth retardation and accumulation of cells in G_1 phase (16). The mechanism of growth stimulus and nutrient level integration by mTOR is, as yet, not fully understood. However, an increasing body of evidence suggests the involvement of the phosphatidylinositol 3′-kinase/Akt/TSC/Rheb pathway (12, 17–23). Indeed, it has been suggested that, in tumor cells, the activation status of the Akt pathway may be indicative of responsiveness to rapamycin or its derivatives (24–27).

mTOR is part of a multisubunit complex that contains the regulatory proteins raptor (28, 29) and GβL (30). The mTOR complex signals to at least two downstream effectors, the translational repressor protein eukaryotic initiation factor 4E (eIF-4E)-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1). These share an evolutionary conserved amino acid motif, the TOS motif, that functions as a docking site for raptor (31–33). Binding of 4E-BP1 to the translational activator eIF-4E is modulated by mTOR-dependent phosphorylation of specific serine and threonine residues (5). Ser37 and Ser46 are constitutively phosphorylated, acting as priming sites for the mitogen-induced, rapamycin-sensitive phosphorylation of Thr70 and Ser65 (34). After a final phosphorylation event at Ser65, 4E-BP1 dissociates from eIF-4E (35), thereby allowing the reconstitution of a translationally competent initiation factor complex (eIF-4F; Ref. 5). eIF-4F activation results in the translation of a subset of capped mRNA containing highly structured 5′-untranslated regions and encoding proteins involved in G_1- to S-phase progression (13, 14). Mitogen-induced activation of the S6K1 is also dependent on mTOR function and has been implicated in the translational regulation of mRNAs possessing a 5′-terminal oligopyrimidine tract (36–38). 5′-Terminal oligopyrimidine tract mRNAs are characterized by a stretch of 4–14 pyrimidines located at their extreme 5′ terminus and typically encode ribosomal proteins as well as components of the

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translational machinery. Activation of S6K1 itself is also tightly regulated by hierarchical phosphorylation events, which are dependent on the activation of various signal transduction pathways and culminate in the phosphorylation of the rapamycin-sensitive site Thr389, an event closely paralleling kinase activation (12, 39). Immunopurified mTOR has been shown to autophosphorylate on Ser2481 (40) and to phosphorylate Ser37, Ser46, and Ser65 on 4E-BP1 *in vitro* (11, 34, 41, 42). However, some of these events have been demonstrated to be resistant to antiproliferative concentrations of rapamycin (40–42). It is therefore unclear what role mTOR kinase activity plays *per se* in rapamycin-sensitive signaling events.

Because mTOR couples nutrient/growth factor availability to cell growth and proliferation in a variety of cell types, there is a potential for developing rapamycin derivatives such as RAD001 as novel inhibitors of the deregulated cell growth characteristic of human cancers. Consistent with this, RAD001 inhibits the proliferation of a wide variety of human solid tumor cell lines both *in vitro* in cell culture and *in vivo* in animal xenograft models (2, 3, 27, 43, 44). Furthermore, antiproliferative effects of RAD001 in posttransplant lymphoproliferative disorder-like B cell lines have been observed *in vitro* and *in vivo* (45, 46). In the present study, we have demonstrated that RAD001 displays significant antitumor activity in the syngeneic CA20948 rat pancreatic tumor model. Equivalent activity was observed with daily and intermittent treatment schedules, suggesting the possibility of a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical analysis of the mTOR effectors 4E-BP1 and S6K1 in tumor, skin, and peripheral blood mononuclear cell (PBMC) extracts obtained from RAD001-treated rats suggests that modulation of 4E-BP1 activity and significant inactivation of S6K1 are associated with antitumor activity. Furthermore, the efficacy observed using intermittent treatment schedules is paralleled by long-term down-regulation of S6K1 activity in all three tissues. We also provide evidence that the duration of S6K1 inactivation in PBMCs correlates with the dose-dependent suppression of tumor growth observed with weekly regimens. Moreover, unlike 4E-BP1 phosphorylation, S6K1 activity can be reproducibly measured in human PBMCs and represents a potentially valuable pharmacodynamic biomarker by which to monitor RAD001 treatment schedules in cancer patients.

MATERIALS AND METHODS

Drug Preparation. RAD001 (everolimus) is a derivative of rapamycin [40-*O*-(2-hydroxyethyl)-rapamycin; Ref. 47]. For animal studies, RAD001 was formulated at 2% (w/v) in a microemulsion vehicle, which was diluted to the appropriate concentration in 5% (w/v) glucose solution just before administration by gavage. For *in vitro* and *ex vivo* analyses, RAD001 was prepared in DMSO before addition to cell culture or human volunteer blood samples.

Antitumor Efficacy Studies and Statistical Analyses. Male Lewis rats were purchased from Iffa Credo (L'Abresque, France) and allowed food and water *ad libitum*. A suspension of CA20948 tumor cells (obtained from donor rats because this line is nonculturable *in vitro*) in Ham's F-12 medium supplemented with 10% FCS, 0.1 g/100 ml $NaHCO_3$, 1% penicillin, and 1% fungizone was injected s.c. into the left flank of rats. Treatment of randomized rats started when the tumors reached about 100 mm^3. RAD001 was administered p.o. daily at 0.5 or 2.5 mg/kg (×6/week), twice weekly at 5 mg/kg, or weekly at 0.5, 1, 2, 3, or 5 mg/kg. A volume of vehicle equivalent to the highest dose of RAD001 administered in the experiment was used as a negative control. As a positive control, the cytotoxic agent 5-fluorouracil (5-FU; ICN Pharmaceuticals Inc., Costa Mesa, CA) was administered at a near maximum tolerated dose (15 mg/kg, i.v., 4×/week, 2 days treatment/2 days rest), which gives maximal antitumor effect. Tumors were measured every day or every other day with a caliper, and the volumes were calculated by using the formula of an ellipsoid [$V = \pi/6\ (d_1 \times d_2 \times d_3)$, where d_1, d_2, and d_3 represent the three largest diameters]. Animals were also weighed the same day tumors were measured. The animals were sacrificed when either their tumor burden exceeded 25,000 mm^3 or when skin overlaying the tumor exhibited evidence of necrosis. All protocols involving animals were approved by the Veterinäramt of Baselstadt, Switzerland.

Results are presented as mean ± 1 SEM or as percentage of T/C (mean increase of tumor volumes of treated animals divided by the mean increase of tumor volumes of control animals multiplied by 100). The statistical significance of differences between treatment and control groups were determined by ANOVA followed by the Dunnett test. Statistical analyses on body weight were performed by ANOVA followed by Tukey's test, and for comparison between weight at start and end of the experiment for individual animals, the paired *t* test was used. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific).

Rat-Derived and Human Volunteer-Derived Tissue/PBMC Protein Extract Preparation. CA20948 tumor-bearing rats were given 0.5, 1, 2, or 5 mg/kg RAD001 or an equivalent volume of vehicle. At the indicated times after administration, rats were sacrificed, and tumor and shaved skin samples (for 0.5 and 5 mg/kg RAD001 doses) were dissected and weighed. Samples were rinsed in ice-cold PBS and immediately extracted in ice-cold extraction buffer [50 mM Tris-HCl (pH 8.0), 120 mM NaCl, 20 mM NaF, 1 mM EDTA, 6 mM EGTA, 15 mM PP_i, 30 mM *p*-nitrophenyl phosphate, 1 mM benzamidine, 0.2 mM phenylmethylsulfonyl fluoride, and 0.1% NP40] with a constant ratio of 45 mg tumor/ml extraction buffer and 90 mg skin/ml extraction buffer, using a PT3000 Polytron (probe PT-DA 3012/2S; Kinematica AG) or a hand-held PT2100 Polytron (probe PT-DA 2112/2EC), respectively. Lysates were cleared by centrifugation for 30 min at 12,000 × *g* at 4°C. Supernatants were subsequently aliquoted, snap frozen on dry ice, and stored at −80°C. In the case of skin samples, before further analysis, samples were centrifuged for 20 min at 436,000 × *g* at 4°C to remove the fat fraction.

Blood (for 0.5, 1, 2, and 5 mg/kg RAD001 doses) from tumor-bearing and non-tumor-bearing rats was withdrawn into syringes containing EDTA [0.5% (w/v) final] and then placed into an ice-cold tube and mixed. Unless otherwise stated, the blood from individual animals within the same treatment group was analyzed separately. The blood was immediately centrifuged for 20 min at 430 × *g* at 4°C. The PBMCs, deposited at the interface between the RBCs and the plasma, were collected and pelleted by centrifugation for 5 min at 3000 × *g* at 4°C. PBMCs were washed with 10 ml of ice-cold PBS and then repelleted by centrifugation for 5 min at 3000 × *g* at 4°C. Cell pellets were resuspended in ice-cold extraction buffer containing 1% NP40 at the fixed ratio of 500 μl extraction buffer/10 ml initial blood volume. The cells were sheared by vigorous pipetting and then centrifuged for 30 min at 12,000 × *g* at 4°C. Supernatants were aliquoted, snap frozen on dry ice, and stored at −80°C.

Human blood from healthy volunteers was collected under medical supervision into tubes containing either sodium citrate (BD Vacutainer 9NC; BD Vacutainer Systems, Plymouth, United Kingdom) or EDTA (BD Vacutainer K3E) as an anticoagulant. The blood was either immediately processed or, for *ex vivo* treatments, treated with 2, 20, and 200 nM RAD001 or DMSO vehicle for 30 min at room temperature. Human PBMCs were isolated and extracted as described for rat PBMCs.

A549 Cell Culture and Protein Extract Preparation. A549 human lung carcinoma cells (CCL185) were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 medium (Amimed, Allschwil, Switzerland) supplemented with 10% FCS, 2 mM L-glutamine, and 100 μg/ml penicillin/streptomycin at 37°C and 5% CO_2. Cell lysates were prepared as described previously (48).

Immunoblot Analysis. Cell lysates (30–40 μg) were electrophoretically resolved on denaturing SDS polyacrylamide gels (SDS-PAGE), transferred to polyvinylidene difluoride (Millipore Corp., Bedford, MA), and probed with the following primary antibodies: anti-S6 (provided by J. Mestan; Oncology Research, Novartis Pharma AG, Basel, Switzerland); anti-4E-BP1 (kindly provided by N. Sonenberg; McGill University, Montreal, Quebec, Canada); anti-eIF-4E (kindly provided by S. J. Morley; University of Sussex, Brighton, United Kingdom); anti-phospho-4E-BP1 Thr70, anti-S6K1, and anti-phospho-S6 Ser240/Ser244 (all from Cell Signaling Technology Inc., Beverly, MA); and anti-β-tubulin (Tub2.1; Sigma, St. Louis, MO). "Decorated" proteins were revealed using horseradish peroxidase-conjugated antimouse or antirabbit immunoglobulins in conjunction with the enhanced chemiluminescence procedure (Amersham Pharmacia Biotech Inc., Buckinghamshire, United Kingdom).

Affinity Purification of 4E-BP1·eIF-4E Complexes with 7-Methyl-GTP-Sepharose. Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 500 μl in ice-cold extraction buffer and adjusted to a final NP40 concentration of 0.1%. The 4E-BP1·eIF-4E complexes were affinity purified with 20 μl of 7-methyl-GTP-Sepharose beads (Amersham Pharmacia Biotech Inc., Piscataway, NJ) by gentle rotation for 2.5 h at 4°C. Proteins retained on the beads were washed twice with extraction buffer in the absence of NP40 and resuspended in 15 μl of Laemmli buffer. Denatured samples were subjected to 15% SDS-PAGE and transferred to polyvinylidene difluoride membranes. Membranes were first immunoblotted for 4E-BP1 protein, followed by stripping as described previously (49) and reprobing for eIF-4E protein (see above).

40S Ribosomal S6 Kinase Assay. Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 1 ml (tumor and skin) or 500 μl (PBMC) with ice-cold extraction buffer and adjusted to a final NP40 concentration of 1%. Human-derived PBMC extracts (0.8–1 mg) were diluted to a final volume of 750 μl with ice-cold extraction buffer (final NP40 concentration, 1%). In some experiments, human-derived PBMC extracts were first precleared with 20 μl of 50% protein A-Sepharose (Amersham Pharmacia Biotech, Uppsala, Sweden) by rotating for 20 min at 4°C. S6K1 was immunoprecipitated from all extracts by addition of 2.5 μl of the M5 S6K1-specific polyclonal antibody and incubation on ice for 1 h, followed by retrieval of immunocomplexes with 20 μl of 50% protein A-Sepharose. S6K1 activity was measured using rat liver 40S ribosomal subunits as a specific substrate, as described previously (50), except that *p*-nitrophenyl phosphate was omitted in the reaction mixture. Phosphorylated S6 was resolved by 12.5% SDS-PAGE and analyzed using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). [γ-^{32}P]phosphate incorporation into S6 was quantified using ImageQuant (Molecular Dynamics). Where appropriate, the statistical significance of differences between treatment groups and untreated control groups was determined using ANOVA or ANOVA on ranks followed by the Dunnett test. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific). Coefficient of variation is defined as SD divided by the mean and multiplied by 100.

RESULTS

Intermittent RAD001 Treatment Schedules Display Antitumor Efficacy. Short-term exposure to rapamycin *in vitro* has long-term antiproliferative effects on tumor cell lines (51), suggesting that intermittent treatment schedules may retain antitumor activity. Furthermore, daily oral administration of RAD001 is effective in rat models of autoimmune disease and allotransplantation (47, 52), whereas we have found that weekly (5 mg/kg) RAD001 dosing schedules have reduced immunosuppressive properties in rats as compared with daily treatment (2.5 mg/kg): 66 ± 18% and 98 ± 1% inhibition of IgG antibody response after dinitrophenol-coupled keyhole limpet hemocyanogen immunization, respectively.[3] With these observations in mind, we evaluated whether RAD001 treatment schedules, with potentially reduced immunosuppressive properties, could elicit antitumor responses. Daily *versus* intermittent RAD001 administration schedules were compared using the s.c. CA20948 rat pancreatic tumor model. Vehicle was used as a negative control, and the cytotoxic agent 5-FU was used as a positive control (Fig. 1; Table 1, Experiment 1). RAD001 treatment at 0.5 or 2.5 mg/kg/day, six times a week, resulted in antitumor activity characterized by statistically significant inhibition of tumor growth as compared with vehicle controls [treated tumor *versus* control tumor size (T/C), 30% and 23%, respectively; $P < 0.05$ after 10 days of treatment; Fig. 1*A*; Table 1, Experiment 1]. Statistically significant tumor growth suppression was also observed after intermittent administration of 5 mg/kg RAD001 twice a week (T/C, 36%) or once a week (T/C, 36%). Moreover, all RAD001 treatment schedules suppressed tumor growth to a similar extent as the cytotoxic 5-FU (T/C, 23%). Continued treatment with RAD001 after vehicle controls were sacrificed due to tumor burden led to a prolonged low tumor growth rate with all treatment schedules, resulting in similar tumor burden after 17 days of treatment as compared with 5-FU (Fig. 1*A*). For all treatment schedules, RAD001 was well tolerated, with no significant body weight loss or mortalities observed (Fig. 1*B*; Table 1, Experiment 1). These results demonstrate that RAD001 is a well-tolerated antitumor agent in a rat model of pancreatic cancer and indicate a potential for intermittent administration schedules that may allow dissociation of antitumor from immunosuppressive effects.

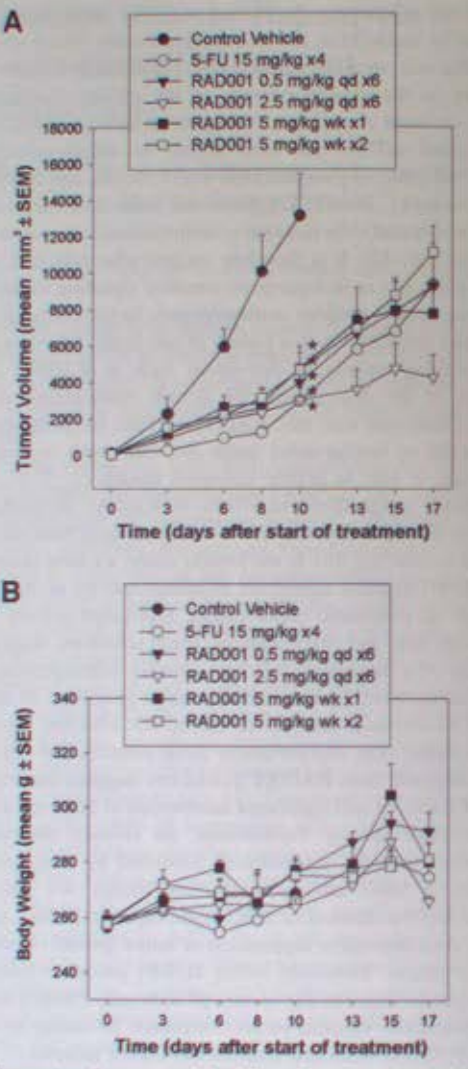

Fig. 1. Suppression of tumor growth by daily and intermittent dosing schedules of RAD001. Tumors were established in male Lewis rats by s.c. injection of CA20948 tumor suspension obtained from donor rats. Treatments started on day 4 after inoculation. Formulated RAD001 was diluted in a 5% glucose solution and administered p.o. daily at a dose of 0.5 or 2.5 mg/kg (*qd* ×6, 6 times/week) or once (*wk* ×1) or twice (*wk* ×2) weekly at 5 mg/kg RAD001. Vehicle and 5-fluorouracil (*5-FU* ×4; 4 times/week) were administered as negative and positive controls, respectively. Tumor volumes were measured (*A*), and rats were weighed (*B*) as described in "Materials and Methods." Vehicle control-treated rats were sacrificed on day 10 due to tumor burden. Data are means ± SEM ($n = 7$–8 animals/group). *Stars* represent $P < 0.05$ *versus* vehicle controls.

RAD001 Modulates 4E-BP1 and S6K1 Activity in Tumor, Skin, and PBMCs Obtained from CA20948 Pancreatic Tumor-Bearing Rats. To investigate RAD001-specific effects on mTOR signaling *in vivo*, three CA20948 tumor-bearing rats were treated with vehicle or a single efficacious dose of RAD001 (5 mg/kg). Rats were sacrificed

[3] T. O'Reilly, H. A. Lane, and C. Heusser, unpublished data.

Table 1 *Effect of daily and intermittent RAD001 administration on CA20948 rat pancreatic tumor-bearing rats*

Compound	Schedule	Tumor response		Host response		
		% T/C[a]	Δ Tumor volume (mm^3)	Δ Body weight (g)	%Δ Body weight	Survival (alive/total)
Experiment 1						
Vehicle	2 ml/kg p.o. daily	100	12972 ± 2188	12 ± 8	5	8/8
5-FU	15 mg/kg i.v. 4× weekly	23	2863 ± 764[b]	18 ± 4	7	7/7
RAD001	0.5 mg/kg p.o. daily	30	3904 ± 856[b]	35 ± 7	14	7/7
RAD001	2.5 mg/kg p.o. daily	23	2959 ± 624[b]	7 ± 2	3	7/7
RAD001	5 mg/kg p.o. weekly	36	4652 ± 1220[b]	22 ± 5	8	7/7
RAD001	5 mg/kg p.o. twice weekly	36	4604 ± 928[b]	21 ± 3	8	7/7
Experiment 2						
Vehicle	2 ml/kg p.o. daily	100	12331 ± 1410	29 ± 2	14	8/8
RAD001	0.5 mg/kg p.o. daily	23	2894 ± 567[b]	30 ± 5	17	8/8
RAD001	0.5 mg/kg p.o. weekly	48	5951 ± 1739	36 ± 2	15	8/8
RAD001	5 mg/kg p.o. weekly	14	1708 ± 339[b]	32 ± 2	15	8/8
Experiment 3						
Vehicle	2 ml/kg p.o. weekly	100	19270 ± 3918	28.3 ± 2.1	10	8/8
RAD001	0.5 mg/kg p.o. weekly	48	9275 ± 1926	21 ± 2.4	8	8/8
RAD001	1 mg/kg p.o. weekly	45	8617 ± 1704	32.8 ± 2.7	12	8/8
RAD001	2 mg/kg p.o. weekly	32	6161 ± 1079[b]	24.9 ± 1.9	9	8/8
RAD001	3 mg/kg p.o. weekly	36	6869 ± 611[b]	24.3 ± 3.3	9	6/6
RAD001	5 mg/kg p.o. weekly	24	4680 ± 1593[b]	22.8 ± 1.7	8	8/8

[a] T/C, treated tumor *versus* control tumor size.
[b] $P < 0.05$ *versus* control, Dunnett test.

24 h later, and protein extracts were prepared from tumors, skin, and PBMCs. By immunoblot analysis, mTOR could be detected in tumor and PBMC extracts; however, neither mTOR expression nor phosphorylation on Ser2448 was modified on RAD001 treatment.[4] In contrast, 4E-BP1 exhibited a decrease in Thr70 phosphorylation in tumor, skin, and PBMC extracts (Fig. 2*A*), a phenomenon associated with changes in 4E-BP1 electrophoretic mobility, particularly striking in PBMCs. This observation is consistent with previous work demonstrating dephosphorylation of 4E-BP1 on Thr70 in tumors derived from mouse xenograft models after five daily treatments with an ester of rapamycin CCI-779 (1 h after last administration; Ref. 53). Interestingly, the phosphorylation of another rapamycin-sensitive residue (Ser65; Refs. 5, 34, and 35) was unaffected by RAD001 treatment,[4] indicating that RAD001-insensitive phosphorylation of this site can occur as reported previously (54).

To determine whether the decreased phosphorylation state of 4E-BP1 resulted in a change in functionality, the eIF-4E binding activity of 4E-BP1 was assessed using an *in vitro* 7-methyl-GTP-binding assay (Fig. 2*B*). Whereas similar levels of eIF-4E were recovered in the control- and RAD001-treated extracts, in two animals increased eIF-4E·4E-BP1 complex formation was clearly observed in skin and PBMC samples after RAD001 treatment. In tumor samples, two electrophoretically distinct forms of 4E-BP1 protein were bound to eIF-4E in vehicle control-treated rats (Fig. 2*B*). After RAD001 treatment, only the lower migrating form was found bound to eIF-4E, with an associated loss of the upper band consistent with reduced 4E-BP1 phosphorylation levels (Fig. 2*A*). A similar 4E-BP1 doublet with eIF-4E binding activity has been observed previously in proliferating cells/tissue (29, 54) and presumably reflects differential 4E-BP1 phosphorylation states within the proliferating tumor.

To further assess the effect of RAD001 administration on the mTOR pathway, S6K1 protein and activity levels were also analyzed (Fig. 2, *C* and *D*). Whereas S6K1 protein levels were unaffected by RAD001 treatment (Fig. 2*C*), *in vitro* kinase assay using 40*S* ribosomal subunits as a substrate revealed a statistically significant reduction in S6K1 activity in all extracts [Fig. 2*D*; 83% (tumors), 80% (skin), and 75% (PBMC); all $P < 0.05$ *versus* vehicle-treated controls]. This reduction in S6K1 activity was associated with the dramatic dephosphorylation of its physiological substrate, 40*S* ribosomal protein S6, in tumor extracts (Fig. 2*C*). A similar reduction was not observed in skin and PBMC extracts because these tissues exhibited no detectable S6 phosphorylation in control animals. Interestingly, a

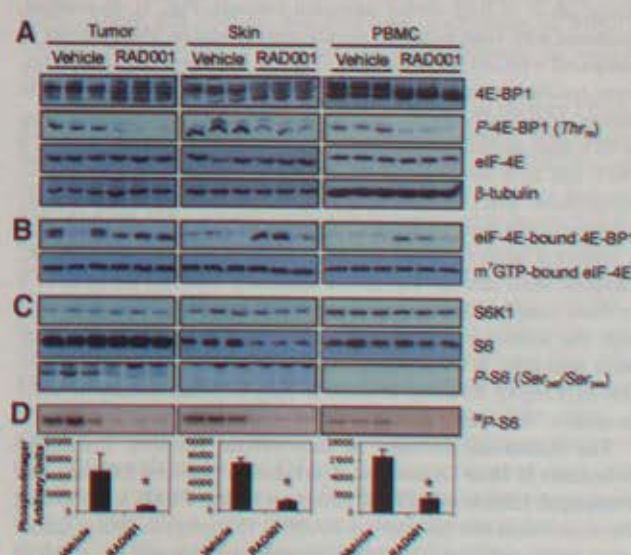

Fig. 2. RAD001 administration inhibits mammalian target of rapamycin signaling in CA20948 tumor-bearing rats. S.c. CA20948 tumor-bearing rats received a single administration of an efficacious dose of RAD001 (5 mg/kg) or vehicle and were sacrificed 24 h after administration (3 rats/group). Tumors, skin, and PBMCs were individually prepared and extracted as described in "Materials and Methods." Results from individual rats are presented. *A* and *C*, total protein was subjected to electrophoresis followed by immunoblot analysis. Membranes were probed for eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and phospho-threonine 70 4E-BP1 [*P-4E-BP1* (Thr_{70})] levels, with eukaryotic initiation factor 4E (eIF-4E) and β-tubulin levels acting as loading controls (*A*) or ribosomal protein S6 kinase 1 protein, S6 40*S* ribosomal protein, and phospho-serine 240/244 S6 [*P-S6* (Ser_{240}/Ser_{244})] levels (*C*). *B*, the level of 4E-BP1 bound to eIF-4E was measured by purification of 4E-BP1·eIF-4E complexes on 7-methyl-GTP-Sepharose, as described in "Materials and Methods," followed by immunoblot analysis. *D*, ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of total protein extract, and activity was measured by *in vitro* kinase assay using 40*S* ribosomal subunits as a specific substrate, as described in "Materials and Methods." Phosphorimages (^{32}P-*S6*) and PhosphorImager quantifications of the kinase assay are presented. Data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* vehicle-treated controls (Dunnett test).

[4] A. Boulay and H. A. Lane, unpublished data.

reduction in S6 protein expression was observed in RAD001-treated skin, but not in tumor or PBMC extracts. A similar phenomenon has been reported previously in tumors after treatment of mice bearing human prostate cancer xenografts with CCI-779 (24). Moreover, the translation of S6 (as a 5′-terminal oligopyrimidine tract mRNA) has been shown to be specifically inhibited by rapamycin in 3T3 cells (36). It is not known why, in this model, RAD001 treatment only has effects on S6 expression in skin; however, differential downstream effects of mTOR pathway inhibition, depending on the tissue source, are a plausible possibility (54). Taken together, these data demonstrate that both 4E-BP1 and S6K1 pathways are affected in tumors, skin, and PBMC samples obtained from CA20948 tumor-bearing rats after a single administration of an efficacious dose of RAD001.

Prolonged Inactivation of S6K1 in Tumors, Skin, and PBMCs Correlates with the Efficacy of Intermittent RAD001 Treatment Schedules. To investigate whether the antitumor efficacy of intermittent RAD001 treatment schedules is associated with prolonged effects on the mTOR pathway, CA20948 tumor-bearing rats were treated with a single dose of RAD001 (5 mg/kg) or vehicle, and tumor, skin, and PBMC extracts were prepared 12, 24, 48, or 72 h after administration. Because S6K1 was significantly inactivated 24 h after a single RAD001 administration in all tissues analyzed (Fig. 2*D*), long-term effects on mTOR function were assessed using the 40*S* kinase assay (Fig. 3). Tumor and skin extracts were obtained from each of 3 rats/treatment group, whereas PBMC extracts were obtained from pooled blood from each treatment group. A dramatic reduction in S6K1 activity was already observed in tumors, skin, and PBMCs 12 h after RAD001 administration (91%, 91%, and 82% inhibition, respectively; all $P < 0.05$ *versus* untreated controls; Fig. 3). In contrast, treatment with vehicle did not significantly modulate S6K1 activity as compared with untreated controls (Fig. 3). Moreover, RAD001 treatment resulted in the sustained inactivation of S6K1 in all tissues. In tumors, statistically significant inhibition of S6K1 was maintained up to 48 h after administration, with some evidence of recovery after 72 h (80% and 62% inhibition at 48 and 72 h, respectively; Fig. 3*A*). In comparison, S6K1 derived from skin samples remained significantly inhibited for at least 72 h (72% inhibition at 72 h; Fig. 3*B*). Although a statistical analysis could not be performed on the pooled PBMC samples, S6K1 activity was also dramatically inhibited for up to 72 h in these samples (82% inhibition at 72 h; Fig. 3*C*). Thus, consistent with the antitumor efficacy of intermittent 5 mg/kg RAD001 treatment schedules in CA20948 tumor-bearing rats, a single administration of 5 mg/kg RAD001 resulted in long-term inactivation of S6K1 in tumors, skin, and PBMCs.

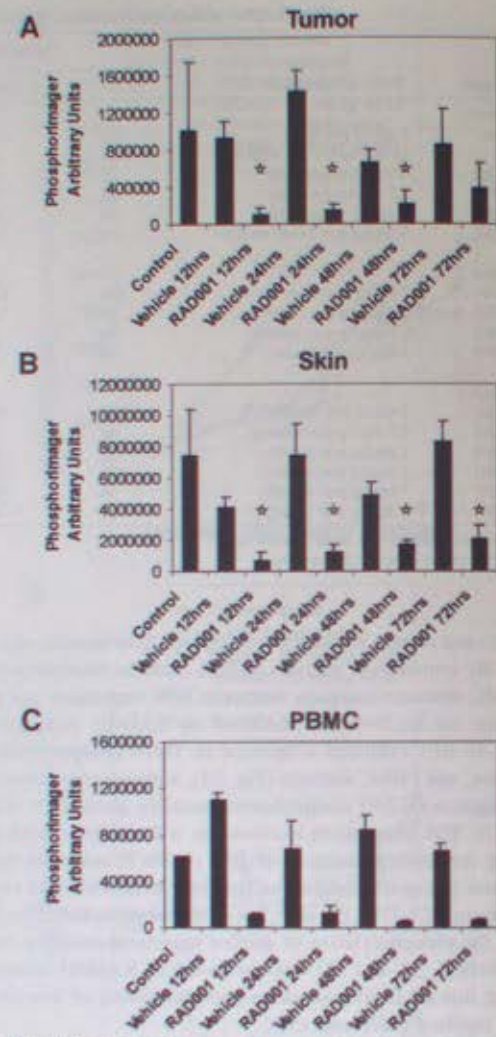

Fig. 3. RAD001 administration (5 mg/kg) causes prolonged inactivation of ribosomal protein S6 kinase 1 in tumors, skin, and PBMCs derived from CA20948 tumor-bearing rats. CA20948 tumor-bearing rats were treated once with 5 mg/kg RAD001 or vehicle (3 rats/group). After 12, 24, 48, and 72 h, tumor and skin samples were individually extracted. Blood obtained from rats within each treatment group was pooled, and peripheral blood mononuclear cells (PBMCs) were isolated and extracted. Assay of ribosomal protein S6 kinase 1 activity was performed using 40S ribosomal subunits as *in vitro* substrate. PhosphorImager quantifications of the S6 kinase assays are presented. *A (Tumor)* and *B (Skin)*: data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C (PBMC)*: data are means; *error bars* represent the range of duplicate assays.

The Antitumor Efficacy of Intermittent RAD001 Treatment Schedules Is Dose Dependent: Correlation Between Efficacy and Prolonged Effects on mTOR Effectors in Rat PBMCs. Following the observation that intermittent RAD001 (5 mg/kg) treatment schedules significantly inhibited tumor growth, we explored the effect of RAD001 dose on the efficacy of weekly treatment schedules (Table 1, Experiments 2 and 3). As expected, 5 mg/kg/week RAD001 significantly suppressed CA20948 tumor growth as compared with vehicle controls (T/C, 14% and 24% at 7 and 8 days, respectively; $P < 0.05$). In contrast, although 0.5 mg/kg RAD001 caused a significant inhibition of tumor growth when administered daily (T/C, 23%), weekly administration of the same dose did not significantly affect tumor growth (T/C, 48%; $P > 0.05$). This apparent dose dependency of weekly RAD001 schedules was confirmed by a more stringent analysis comprising doses between 5 and 0.5 mg/kg (Table 1, Experiment 3). Statistically significant antitumor responses were observed with 3 and 2 mg/kg RAD001 (T/C, 36% and 32%, respectively), but not with 1 mg/kg (T/C, 45%). Interestingly, 3 mg/week elicited a similar antitumor response (T/C, 36%) as 0.5 mg/kg/day (×6/week; T/C, 30% and 23%). Because both these schedules involve administration of 3 mg/kg RAD001 per week, these data indicate that, with the same total RAD001 exposure, intermittent dosing schedules can elicit equivalent antitumor responses as daily schedules.

To further investigate the dose dependency of weekly schedules in terms of effects on mTOR signaling in a surrogate tissue, the duration of S6K1 inactivation in response to a single administration of 0.5 *versus* 5 mg/kg RAD001 was determined in PBMCs derived from three non-tumor-bearing rats (Fig. 4, *A* and *B*). Whereas in vehicle controls, no effect on S6K1 activity could be observed (24 h after administration), a single administration of 5 mg/kg RAD001 resulted in statistically significant, prolonged inactivation of the S6K1 for up to 7 days (99% and 86% inhibition after 24 h and 7 days, respectively; $P < 0.05$). In comparison, 0.5 mg/kg RAD001 caused a significant inhibition of PBMC-derived S6K1 activity 24 h after administration

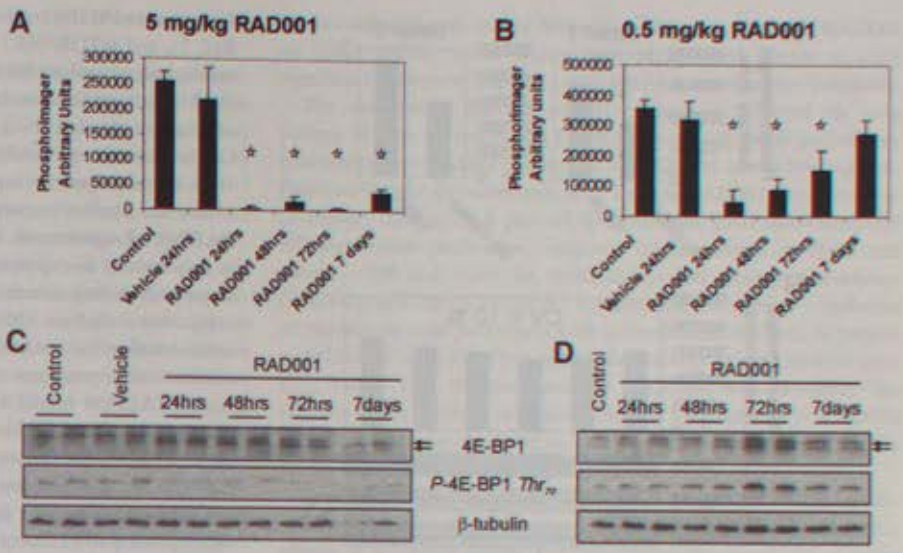

Fig. 4. Dose-dependent effects of RAD001 on ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) in peripheral blood mononuclear cells (PBMCs) obtained from non-tumor-bearing rats. Rats were treated with a single optimal (*A* and *C*) *versus* suboptimal (*B* and *D*) RAD001 dose (5 and 0.5 mg/kg, respectively) or vehicle (3 rats/group). At the times indicated, PBMC samples were collected and individually extracted. *A* and *B*, S6K1 was immunoprecipitated from equal amounts of protein extract, and S6K1 activity was assayed using 40S ribosomal subunits as a substrate. PhosphorImager quantification of the kinase assays are presented (means ± SD of $n = 3$ animals/group). *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C* and *D*, equal amounts of PBMC extracts were resolved by SDS-PAGE, transferred onto a polyvinylidene difluoride membrane, and probed for 4E-BP1 protein, phospho-threonine 70 4E-BP1 (*P-4E-BP1 Thr*$_{70}$), or β-tubulin as a loading control. *Arrows* denote hypophosphorylated (*bottom arrow*) and hyperphosphorylated (*top arrow*) forms of 4E-BP1 protein.

(88% inhibition); however, kinase activity began to recover after 48 h (75% inhibition) and was almost totally recovered after 7 days [23% inhibition; not significant ($P > 0.05$ *versus* controls)]. In contrast to effects on S6K1 activity, no effect on Thr70 phosphorylation or the electrophoretic mobility of 4E-BP1 was observed with the 0.5 mg/kg RAD001 dose, whereas decreased Thr70 phosphorylation and a shift to a lower migrating form were observed with the 5 mg/kg RAD001 dose (Fig. 4, *C* and *D*). The latter effect was maintained for 72 h, with evidence of recovery by 7 days.

The above observations indicate that RAD001 has dose-dependent effects on the mTOR pathway in rat PBMCs. Moreover, long-term effects are associated with a RAD001 dose shown to have significant antitumor efficacy with intermittent treatment schedules. To confirm this hypothesis, a more stringent RAD001 titration was also performed to analyze effects on PBMC-derived S6K1 activity after a single administration of 0.5, 1, 2, or 5 mg/kg RAD001 (Fig. 5). In all cases, inactivation of S6K1 was observed 24 h after RAD001 administration. However, at RAD001 doses that do not elicit a significant antitumor response with weekly schedules (0.5 and 1 mg/kg; see Table 1), evidence of recovery of S6K1 activity was already observed at 72 h (34% and 13% recovery *versus* untreated controls, respectively) and was dramatic at 7 days [73% and 61%, respectively; no significant inhibition of S6K1 ($P > 0.05$ *versus* controls)]. In contrast, at RAD001 doses that do elicit a significant antitumor response with weekly schedules (2 and 5 mg/kg; see Table 1), minimal recovery was observed at 72 h (3% and 1%, respectively) or 7 days [30% and 12%, respectively; significant inhibition of S6K1 ($P < 0.05$ *versus* controls)]. These data confirm that long-term inactivation of PBMC-derived S6K1 correlates with the antitumor efficacy of weekly RAD001 treatment schedules.

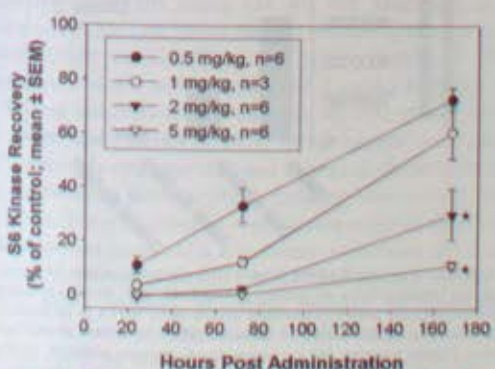

Fig. 5. Association between antitumor efficacy of weekly RAD001 schedules and long-term down-regulation of ribosomal protein S6 kinase 1 (S6K1) activity in rat peripheral blood mononuclear cells (PBMCs). Non-tumor-bearing rats were treated with a single RAD001 dose (0.5, 1, 2, or 5 mg/kg). At the times indicated, PBMC samples were collected and individually extracted and assayed for S6K1 activity. Data are presented as mean percentage recovery of S6K1 activity *versus* untreated control animals ± SEM of $n = 3$ or 6 S6K1 assays from different rat PBMC extracts. All data are derived from two separate experiments, except in the case of 1 mg/kg, where data from a single experiment are presented. *Stars* represent $P < 0.05$ *versus* untreated controls (ANOVA on ranks test).

S6K1 Activity Can Be Reproducibly Detected in Human PBMC Extracts: RAD001 Induces Concentration-Dependent S6K1 Inactivation *Ex Vivo*. To evaluate the potential of using mTOR effectors as biomarkers to evaluate RAD001 treatment schedules, we assessed whether basal S6K1 activity could also be measured in human PBMC extracts obtained from healthy volunteers. Human blood was collected into tubes containing either sodium citrate or EDTA as an anticoagulant, and PBMC extracts were prepared. Subsequent assay of S6K1 activity demonstrated that activity could indeed be detected in non-challenged human PBMCs derived from unrelated donors (Fig. 6*A*). Interestingly, S6K1 activity was reproducibly higher when the blood was initially collected in EDTA as compared with sodium citrate, a phenomenon potentially related to the different chelating properties of these anticoagulants. Using EDTA, a coefficient of variation of 10% was obtained among six assays on PBMC extracts prepared separately from the same blood donor, indicating good reproducibility of preparation (Fig. 6*B*). Accordingly, equivalent S6K1 protein levels were detected in the same extracts by immunoblot analysis (Fig. 6*B*). These results demonstrate that, in analogy with the rat PBMC data, basal S6K1 activity can be detected in human PBMCs. However, unlike control rat PBMC extracts (see Fig. 2*A*), there was no evidence of Thr70 phosphorylation in any of the human PBMC extracts analyzed,[5] an observation correlating with the fact that most of the 4E-BP1 protein was present in the hypophosphorylated/fast migrating state (when compared with 4E-BP1 derived from proliferating human tumor cells; Fig. 7*A*, *DMSO*). *Ex vivo* treatment of whole blood with 20 nM RAD001 for 30 min did not further increase protein mobility (Fig. 7*A*, *RAD001*), suggesting that 4E-BP1 is largely active as a translational repressor in human PBMCs. Hence, unlike the situation

[5] A. Boulay, S. Zumstein-Mecker, and H. A. Lane, unpublished data.

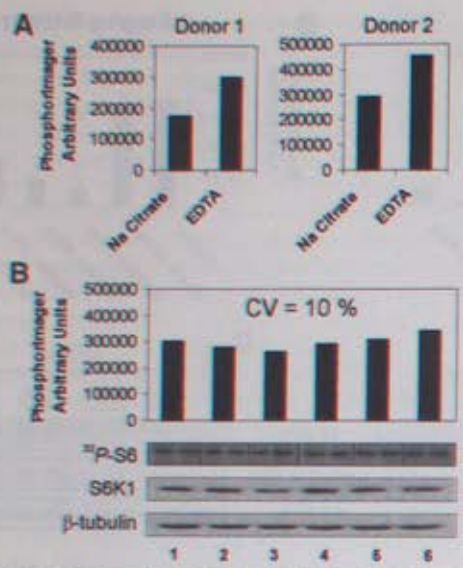

Fig. 6. Detection of ribosomal protein S6 kinase 1 (S6K1) activity in human peripheral blood mononuclear cells (PBMCs). Blood from healthy volunteers was withdrawn at the same time into tubes containing either sodium citrate or EDTA as an anticoagulant. PBMCs were immediately isolated and extracted. *A*, S6K1 was immunoprecipitated from equal amounts of PBMC protein extracts, and activity was assessed using 40S ribosomal subunits as a substrate. PhosphorImager quantifications are presented and represent basal S6K1 activity (means of duplicate assays of a single sample) from two unrelated donors. *B*, blood from a single volunteer was withdrawn into tubes containing EDTA as an anticoagulant and was split into six equal fractions. PBMCs were prepared separately and extracted from each blood fraction, and extracts were simultaneously assayed for S6K1 kinase activity. Phosphorimages (^{32}P-*S6*) and PhosphorImager quantifications (*graph*) of duplicate kinase assays are presented. As internal controls, equal amounts of PBMC protein extracts were analyzed by immunoblot for S6K1 and β-tubulin protein levels.

in rat, this protein may not be applicable as a biomarker for monitoring RAD001-specific effects on mTOR signaling in human PBMCs.

To assess whether human PBMC-derived S6K1 is inactivated in the presence of RAD001, whole blood from two unrelated healthy volunteers was treated *ex vivo* with either DMSO vehicle or increasing concentrations of RAD001 for 30 min, followed by isolation, extraction, and assay of PBMC-derived S6K1 activity (Fig. 7*B*). Treatment with 2 nM RAD001 diminished PBMC-derived S6K1 activity as compared with DMSO vehicle controls (44% and 63% inhibition in donor 1 and 2, respectively). Furthermore, increasing RAD001 concentrations led to almost complete inactivation of S6K1 (≥95% inhibition with ≥20 nM RAD001 in donor 1 and 2). These results demonstrate that RAD001 treatment of human blood *ex vivo* results in a concentration-dependent inactivation of PBMC-derived S6K1, supporting the notion that changes in PBMC-derived S6K1 activity could serve as a biomarker when assessing treatment schedules with rapamycin derivatives such as RAD001 in clinical trials for cancer.

DISCUSSION

The mTOR pathway plays a major role in cell proliferation by coupling cell growth with G_1-S progression. Compounds targeting the mTOR pathway have potential, therefore, for application in cancer treatment modalities (2, 3, 4). In this context, RAD001 potently inhibits the proliferation of numerous tumor cell lines *in vitro* and inhibits the growth of a range of human xenografts in nude mice (2, 27, 43–46).[6] Rapamycin and the rapamycin ester CCI-779 also present antitumor activity in a number of animal models of cancer (2, 24–26, 53, 55–59). However, although human pancreatic tumors have been reported in abstract form to be sensitive to CCI-779 (reviewed in Ref. 2), and mTOR/S6K1 signaling appears to be required for pancreatic cancer cell proliferation (60, 61), the work presented here is the first full publication demonstrating significant antitumor efficacy of a rapamycin derivative in an animal model of pancreatic cancer. Orally administered RAD001 was found to be well tolerated and to elicit antitumor potency equivalent to that of the cytotoxic agent 5-FU. Moreover, similar responses were achieved with daily or weekly RAD001 administrations, indicating that frequent drug administration is unnecessary to maintain an antitumor response. Although weekly rapamycin dosing schedules have been used previously (55, 56), a comparative analysis addressing the efficacy of daily *versus* weekly administration had not been performed. The fact that weekly RAD001 administration produces statistically significant antitumor responses in the CA20948 model is supported by a number of experimental observations. First, *in vitro* pulse treatment with either RAD001 (43) or rapamycin (51) causes prolonged down-regulation of the mTOR pathway in tumor cell lines. Indeed, Hosoi *et al.* (51) postulated that this phenomenon was due to the slow dissociation rate of the rapamycin·FKBP12 complex. Second, prolonged effects of CCI-779 on xenograft tumor growth were evident after cessation of daily treatment schedules (24, 53, 57), and antitumor responses have been

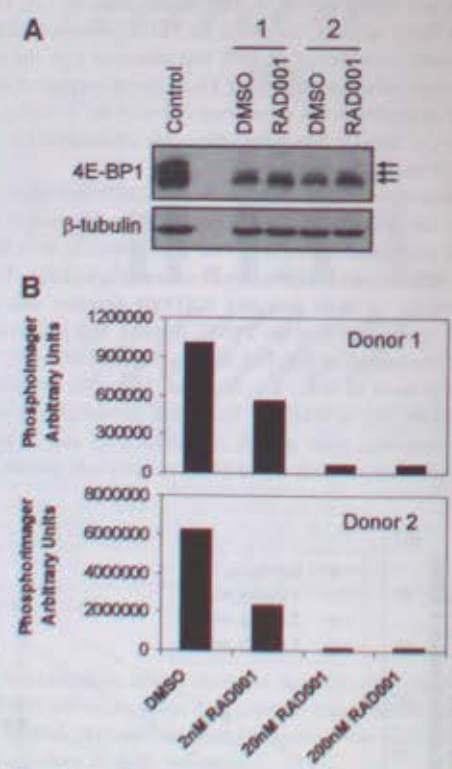

Fig. 7. Effects of *ex vivo* RAD001 treatment on ribosomal protein S6 kinase 1 activity and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) mobility in human PBMCs. *A*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with DMSO vehicle or 20 nM RAD001 for 30 min at room temperature, followed by PBMC isolation and extraction. Equal amounts of PBMC protein extracts were resolved by SDS-PAGE and transferred onto a polyvinylidene difluoride membrane. The membrane was probed for 4E-BP1 protein, with β-tubulin as a loading control. Human lung adenocarcinoma tumor cell lines lysates (*Control*; A549) were included as an example of 4E-BP1 mobility in a highly proliferative human cell population. *B*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with 2, 20, or 200 nM RAD001 or DMSO vehicle for 30 min at room temperature, followed by PBMC isolation and extraction. Ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of PBMC protein extract, and activity was assessed *in vitro* using 40S ribosomal subunits as a substrate. PhosphorImager quantifications of the kinase assay are presented and represent means of duplicate assays of a single sample.

[6] A. Boulay, T. O'Reilly, and H. A. Lane, unpublished data.

reported in Phase I clinical trials with weekly CCI-779 administration (2, 4).

One advantage of administering RAD001 intermittently in oncology is the avoidance of prolonged immunosuppression (1). In this context, the minimal effective dose of RAD001 in stringent rat kidney and heart allotransplantation models is ≥5 mg/kg administered daily (47, 52). Moreover, the immunosuppressive capacity of RAD001 (everolimus in combination with cyclosporin) in transplant patients has been related to maintenance of blood drug trough levels (1, 62), suggesting that constant drug exposure is required to provide clinically relevant immunosuppression. The demonstration that weekly administration of RAD001 (at doses of 2–5 mg/kg) is sufficient to elicit a significant antitumor response indicates that the above premise does not apply to oncology. Indeed, in support of this notion, as compared with daily RAD001 administration (2.5 mg/kg), a 5 mg/kg weekly RAD001 regimen allows a 20-fold higher T-cell-dependent antibody response, as measured by serum IgG antibody titers after immunization of rats with dinitrophenol-coupled keyhole limpet hemocyanogen.[3] Hence, intermittent dosing allows for differentiation between immunosuppressive and antitumor effects, a possibility also suggested from preliminary clinical data (2, 4). The basis of this is presumably related to the biology of T cells as compared with tumor cells. In this respect, rapamycin potently prevents resting T cells from entering the cell cycle in response to interleukin 2 but has little effect on proliferating T cells (63, 64). This may explain why constant drug exposure is required in the immunosuppression setting, as opposed to the antitumor setting where the proliferation of cycling tumor cells is potently inhibited (2, 4) for long periods (51). This possibility is worthy of further investigation.

A limited analysis of the effects of rapamycin derivatives on mTOR effectors in tumor material derived from xenograft models was reported previously (24, 53). Until now, however, a comprehensive analysis had not been performed. Similarly, the possibility that the efficacy of intermittent treatment schedules correlates with long-term effects on the mTOR pathway in tumors and surrogate tissues had not been addressed. This prompted us to profile RAD001-mediated effects on mTOR signaling in CA20948 tumors and normal rat tissues. Mitogen-induced, multisite phosphorylation of the translational suppressor protein 4E-BP1 is known to cause its release from the initiation factor eIF-4E, thereby facilitating formation of the eIF-4F initiation complex and derepression of cap-dependent mRNA translation (2, 5). Indeed, the 4E-BP1 protein has been proposed to be a direct substrate for the mTOR kinase (34, 41, 42). Moreover, rapamycin treatment of cell lines decreases 4E-BP1 phosphorylation, resulting in increased affinity for eIF-4E *in vitro* (2, 5). Consistent with these observations, a single administration of 5 mg/kg RAD001 to three tumor-bearing rats reproducibly inhibited 4E-BP1 phosphorylation in tumors, skin, and PBMCs at 24 h, in accordance with changes in 4E-BP1 electrophoretic mobility and increased 4E-BP1-eIF-4E association. In the same animals, S6K1 signaling was virtually abolished in all tissues. The physiological downstream target of the S6K1 is the S6 40S ribosomal protein (12, 65). Hence, reductions in S6 phosphorylation are expected to parallel S6K1 inactivation, as observed in CA20948 tumor extracts. However, because S6 phosphorylation could not be detected in either skin or PBMC control extracts, no such correlation could be made in these tissues. This failure to detect S6 phosphorylation could reflect a reduced proliferation index as compared with the aggressively growing CA20948 tumors. Strikingly, and in agreement with previous *in vitro* analyses (43, 51), tumors, skin, and PBMC extracts derived from rats treated with a single 5 mg/kg RAD001 dose demonstrated prolonged inactivation of the S6K1 for ≥72 h. Taken together, these data suggest that RAD001-specific effects on 4E-BP1 and S6K1 activity can be reproducibly observed in tumors and surrogate tissues. Moreover, long-term effects of RAD001 on S6K1 activity occur with a dose of RAD001 known to elicit significant antitumor responses with intermittent treatment schedules.

The observation that the mTOR pathway is affected for long periods of time in tumors and PBMCs is consistent with preliminary pharmacokinetic studies performed in CA20948 tumor-bearing rats. Pharmacokinetic measurements after a single RAD001 administration (5 mg/kg, over a 72 h period) demonstrated good bioavailability/efficient tumor penetration (maximal concentrations in blood and tumor, ~200 and ~700 nM, respectively) and prolonged residency [RAD001 half-life, ~20–22 h.[7] Unfortunately, a precise correlation of pharmacokinetic parameters with antiproliferative effects in tumors is difficult in this model because of the inability to determine *in vitro* IC_{50} values with the nonculturable CA20948 line. However, the efficient tumor accumulation and relatively long half-life of RAD001 provide further rationale for the long-term effects observed in this model.

Sequential tumor sampling is difficult in the clinical setting, necessitating some reliance on surrogate tissue to assess pharmacodynamic effects of antitumor agents. For this reason, the possibility of using PBMCs as a source for biomarker analysis when assessing RAD001 treatment schedules was evaluated. Detailed efficacy experiments demonstrated that antitumor response to weekly administration of RAD001 was dose dependent. Moreover, significant antitumor responses were associated with long-term effects on the mTOR pathway in PBMCs. Interestingly, PBMC-derived 4E-BP1 was unaffected by a suboptimal RAD001 dose (0.5 mg/kg), despite transient effects on S6K1 activity. This suggests that S6K1 is a more sensitive marker of RAD001 exposure in PBMCs than 4E-BP1. Indeed, all doses of RAD001 evaluated elicited a dramatic inhibition of PBMC-derived S6K1 after 24 h. However, the rate at which S6K1 activity subsequently recovered differed, with RAD001 doses that were efficacious with weekly schedules causing more profound long-term effects on S6K1 activity (≥7 days). The demonstration that the mTOR pathway is affected in PBMCs for a week after administration of 5 mg/kg RAD001 may be interpreted as being contrary to our observations that weekly treatment with this dose is suboptimal in terms of suppression of T-cell-dependent antigen responses. To reconcile these observations, one has to consider that T- and B-cell proliferative responses to foreign antigen presentation occur mainly in the secondary lymphoid organs (64). Here we assayed S6K1 derived from PBMCs, a source that does not reflect the situation in these organs. We therefore speculate that, using weekly schedules, there is a possibility to recover T-cell responses, a phenomenon that may also reflect the pharmacokinetic characteristics of RAD001.

To most efficiently exploit the pharmacological profile of targeted agents such as RAD001, it is important to carefully monitor the dose given to a cancer patient, especially considering the observation that rapamycin can be less effective as an antitumor agent in animal models if overdosed (59). The ease of human PBMC preparation suggests that this could be a valuable surrogate tissue when establishing treatment regimens for RAD001 in clinical trials for oncology. Based on this premise, S6K1 activity could be reproducibly assayed in PBMC extracts prepared from healthy volunteers, and RAD001 treatment of whole blood *ex vivo* resulted in concentration-dependent inactivation of the kinase. In contrast, despite promising results in tumor extracts derived from xenograft models (53) and suggestions that 4E-BP1 phosphorylation could be used as a confirmatory measure of mTOR inhibition in PBMCs (66), we have shown that 4E-BP1 phosphorylation cannot be detected in human PBMCs. During the

[7] T. O'Reilly and L. McMahon, unpublished data.

revision of this manuscript, others (66, 67) also reported on the potential for PBMC-derived S6K1 activity measurements to aid pharmacodynamic evaluation of rapamycin derivatives. Analysis of cancer patient-derived PBMCs after i.v. administration of 25, 75, and 250 mg CCI-779 demonstrated inactivation of PBMC-derived S6K1 for up to 8 days, with no evidence of dose dependency at the doses used (66–68). Although a limited feasibility study in nine patients indicated an association between time to disease progression and the degree of inhibition of S6K1 24 h after CCI-779 administration, no conclusions were drawn regarding the predictive nature of this biomarker or associated implications of the long-term S6K1 inactivation observed in patients (67). Our data provide a strong experimental rationale for analyzing long-term effects on PBMC-derived S6K1 activity when establishing weekly administration schedules. Indeed, recent Phase I trials with weekly administration of RAD001 in patients with advanced cancer have demonstrated a clear association between RAD001 dose and the recovery of PBMC-derived S6K1 activity over a ≥7-day period (69). The value of these observations in terms of prediction of patient response is now being pursued in clinical trials of RAD001 in oncology.

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REFERENCES

1. Nashan, B. Early clinical experience with a novel rapamycin derivative. Ther. Drug Monit., *24:* 53–58, 2002.
2. Huang, S., and Houghton, P. J. Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic. Curr. Opin. Investig. Drugs, *3:* 295–304, 2002.
3. Mita, M. M., Mita, A., and Rowinski, E. K. Mammalian target of rapamycin: a new molecular target for breast cancer. Clin. Breast Cancer, *4:* 126–137, 2003.
4. Hidalgo, M., and Rowinsky, E. K. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. Oncogene, *19:* 6680–6686, 2000.
5. Gingras, A. C., Raught, B., and Sonenberg, N. Regulation of translation initiation by FRAP/mTOR. Genes Dev., *15:* 807–826, 2001.
6. Tibbetts, R. S., and Abraham, R. T. PI3K-related kinases: roles in cell-cycle regulation and DNA damage responses. *In:* J. S. Gutkind (eds.), Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases. Vol. 5, pp. 267–301. Totowa, NJ: Humana Press, 2000.
7. Desai, B. N., Myers, B. R., and Schreiber, S. L. FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. Proc. Natl. Acad. Sci. USA, *99:* 4319–4324, 2002.
8. Hara, K., Yonezawa, K., Weng, Q. P., Kozlowski, M. T., Belham, C., and Avruch, J. Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 through a common effector mechanism. J. Biol. Chem., *273:* 14484–14494, 1998.
9. Xu, G., Kwon, G., Marshall, C. A., Lin, T. A., Lawrence, J. C., Jr., and McDaniel, M. L. Branched-chain amino acids are essential in the regulation of PHAS-I and p70 S6 kinase by pancreatic β-cells. A possible role in protein translation and mitogenic signaling. J. Biol. Chem., *273:* 28178–28184, 1998.
10. Iiboshi, Y., Papst, P. J., Kawasome, H., Hosoi, H., Abraham, R. T., Houghton, P. J., and Terada, N. Amino acid-dependent control of p70(s6k). involvement of tRNA aminoacylation in the regulation. J. Biol. Chem., *274:* 1092–1099, 1999.
11. Dennis, P. B., Jaeschke, A., Saitoh, M., Fowler, B., Kozma, S. C., and Thomas, G. Mammalian TOR: a homeostatic ATP sensor. Science (Wash. DC), *294:* 1102–1105, 2001.
12. Dufner, A., and Thomas, G. Ribosomal S6 kinase signaling and the control of translation. Exp. Cell Res., *253:* 100–109, 1999.
13. Hashemolhosseini, S., Nagamine, Y., Morley, S. J., Desrivieres, S., Mercep, L., and Ferrari, S. Rapamycin inhibition of the G_1 to S transition is mediated by effects on cyclin D1 mRNA and protein stability. J. Biol. Chem., *273:* 14424–14429, 1998.
14. West, M. J., Stoneley, M., and Willis, A. E. Translational induction of the c-myc oncogene via activation of the FRAP/TOR signalling pathway. Oncogene, *17:* 769–780, 1998.
15. Peng, T., Golub, T. R., and Sabatini, D. M. The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. Mol. Cell. Biol., *22:* 5575–5584, 2002.
16. Fingar, D. C., Salama, S., Tsou, C., Harlow, E., and Blenis, J. Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. Genes Dev., *16:* 1472–1487, 2002.
17. Scott, P. H., Brunn, G. J., Kohn, A. D., Roth, R. A., and Lawrence, J. C., Jr. Evidence of insulin-stimulated phosphorylation and activation of the mammalian target of rapamycin mediated by a protein kinase B signaling pathway. Proc. Natl. Acad. Sci. USA, *95:* 7772–7777, 1998.
18. Nave, B. T., Ouwens, M., Withers, D. J., Alessi, D. R., and Shepherd, P. R. Mammalian target of rapamycin is a direct target for protein kinase B: identification of a convergence point for opposing effects of insulin and amino-acid deficiency on protein translation. Biochem. J., *344:* 427–431, 1999.
19. Sekulic, A., Hudson, C. C., Homme, J. L., Yin, P., Otterness, D. M., Karnitz, L. M., and Abraham, R. T. A direct linkage between the phosphoinositide 3-kinase-AKT signaling pathway and the mammalian target of rapamycin in mitogen-stimulated and transformed cells. Cancer Res., *60:* 3504–3513, 2000.
20. Inoki, K., Li, Y., Zhu, T., Wu, J., and Guan, K. L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat. Cell Biol., *4:* 648–657, 2002.
21. Potter, C. J., Pedraza, L. G., and Xu, T. Akt regulates growth by directly phosphorylating Tsc2. Nat. Cell Biol., *4:* 658–665, 2002.
22. Garami, A., Zwartkruis, F. J., Nobukuni, T., Joaquin, M., Roccio, M., Stocker, H., Kozma, S. C., Hafen, E., Bos, J. L., and Thomas, G. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mol. Cell, *11:* 1457–1466, 2003.
23. Inoki, K., Li, Y., Xu, T., and Guan, K. L. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes Dev., *17:* 1829–1834, 2003.
24. Neshat, M. S., Mellinghoff, I. K., Tran, C., Stiles, B., Thomas, G., Petersen, R., Frost, P., Gibbons, J. J., Wu, H., and Sawyers, C. L. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc. Natl. Acad. Sci. USA, *98:* 10314–10319, 2001.
25. Podsypanina, K., Lee, R. T., Politis, C., Hennessy, I., Crane, A., Puc, J., Neshat, M., Wang, H., Yang, L., Gibbons, J., Frost, P., Dreisbach, V., Blenis, J., Gaciong, Z., Fisher, P., Sawyers, C., Hedrick-Ellenson, L., and Parsons, R. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in PTEN+/− mice. Proc. Natl. Acad. Sci. USA, *98:* 10320–10325, 2001.
26. Shi, Y., Gera, J., Hu, L., Hsu, J. H., Bookstein, R., Li, W., and Lichtenstein, A. Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779. Cancer Res., *62:* 5027–5034, 2002.
27. Lane, H. A., Boulay, A., Hattenberger, M., Maira, S-M., Thomas, G., Merlo, A., and O'Reilly, T. The orally active rapamycin derivative RAD001 has potential as an antitumor agent with a broad antiproliferative activity: PTEN as a molecular determinant of response. Proc. Am. Assoc. Cancer Res., *44:* 314, 2003.
28. Kim, D. H., Sarbassov, D. D., Ali, S. M., King, J. E., Latek, R. R., Erdjument-Bromage, H., Tempst, P., and Sabatini, D. M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell, *110:* 163–175, 2002.
29. Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J., and Yonezawa, K. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell, *110:* 177–189, 2002.
30. Kim, D. H., Sarbassov dos, D., Ali, S. M., Latek, R. R., Guntur, K. V., Erdjument-Bromage, H., Tempst, P., and Sabatini, D. M. GβL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol. Cell, *11:* 895–904, 2003.
31. Schalm, S. S., and Blenis, J. Identification of a conserved motif required for mTOR signaling. Curr. Biol., *12:* 632–639, 2002.
32. Schalm, S. S., Fingar, D. C., Sabatini, D. M., and Blenis, J. TOS motif-mediated raptor binding regulates 4E-BP1 multisite phosphorylation and function. Curr. Biol., *13:* 797–806, 2003.
33. Nojima, H., Tokunaga, C., Eguchi, S., Oshiro, N., Hidayat, S., Yoshino, K., Hara, K., Tanaka, N., Avruch, J., and Yonezawa, K. The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. J. Biol. Chem., *278:* 15461–15464, 2003.
34. Gingras, A. C., Gygi, S. P., Raught, B., Polakiewicz, R. D., Abraham, R. T., Hoekstra, M. F., Aebersold, R., and Sonenberg, N. Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism. Genes Dev., *13:* 1422–1437, 1999.
35. Mothe-Satney, I., Brunn, G. J., McMahon, L. P., Capaldo, C. T., Abraham, R. T., and Lawrence, J. C., Jr. Mammalian target of rapamycin-dependent phosphorylation of PHAS-I in four (S/T)P sites detected by phospho-specific antibodies. J. Biol. Chem., *275:* 33836–33843, 2000.
36. Jefferies, H. B., Reinhard, C., Kozma, S. C., and Thomas, G. Rapamycin selectively represses translation of the "polypyrimidine tract" mRNA family. Proc. Natl. Acad. Sci. USA, *91:* 4441–4445, 1994.
37. Jefferies, H. B., Fumagalli, S., Dennis, P. B., Reinhard, C., Pearson, R. B., and Thomas, G. Rapamycin suppresses 5'TOP mRNA translation through inhibition of p70s6k. EMBO J., *16:* 3693–3704, 1997.
38. Meyuhas, O. Synthesis of the translational apparatus is regulated at the translational level. Eur. J. Biochem., *267:* 6321–6330, 2000.
39. Pearson, R. B., Dennis, P. B., Han, J. W., Williamson, N. A., Kozma, S. C., Wettenhall, R. E., and Thomas, G. The principal target of rapamycin-induced p70s6k inactivation is a novel phosphorylation site within a conserved hydrophobic domain. EMBO J., *14:* 5279–5287, 1995.

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40. Peterson, R. T., Beal, P. A., Comb, M. J., and Schreiber, S. L. FKBP12-rapamycin-associated protein (FRAP) autophosphorylates at serine 2481 under translationally repressive conditions. J. Biol. Chem., *275:* 7416–7423, 2000.
41. Brunn, G. J., Hudson, C. C., Sekulic, A., Williams, J. M., Hosoi, H., Houghton, P. J., Lawrence, J. C., Jr., and Abraham, R. T. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. Science (Wash. DC), *277:* 99–101, 1997.
42. Burnett, P. E., Barrow, R. K., Cohen, N. A., Snyder, S. H., and Sabatini, D. M. RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. Proc. Natl. Acad. Sci. USA, *95:* 1432–1437, 1998.
43. Beuvink, I., O'Reilly, T., Zumstein-Mecker, S., Zilbermann, F., Sedrani, R., Kozma, S. C., Thomas, G., and Lane, H. A. Antitumor activity of RAD001, an orally active rapamycin derivative. Proc. Am. Assoc. Cancer Res., *42:* 366, 2001.
44. O'Reilly, T., Vaxelaire, J., Muller, M., Fiebig, H. H., Hattenberger, M., and Lane, H. A. *In vivo* activity of RAD001, an orally active rapamycin derivative, in experimental tumor models. Proc. Am. Assoc. Cancer Res., *43:* 71, 2002.
45. Majewski, M., Korecka, M., Kossev, P., Li, S., Goldman, J., Moore, J., Silberstein, L. E., Nowell, P. C., Schuler, W., Shaw, L. M., and Wasik, M. A. The immunosuppressive macrolide RAD inhibits growth of human Epstein-Barr virus-transformed B lymphocytes *in vitro* and *in vivo*: a potential approach to prevention and treatment of posttransplant lymphoproliferative disorders. Proc. Natl. Acad. Sci. USA, *97:* 4285–4290, 2000.
46. Majewski, M., Korecka, M., Joergensen, J., Fields, L., Kossev, P., Schuler, W., Shaw, L., and Wasik, M. A. Immunosuppressive TOR kinase inhibitor everolimus (RAD) suppresses growth of cells derived from posttransplant lymphoproliferative disorder at allograft-protecting doses. Transplantation, *75:* 1710–1717, 2003.
47. Schuler, W., Sedrani, R., Cottens, S., Häberlin, B., Schulz, M., Schuurman, H. J., Zenke, G., Zerwes, H. G., and Schreier, M. H. SDZ RAD, a new rapamycin derivative: pharmacological properties *in vitro* and *in vivo*. Transplantation, *64:* 36–42, 1997.
48. Lane, H. A., Beuvink, I., Motoyama, A. B., Daly, J. M., Neve, R. M., and Hynes, N. E. ErbB2 potentiates breast tumor proliferation through modulation of p27(Kip1)-Cdk2 complex formation: receptor overexpression does not determine growth dependency. Mol. Cell. Biol., *20:* 3210–3223, 2000.
49. Olayioye, M. A., Graus-Porta, D., Beerli, R. R., Rohrer, J., Gay, B., and Hynes, N. E. ErbB-1 and ErbB-2 acquire distinct signaling properties dependent upon their dimerization partner. Mol. Cell. Biol., *18:* 5042–5051, 1998.
50. Lane, H. A., and Thomas, G. Purification and properties of mitogen-activated S6 kinase from rat liver and 3T3 cells. Methods Enzymol., *200:* 268–291, 1991.
51. Hosoi, H., Dilling, M. B., Shikata, T., Liu, L. N., Shu, L., Ashmun, R. A., Germain, G. S., Abraham, R. T., and Houghton, P. J. Rapamycin causes poorly reversible inhibition of mTOR and induces p53-independent apoptosis in human rhabdomyosarcoma cells. Cancer Res., *59:* 886–894, 1999.
52. Schuurman, H. J., Cottens, S., Fuchs, S., Joergensen, J., Meerloo, T., Sedrani, R., Tanner, M., Zenke, G., and Schuler, W. SDZ RAD, a new rapamycin derivative: synergism with cyclosporine. Transplantation, *64:* 32–35, 1997.
53. Daskin, L., Dilling, M. B., Cheshire, P. J., Harwood, F. C., Hollingshead, M., Arbuck, S. G., Travis, R., Sausville, E. A., and Houghton, P. J. Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition. Clin. Cancer Res., *7:* 1758–1764, 2001.
54. Jiang, Y. P., Ballou, L. M., and Lin, R. Z. Rapamycin-insensitive regulation of 4E-BP1 in regenerating rat liver. J. Biol. Chem., *276:* 10943–10951, 2001.
55. Eng, C. P., Sehgal, S. N., and Vezina, C. Activity of rapamycin (AY-22,989) against transplanted tumors. J. Antibiot., *37:* 1231–1237, 1984.
56. Houchens, D. P., Ovejera, A. A., Riblet, S. M., and Slagel, D. E. Human brain tumor xenografts in nude mice as a chemotherapy model. Eur. J. Cancer Clin. Oncol., *19:* 799–805, 1983.
57. Geoerger, B., Kerr, K., Tang, C. B., Fung, K. M., Powell, B., Sutton, L. N., Phillips, P. C., and Janss, A. J. Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy. Cancer Res., *61:* 1527–1532, 2001.
58. Yu, K., Toral-Barza, L., Discafani, C., Zhang, W. G., Skotnicki, J., Frost, P., and Gibbons, J. J. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. Endocr. Relat. Cancer, *8:* 249–258, 2001.
59. Guba, M., von Breitenbuch, P., Steinbauer, M., Koehl, G., Flegel, S., Hornung, M., Bruns, C. J., Zuelke, C., Farkas, S., Anthuber, M., Jauch, K. W., and Geissler, E. K. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat. Med., *8:* 128–135, 2002.
60. Grewe, M., Gansauge, F., Schmid, R. M., Adler, G., and Seufferlein, T. Regulation of cell growth and cyclin D1 expression by the constitutively active FRAP-p70s6K pathway in human pancreatic cancer cells. Cancer Res., *59:* 3581–3587, 1999.
61. Shah, S. A., Potter, M. W., Ricciardi, R., Perugini, R. A., and Callery, M. P. FRAP-p70S6K signaling is required for pancreatic cancer cell proliferation. J. Surg. Res., *97:* 123–130, 2001.
62. Kovarik, J. M., Kaplan, B., Tedesco Silva, H., Kahan, B. D., Dantal, J., Vitko, S., Boger, R., and Rordorf, C. Exposure-response relationships for everolimus in *de novo* kidney transplantation: defining a therapeutic range. Transplantation, *73:* 920–925, 2002.
63. Terada, N., Franklin, R. A., Lucas, J. J., Blenis, J., and Gelfand, E. W. Failure of rapamycin to block proliferation once resting cells have entered the cell cycle despite inactivation of p70 S6 kinase. J. Biol. Chem., *268:* 12062–12068, 1993.
64. Zenke, G., Strittmatter, U., Fuchs, S., Quesniaux, V. F., Brinkmann, V., Schuler, W., Zurini, M., Enz, A., Billich, A., Sanglier, J. J., and Fehr, T. Sanglifehrin A, a novel cyclophilin-binding compound showing immunosuppressive activity with a new mechanism of action. J. Immunol., *166:* 7165–7171, 2001.
65. Chung, J., Kuo, C. J., Crabtree, G. R., and Blenis, J. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. Cell, *69:* 1227–1236, 1992.
66. Harding, M. W. Immunophilins, mTOR, and pharmacodynamic strategies for a targeted cancer therapy. Clin. Cancer Res., *9:* 2882–2886, 2003.
67. Peralba, J. M., deGraffenried, L., Friedrichs, W., Fulcher, L., Grünwald, V., Weiss, G., and Hidalgo, M. Pharmacodynamic evaluation of CCI-779, an inhibitor of mTOR, in cancer patients. Clin. Cancer Res., *9:* 2887–2892, 2003.
68. Stadler, W., Logan, T., Dutcher, J., Hudes, G., Park, Y., Marshall, B., Boni, J., and Dukart, J. A randomized double-blind phase 2 study of intravenous CCI-779 administered weekly to patients with advanced renal cell carcinoma. Proc. Am. Soc. Clin. Oncol., *21:* 10a, 2002.
69. O'Donnell, A., Faivre, S., Judson, I., Delbaldo, C., Brock, C., Lane, H., Shand, N., Hazell, K., Armand, J-P., and Raymond, E. Phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours. Proc. Am. Soc. Clin. Oncol., *22:* 200, 2003.

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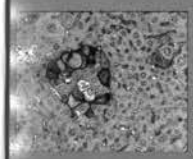

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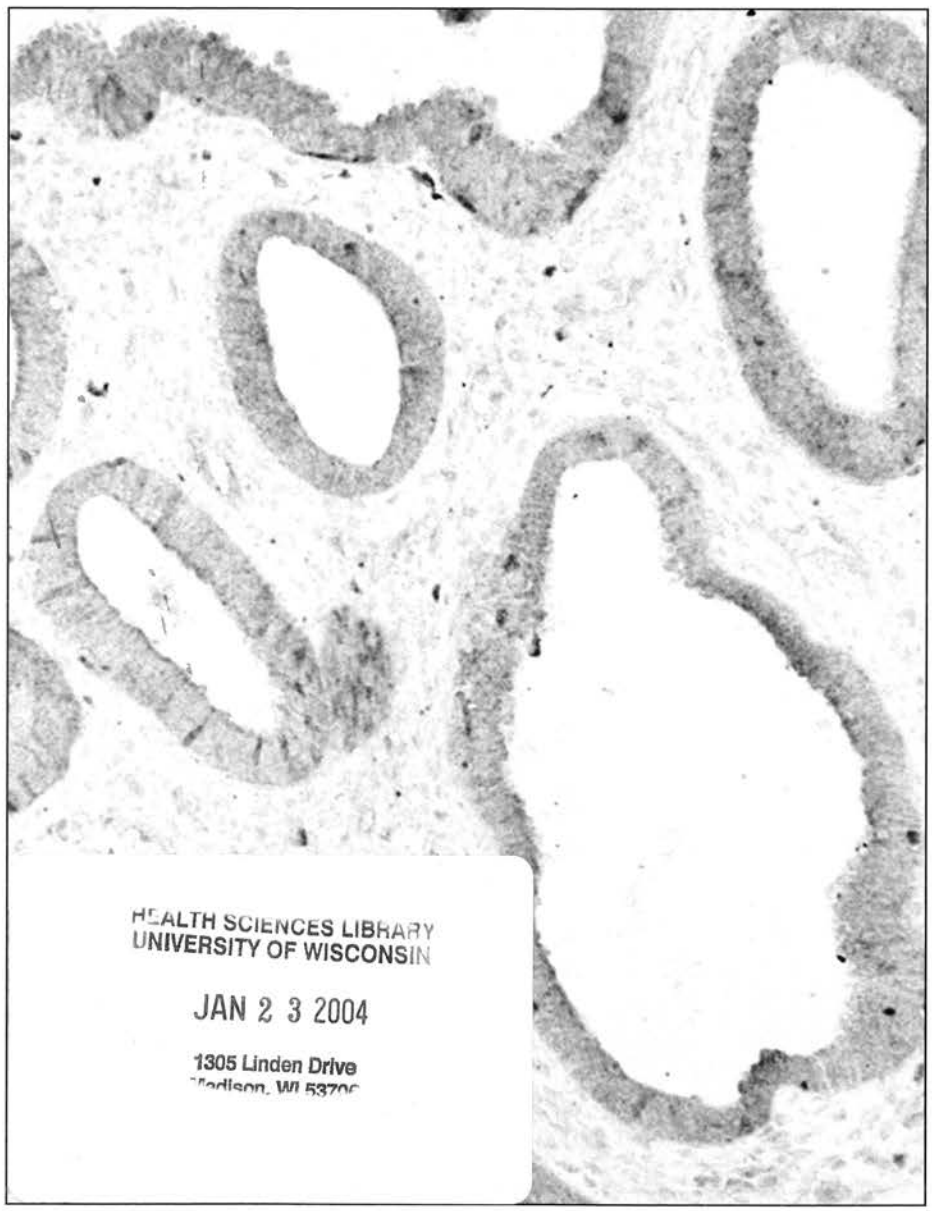

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Antitumor Efficacy of Intermittent Treatment Schedules with the Rapamycin Derivative RAD001 Correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells

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ABSTRACT

The orally bioavailable rapamycin derivative RAD001 (everolimus) targets the mammalian target of rapamycin pathway and possesses potent immunosuppressive and anticancer activities. Here, the antitumor activity of RAD001 was evaluated in the CA20948 syngeneic rat pancreatic tumor model. RAD001 demonstrated dose-dependent antitumor activity with daily and weekly administration schedules; statistically significant antitumor effects were observed with 2.5 and 0.5 mg/kg RAD001 administered daily [treated tumor *versus* control tumor size (T/C), 23% and 23–30%, respectively], with 3–5 mg/kg RAD001 administered once weekly (T/C, 14–36%), or with 5 mg/kg RAD001 administered twice weekly (T/C, 36%). These schedules were well tolerated and exhibited antitumor potency similar to that of the cytotoxic agent 5-fluorouracil (T/C, 23%). Moreover, the efficacy of intermittent treatment schedules suggests a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical profiling of mammalian target of rapamycin signaling in tumors, skin, and peripheral blood mononuclear cells (PBMCs), after a single administration of 5 mg/kg RAD001, indicated that RAD001 treatment blocked phosphorylation of the translational repressor eukaryotic initiation factor 4E-binding protein 1 and inactivated the translational activator ribosomal protein S6 kinase 1 (S6K1). The efficacy of intermittent treatment schedules was associated with prolonged inactivation of S6K1 in tumors and surrogate tissues (≥72 h). Furthermore, detailed analysis of the dose dependency of weekly treatment schedules demonstrated a correlation between antitumor efficacy and prolonged effects (≥7 days) on PBMC-derived S6K1 activity. Analysis of human PBMCs revealed that S6K1 also underwent a concentration-dependent inactivation after RAD001 treatment *ex vivo* (>95% inactivation with 20 nM RAD001). In contrast, human PBMC-derived eukaryotic initiation factor 4E-binding protein 1 was present predominantly in the hypophosphorylated form and was unaffected by RAD001 treatment. Taken together, these results demonstrate a correlation between the antitumor efficacy of intermittent RAD001 treatment schedules and prolonged S6K1 inactivation in PBMCs and suggest that long-term monitoring of PBMC-derived S6K1 activity levels could be used for assessing RAD001 treatment schedules in cancer patients.

INTRODUCTION

RAD001 (everolimus), an orally bioavailable derivative of rapamycin, is a macrolide antifungal antibiotic that demonstrates potent antiproliferative effects against a variety of mammalian cell types. Specifically, RAD001 inhibits cytokine-driven lymphocyte proliferation (1), as well as the proliferation of human tumor-derived cells grown either in culture or as tumors in animal models (2, 3). As a result of these properties, RAD001 is being clinically developed both as an immunosuppressant for prevention of allograft rejection (Certican; Ref. 1) and as a novel therapeutic in the fight against human cancer (2–4).

RAD001, like rapamycin, binds with high affinity to a ubiquitous intracellular receptor, the immunophilin FKBP12. This complex specifically interacts with the mammalian target of rapamycin (mTOR) protein kinase; inhibiting downstream signaling events (5). The mTOR kinase is a member of the phosphoinositide kinase-related kinase family, which consists of high molecular weight serine/threonine kinases involved in cell cycle checkpoint control (6). Several lines of evidence suggest that mTOR acts as a sensor for stress (7) and the availability of amino acids (8–10) or intracellular ATP (11). In the presence of mitogens and sufficient nutrients, mTOR relays a signal to translational regulators, specifically enhancing the translation of mRNAs encoding proteins essential for cell growth (12) and progression through the G_1 to S transition (13, 14). Consistent with targeting the mTOR pathway, treatment of mammalian cells with rapamycin has been shown to inhibit these signaling events, mimicking a starvation phenotype (15) and leading to growth retardation and accumulation of cells in G_1 phase (16). The mechanism of growth stimulus and nutrient level integration by mTOR is, as yet, not fully understood. However, an increasing body of evidence suggests the involvement of the phosphatidylinositol 3′-kinase/Akt/TSC/Rheb pathway (12, 17–23). Indeed, it has been suggested that, in tumor cells, the activation status of the Akt pathway may be indicative of responsiveness to rapamycin (or its derivatives (24–27).

mTOR is part of a multisubunit complex that contains the regulatory proteins raptor (28, 29) and GβL (30). The mTOR complex signals to at least two downstream effectors, the translational repressor protein-eukaryotic initiation factor 4E (eIF-4E)-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1). These share an evolutionary conserved amino acid motif, the TOS motif, that functions as a docking site for raptor (31–33). Binding of 4E-BP1 to the translational activator eIF-4E is modulated by mTOR-dependent phosphorylation of specific serine and threonine residues (5). Ser37 and Ser46 are constitutively phosphorylated, acting as priming sites for the mitogen-induced, rapamycin-sensitive phosphorylation of Thr70 and Ser65 (34). After a final phosphorylation event at Ser65, 4E-BP1 dissociates from eIF-4E (35), thereby allowing the reconstitution of a translationally competent initiation factor complex (eIF-4F; Ref. 5). eIF-4F activation results in the translation of a subset of capped mRNA containing highly structured 5′-untranslated regions and encoding proteins involved in G_1- to S-phase progression (13, 14). Mitogen-induced activation of the S6K1 is also dependent on mTOR function and has been implicated in the translational regulation of mRNAs possessing a 5′-terminal oligopyrimidine tract (36–38). 5′-Terminal oligopyrimidine tract mRNAs are characterized by a stretch of 4–14 pyrimidines located at their extreme 5′ terminus and typically encode ribosomal proteins as well as components of the

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translational machinery. Activation of S6K1 itself is also tightly regulated by hierarchical phosphorylation events, which are dependent on the activation of various signal transduction pathways and culminate in the phosphorylation of the rapamycin-sensitive site Thr389, an event closely paralleling kinase activation (12, 39). Immunopurified mTOR has been shown to autophosphorylate on Ser2481 (40) and to phosphorylate Ser37, Ser46, and Ser65 on 4E-BP1 *in vitro* (11, 34, 41, 42). However, some of these events have been demonstrated to be resistant to antiproliferative concentrations of rapamycin (40–42). It is therefore unclear what role mTOR kinase activity plays *per se* in rapamycin-sensitive signaling events.

Because mTOR couples nutrient/growth factor availability to cell growth and proliferation in a variety of cell types, there is a potential for developing rapamycin derivatives such as RAD001 as novel inhibitors of the deregulated cell growth characteristic of human cancers. Consistent with this, RAD001 inhibits the proliferation of a wide variety of human solid tumor cell lines both *in vitro* in cell culture and *in vivo* in animal xenograft models (2, 3, 27, 43, 44). Furthermore, antiproliferative effects of RAD001 in posttransplant lymphoproliferative disorder-like B cell lines have been observed *in vitro* and *in vivo* (45, 46). In the present study, we have demonstrated that RAD001 displays significant antitumor activity in the syngeneic CA20948 rat pancreatic tumor model. Equivalent activity was observed with daily and intermittent treatment schedules, suggesting the possibility of a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical analysis of the mTOR effectors 4E-BP1 and S6K1 in tumor, skin, and peripheral blood mononuclear cell (PBMC) extracts obtained from RAD001-treated rats suggests that modulation of 4E-BP1 activity and significant inactivation of S6K1 are associated with antitumor activity. Furthermore, the efficacy observed using intermittent treatment schedules is paralleled by long-term downregulation of S6K1 activity in all three tissues. We also provide evidence that the duration of S6K1 inactivation in PBMCs correlates with the dose-dependent suppression of tumor growth observed with weekly regimens. Moreover, unlike 4E-BP1 phosphorylation, S6K1 activity can be reproducibly measured in human PBMCs and represents a potentially valuable pharmacodynamic biomarker by which to monitor RAD001 treatment schedules in cancer patients.

MATERIALS AND METHODS

Drug Preparation. RAD001 (everolimus) is a derivative of rapamycin [40-*O*-(2-hydroxyethyl)-rapamycin; Ref. 47]. For animal studies, RAD001 was formulated at 2% (w/v) in a microemulsion vehicle, which was diluted to the appropriate concentration in 5% (w/v) glucose solution just before administration by gavage. For *in vitro* and *ex vivo* analyses, RAD001 was prepared in DMSO before addition to cell culture or human volunteer blood samples.

Antitumor Efficacy Studies and Statistical Analyses. Male Lewis rats were purchased from Iffa Credo (L'Abresque, France) and allowed food and water *ad libitum*. A suspension of CA20948 tumor cells (obtained from donor rats because this line is nonculturable *in vitro*) in Ham's F-12 medium supplemented with 10% FCS, 0.1 g/100 ml $NaHCO_3$, 1% penicillin, and 1% fungizone was injected s.c. into the left flank of rats. Treatment of randomized rats started when the tumors reached about 100 mm^3. RAD001 was administered p.o. daily at 0.5 or 2.5 mg/kg (×6/week), twice weekly at 5 mg/kg, or weekly at 0.5, 1, 2, 3, or 5 mg/kg. A volume of vehicle equivalent to the highest dose of RAD001 administered in the experiment was used as a negative control. As a positive control, the cytotoxic agent 5-fluorouracil (5-FU; ICN Pharmaceuticals Inc., Costa Mesa, CA) was administered at a near maximum tolerated dose (15 mg/kg, i.v., 4×/week, 2 days treatment/2 days rest), which gives maximal antitumor effect. Tumors were measured every day or every other day with a caliper, and the volumes were calculated by using the formula of an ellipsoid [$V = \pi/6\ (d_1 \times d_2 \times d_3)$, where d_1, d_2, and d_3 represent the three largest diameters]. Animals were also weighed the same day tumors were measured. The animals were sacrificed when either their tumor burden exceeded 25,000 mm^3 or when skin overlaying the tumor exhibited evidence of necrosis. All protocols involving animals were approved by the Veterinäramt of Baselstadt, Switzerland.

Results are presented as mean ± 1 SEM or as percentage of T/C (mean increase of tumor volumes of treated animals divided by the mean increase of tumor volumes of control animals multiplied by 100). The statistical significance of differences between treatment and control groups were determined by ANOVA followed by the Dunnett test. Statistical analyses on body weight were performed by ANOVA followed by Tukey's test, and for comparison between weight at start and end of the experiment for individual animals, the paired *t* test was used. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific).

Rat-Derived and Human Volunteer-Derived Tissue/PBMC Protein Extract Preparation. CA20948 tumor-bearing rats were given 0.5, 1, 2, or 5 mg/kg RAD001 or an equivalent volume of vehicle. At the indicated times after administration, rats were sacrificed, and tumor and shaved skin samples (for 0.5 and 5 mg/kg RAD001 doses) were dissected and weighed. Samples were rinsed in ice-cold PBS and immediately extracted in ice-cold extraction buffer [50 mM Tris-HCl (pH 8.0), 120 mM NaCl, 20 mM NaF, 1 mM EDTA, 6 mM EGTA, 15 mM PP_i, 30 mM *p*-nitrophenyl phosphate, 1 mM benzamidine, 0.2 mM phenylmethylsulfonyl fluoride, and 0.1% NP40] with a constant ratio of 45 mg tumor/ml extraction buffer and 90 mg skin/ml extraction buffer, using a PT3000 Polytron (probe PT-DA 3012/2S; Kinematica AG) or a hand-held PT2100 Polytron (probe PT-DA 2112/2EC), respectively. Lysates were cleared by centrifugation for 30 min at 12,000 × *g* at 4°C. Supernatants were subsequently aliquoted, snap frozen on dry ice, and stored at −80°C. In the case of skin samples, before further analysis, samples were centrifuged for 20 min at 436,000 × *g* at 4°C to remove the fat fraction.

Blood (for 0.5, 1, 2, and 5 mg/kg RAD001 doses) from tumor-bearing and non-tumor-bearing rats was withdrawn into syringes containing EDTA [0.5% (w/v) final] and then placed into an ice-cold tube and mixed. Unless otherwise stated, the blood from individual animals within the same treatment group was analyzed separately. The blood was immediately centrifuged for 20 min at 430 × *g* at 4°C. The PBMCs, deposited at the interface between the RBCs and the plasma, were collected and pelleted by centrifugation for 5 min at 3000 × *g* at 4°C. PBMCs were washed with 10 ml of ice-cold PBS and then repelleted by centrifugation for 5 min at 3000 × *g* at 4°C. Cell pellets were resuspended in ice-cold extraction buffer containing 1% NP40 at the fixed ratio of 500 μl extraction buffer/10 ml initial blood volume. The cells were sheared by vigorous pipetting and then centrifuged for 30 min at 12,000 × *g* at 4°C. Supernatants were aliquoted, snap frozen on dry ice, and stored at −80°C.

Human blood from healthy volunteers was collected under medical supervision into tubes containing either sodium citrate (BD Vacutainer 9NC; BD Vacutainer Systems, Plymouth, United Kingdom) or EDTA (BD Vacutainer K3E) as an anticoagulant. The blood was either immediately processed or, for *ex vivo* treatments, treated with 2, 20, and 200 nM RAD001 or DMSO vehicle for 30 min at room temperature. Human PBMCs were isolated and extracted as described for rat PBMCs.

A549 Cell Culture and Protein Extract Preparation. A549 human lung carcinoma cells (CCL185) were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 medium (Amimed, Allschwil, Switzerland) supplemented with 10% FCS, 2 mM L-glutamine, and 100 μg/ml penicillin/streptomycin at 37°C and 5% CO_2. Cell lysates were prepared as described previously (48).

Immunoblot Analysis. Cell lysates (30–40 μg) were electrophoretically resolved on denaturing SDS polyacrylamide gels (SDS-PAGE), transferred to polyvinylidene difluoride (Millipore Corp., Bedford, MA), and probed with the following primary antibodies: anti-S6 (provided by J. Mestan; Oncology Research, Novartis Pharma AG, Basel, Switzerland); anti-4E-BP1 (kindly provided by N. Sonenberg; McGill University, Montreal, Quebec, Canada); anti-eIF-4E (kindly provided by S. J. Morley; University of Sussex, Brighton, United Kingdom); anti-phospho-4E-BP1 Thr70, anti-S6K1, and anti-phospho-S6 Ser240/Ser244 (all from Cell Signaling Technology Inc., Beverly, MA); and anti-β-tubulin (Tub2.1; Sigma, St. Louis, MO). "Decorated" proteins were revealed using horseradish peroxidase-conjugated antimouse or antirabbit immunoglobulins in conjunction with the enhanced chemiluminescence procedure (Amersham Pharmacia Biotech Inc., Buckinghamshire, United Kingdom).

Affinity Purification of 4E-BP1·eIF-4E Complexes with 7-Methyl-GTP-Sepharose. Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 500 μl in ice-cold extraction buffer and adjusted to a final NP40 concentration of 0.1%. The 4E-BP1·eIF-4E complexes were affinity purified with 20 μl of 7-methyl-GTP-Sepharose beads (Amersham Pharmacia Biotech Inc., Piscataway, NJ) by gentle rotation for 2.5 h at 4°C. Proteins retained on the beads were washed twice with extraction buffer in the absence of NP40 and resuspended in 15 μl of Laemmli buffer. Denatured samples were subjected to 15% SDS-PAGE and transferred to polyvinylidene difluoride membranes. Membranes were first immunoblotted for 4E-BP1 protein, followed by stripping as described previously (49) and reprobing for eIF-4E protein (see above).

40*S* Ribosomal S6 Kinase Assay. Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 1 ml (tumor and skin) or 500 μl (PBMC) with ice-cold extraction buffer and adjusted to a final NP40 concentration of 1%. Human-derived PBMC extracts (0.8–1 mg) were diluted to a final volume of 750 μl with ice-cold extraction buffer (final NP40 concentration, 1%). In some experiments, human-derived PBMC extracts were first precleared with 20 μl of 50% protein A-Sepharose (Amersham Pharmacia Biotech, Uppsala, Sweden) by rotating for 20 min at 4°C. S6K1 was immunoprecipitated from all extracts by addition of 2.5 μl of the M5 S6K1-specific polyclonal antibody and incubation on ice for 1 h, followed by retrieval of immunocomplexes with 20 μl of 50% protein A-Sepharose. S6K1 activity was measured using rat liver 40*S* ribosomal subunits as a specific substrate, as described previously (50), except that *p*-nitrophenyl phosphate was omitted in the reaction mixture. Phosphorylated S6 was resolved by 12.5% SDS-PAGE and analyzed using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). [γ-^{32}P]phosphate incorporation into S6 was quantified using ImageQuant (Molecular Dynamics). Where appropriate, the statistical significance of differences between treatment groups and untreated control groups was determined using ANOVA or ANOVA on ranks followed by the Dunnett test. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific). Coefficient of variation is defined as SD divided by the mean and multiplied by 100.

RESULTS

Intermittent RAD001 Treatment Schedules Display Antitumor Efficacy. Short-term exposure to rapamycin *in vitro* has long-term antiproliferative effects on tumor cell lines (51), suggesting that intermittent treatment schedules may retain antitumor activity. Furthermore, daily oral administration of RAD001 is effective in rat models of autoimmune disease and allotransplantation (47, 52), whereas we have found that weekly (5 mg/kg) RAD001 dosing schedules have reduced immunosuppressive properties in rats as compared with daily treatment (2.5 mg/kg): 66 ± 18% and 98 ± 1% inhibition of IgG antibody response after dinitrophenol-coupled keyhole limpet hemocyanogen immunization, respectively.[3] With these observations in mind, we evaluated whether RAD001 treatment schedules, with potentially reduced immunosuppressive properties, could elicit antitumor responses. Daily *versus* intermittent RAD001 administration schedules were compared using the s.c. CA20948 rat pancreatic tumor model. Vehicle was used as a negative control, and the cytotoxic agent 5-FU was used as a positive control (Fig. 1; Table 1, Experiment 1). RAD001 treatment at 0.5 or 2.5 mg/kg/day, six times a week, resulted in antitumor activity characterized by statistically significant inhibition of tumor growth as compared with vehicle controls [treated tumor *versus* control tumor size (T/C), 30% and 23%, respectively; $P < 0.05$ after 10 days of treatment; Fig. 1*A*; Table 1, Experiment 1]. Statistically significant tumor growth suppression was also observed after intermittent administration of 5 mg/kg RAD001 twice a week (T/C, 36%) or once a week (T/C, 36%). Moreover, all RAD001 treatment schedules suppressed tumor growth to a similar extent as the cytotoxic 5-FU (T/C, 23%). Continued

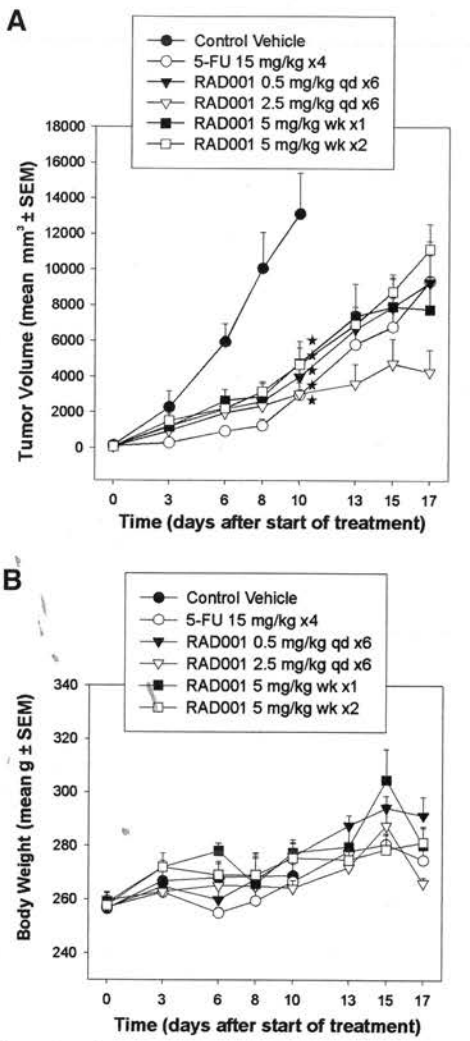

Fig. 1. Suppression of tumor growth by daily and intermittent dosing schedules of RAD001. Tumors were established in male Lewis rats by s.c. injection of CA20948 tumor suspension obtained from donor rats. Treatments started on day 4 after inoculation. Formulated RAD001 was diluted in a 5% glucose solution and administered p.o. daily at a dose of 0.5 or 2.5 mg/kg (*qd* ×6, 6 times/week) or once (*wk* ×1) or twice (*wk* ×2) weekly at 5 mg/kg RAD001. Vehicle and 5-fluorouracil (*5-FU* ×4; 4 times/week) were administered as negative and positive controls, respectively. Tumor volumes were measured (*A*), and rats were weighed (*B*) as described in "Materials and Methods." Vehicle control-treated rats were sacrificed on day 10 due to tumor burden. Data are means ± SEM (n = 7–8 animals/group). *Stars* represent $P < 0.05$ *versus* vehicle controls.

treatment with RAD001 after vehicle controls were sacrificed due to tumor burden led to a prolonged low tumor growth rate with all treatment schedules, resulting in similar tumor burden after 17 days of treatment as compared with 5-FU (Fig. 1*A*). For all treatment schedules, RAD001 was well tolerated, with no significant body weight loss or mortalities observed (Fig. 1*B*; Table 1, Experiment 1). These results demonstrate that RAD001 is a well-tolerated antitumor agent in a rat model of pancreatic cancer and indicate a potential for intermittent administration schedules that may allow dissociation of antitumor from immunosuppressive effects.

RAD001 Modulates 4E-BP1 and S6K1 Activity in Tumor, Skin, and PBMCs Obtained from CA20948 Pancreatic Tumor-Bearing Rats. To investigate RAD001-specific effects on mTOR signaling *in vivo*, three CA20948 tumor-bearing rats were treated with vehicle or a single efficacious dose of RAD001 (5 mg/kg). Rats were sacrificed

[3] T. O'Reilly, H. A. Lane, and C. Heusser, unpublished data.

Table 1 *Effect of daily and intermittent RAD001 administration on CA20948 rat pancreatic tumor-bearing rats*

Compound	Schedule	Tumor response		Host response		
		% T/C[a]	Δ Tumor volume (mm^3)	Δ Body weight (g)	%Δ Body weight	Survival (alive/total)
Experiment 1						
Vehicle	2 ml/kg p.o. daily	100	12972 ± 2188	12 ± 8	5	8/8
5-FU	15 mg/kg i.v. 4× weekly	23	2863 ± 764[b]	18 ± 4	7	7/7
RAD001	0.5 mg/kg p.o. daily	30	3904 ± 856[b]	35 ± 7	14	7/7
RAD001	2.5 mg/kg p.o. daily	23	2959 ± 624[b]	7 ± 2	3	7/7
RAD001	5 mg/kg p.o. weekly	36	4652 ± 1220[b]	22 ± 5	8	7/7
RAD001	5 mg/kg p.o. twice weekly	36	4604 ± 928[b]	21 ± 3	8	7/7
Experiment 2						
Vehicle	2 ml/kg p.o. daily	100	12331 ± 1410	29 ± 2	14	8/8
RAD001	0.5 mg/kg p.o. daily	23	2894 ± 567[b]	30 ± 5	17	8/8
RAD001	0.5 mg/kg p.o. weekly	48	5951 ± 1739	36 ± 2	15	8/8
RAD001	5 mg/kg p.o. weekly	14	1708 ± 339[b]	32 ± 2	15	8/8
Experiment 3						
Vehicle	2 ml/kg p.o. weekly	100	19270 ± 3918	28.3 ± 2.1	10	8/8
RAD001	0.5 mg/kg p.o. weekly	48	9275 ± 1926	21 ± 2.4	8	8/8
RAD001	1 mg/kg p.o. weekly	45	8617 ± 1704	32.8 ± 2.7	12	8/8
RAD001	2 mg/kg p.o. weekly	32	6161 ± 1079[b]	24.9 ± 1.9	9	8/8
RAD001	3 mg/kg p.o. weekly	36	6869 ± 611[b]	24.3 ± 3.3	9	6/6
RAD001	5 mg/kg p.o. weekly	24	4680 ± 1593[b]	22.8 ± 1.7	8	8/8

[a] T/C, treated tumor *versus* control tumor size.
[b] $P < 0.05$ *versus* control, Dunnett test.

24 h later, and protein extracts were prepared from tumors, skin, and PBMCs. By immunoblot analysis, mTOR could be detected in tumor and PBMC extracts; however, neither mTOR expression nor phosphorylation on Ser2448 was modified on RAD001 treatment.[4] In contrast, 4E-BP1 exhibited a decrease in Thr70 phosphorylation in tumor, skin, and PBMC extracts (Fig. 2*A*), a phenomenon associated with changes in 4E-BP1 electrophoretic mobility, particularly striking in PBMCs. This observation is consistent with previous work demonstrating dephosphorylation of 4E-BP1 on Thr70 in tumors derived from mouse xenograft models after five daily treatments with an ester of rapamycin CCI-779 (1 h after last administration; Ref. 53). Interestingly, the phosphorylation of another rapamycin-sensitive residue (Ser65; Refs. 5, 34, and 35) was unaffected by RAD001 treatment,[4] indicating that RAD001-insensitive phosphorylation of this site can occur as reported previously (54).

To determine whether the decreased phosphorylation state of 4E-BP1 resulted in a change in functionality, the eIF-4E binding activity of 4E-BP1 was assessed using an *in vitro* 7-methyl-GTP-binding assay (Fig. 2*B*). Whereas similar levels of eIF-4E were recovered in the control- and RAD001-treated extracts, in two animals increased eIF-4E·4E-BP1 complex formation was clearly observed in skin and PBMC samples after RAD001 treatment. In tumor samples, two electrophoretically distinct forms of 4E-BP1 protein were bound to eIF-4E in vehicle control-treated rats (Fig. 2*B*). After RAD001 treatment, only the lower migrating form was found bound to eIF-4E, with an associated loss of the upper band consistent with reduced 4E-BP1 phosphorylation levels (Fig. 2*A*). A similar 4E-BP1 doublet with eIF-4E binding activity has been observed previously in proliferating cells/tissue (29, 54) and presumably reflects differential 4E-BP1 phosphorylation states within the proliferating tumor.

To further assess the effect of RAD001 administration on the mTOR pathway, S6K1 protein and activity levels were also analyzed (Fig. 2, *C* and *D*). Whereas S6K1 protein levels were unaffected by RAD001 treatment (Fig. 2*C*), *in vitro* kinase assay using 40*S* ribosomal subunits as a substrate revealed a statistically significant reduction in S6K1 activity in all extracts [Fig. 2*D*; 83% (tumors), 80% (skin), and 75% (PBMC); all $P < 0.05$ *versus* vehicle-treated controls]. This reduction in S6K1 activity was associated with the dramatic dephosphorylation of its physiological substrate, 40*S* ribosomal protein S6, in tumor extracts (Fig. 2*C*). A similar reduction was not observed in skin and PBMC extracts because these tissues exhibited no detectable S6 phosphorylation in control animals. Interestingly, a

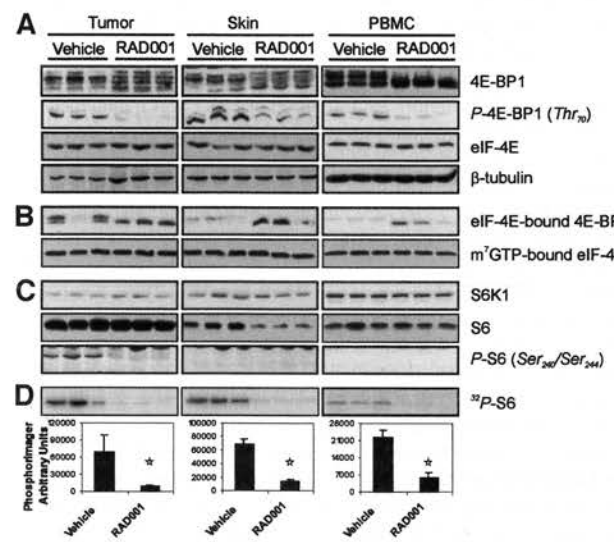

Fig. 2. RAD001 administration inhibits mammalian target of rapamycin signaling in CA20948 tumor-bearing rats. S.c. CA20948 tumor-bearing rats received a single administration of an efficacious dose of RAD001 (5 mg/kg) or vehicle and were sacrificed 24 h after administration (3 rats/group). Tumors, skin, and PBMCs were individually prepared and extracted as described in "Materials and Methods." Results from individual rats are presented. *A* and *C*, total protein was subjected to electrophoresis followed by immunoblot analysis. Membranes were probed for eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and phospho-threonine 70 4E-BP1 [*P-4E-BP1 (Thr_{70})*] levels, with eukaryotic initiation factor 4E (eIF-4E) and β-tubulin levels acting as loading controls (*A*) or ribosomal protein S6 kinase 1 protein, S6 40*S* ribosomal protein, and phospho-serine 240/244 S6 [*P-S6 (Ser_{240}/Ser_{244})*] levels (*C*). *B*, the level of 4E-BP1 bound to eIF-4E was measured by purification of 4E-BP1·eIF-4E complexes on 7-methyl-GTP-Sepharose, as described in "Materials and Methods," followed by immunoblot analysis. *D*, ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of total protein extract, and activity was measured by *in vitro* kinase assay using 40*S* ribosomal subunits as a specific substrate, as described in "Materials and Methods." Phosphorimages (^{32}*P-S6*) and PhosphorImager quantifications of the kinase assay are presented. Data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* vehicle-treated controls (Dunnett test).

[4] A. Boulay and H. A. Lane, unpublished data.

reduction in S6 protein expression was observed in RAD001-treated skin, but not in tumor or PBMC extracts. A similar phenomenon has been reported previously in tumors after treatment of mice bearing human prostate cancer xenografts with CCI-779 (24). Moreover, the translation of S6 (as a 5′-terminal oligopyrimidine tract mRNA) has been shown to be specifically inhibited by rapamycin in 3T3 cells (36). It is not known why, in this model, RAD001 treatment only has effects on S6 expression in skin; however, differential downstream effects of mTOR pathway inhibition, depending on the tissue source, are a plausible possibility (54). Taken together, these data demonstrate that both 4E-BP1 and S6K1 pathways are affected in tumors, skin, and PBMC samples obtained from CA20948 tumor-bearing rats after a single administration of an efficacious dose of RAD001.

Prolonged Inactivation of S6K1 in Tumors, Skin, and PBMCs Correlates with the Efficacy of Intermittent RAD001 Treatment Schedules. To investigate whether the antitumor efficacy of intermittent RAD001 treatment schedules is associated with prolonged effects on the mTOR pathway, CA20948 tumor-bearing rats were treated with a single dose of RAD001 (5 mg/kg) or vehicle, and tumor, skin, and PBMC extracts were prepared 12, 24, 48, or 72 h after administration. Because S6K1 was significantly inactivated 24 h after a single RAD001 administration in all tissues analyzed (Fig. 2*D*), long-term effects on mTOR function were assessed using the 40*S* kinase assay (Fig. 3). Tumor and skin extracts were obtained from each of 3 rats/treatment group, whereas PBMC extracts were obtained from pooled blood from each treatment group. A dramatic reduction in S6K1 activity was already observed in tumors, skin, and PBMCs 12 h after RAD001 administration (91%, 91%, and 82% inhibition, respectively; all $P < 0.05$ *versus* untreated controls; Fig. 3). In contrast, treatment with vehicle did not significantly modulate S6K1 activity as compared with untreated controls (Fig. 3). Moreover, RAD001 treatment resulted in the sustained inactivation of S6K1 in all tissues. In tumors, statistically significant inhibition of S6K1 was maintained up to 48 h after administration, with some evidence of recovery after 72 h (80% and 62% inhibition at 48 and 72 h, respectively; Fig. 3*A*). In comparison, S6K1 derived from skin samples remained significantly inhibited for at least 72 h (72% inhibition at 72 h; Fig. 3*B*). Although a statistical analysis could not be performed on the pooled PBMC samples, S6K1 activity was also dramatically inhibited for up to 72 h in these samples (82% inhibition at 72 h; Fig. 3*C*). Thus, consistent with the antitumor efficacy of intermittent 5 mg/kg RAD001 treatment schedules in CA20948 tumor-bearing rats, a single administration of 5 mg/kg RAD001 resulted in long-term inactivation of S6K1 in tumors, skin, and PBMCs.

The Antitumor Efficacy of Intermittent RAD001 Treatment Schedules Is Dose Dependent: Correlation Between Efficacy and Prolonged Effects on mTOR Effectors in Rat PBMCs. Following the observation that intermittent RAD001 (5 mg/kg) treatment schedules significantly inhibited tumor growth, we explored the effect of RAD001 dose on the efficacy of weekly treatment schedules (Table 1, Experiments 2 and 3). As expected, 5 mg/kg/week RAD001 significantly suppressed CA20948 tumor growth as compared with vehicle controls (T/C, 14% and 24% at 7 and 8 days, respectively; $P < 0.05$). In contrast, although 0.5 mg/kg RAD001 caused a significant inhibition of tumor growth when administered daily (T/C, 23%), weekly administration of the same dose did not significantly affect tumor growth (T/C, 48%; $P > 0.05$). This apparent dose dependency of weekly RAD001 schedules was confirmed by a more stringent analysis comprising doses between 5 and 0.5 mg/kg (Table 1, Experiment 3). Statistically significant antitumor responses were observed with 3 and 2 mg/kg RAD001 (T/C, 36% and 32%, respectively), but not with 1 mg/kg (T/C, 45%). Interestingly, 3 mg/week elicited a similar antitumor response (T/C, 36%) as 0.5 mg/kg/day (×6/week; T/C, 30% and 23%). Because both these schedules involve administration of 3 mg/kg RAD001 per week, these data indicate that, with the same total RAD001 exposure, intermittent dosing schedules can elicit equivalent antitumor responses as daily schedules.

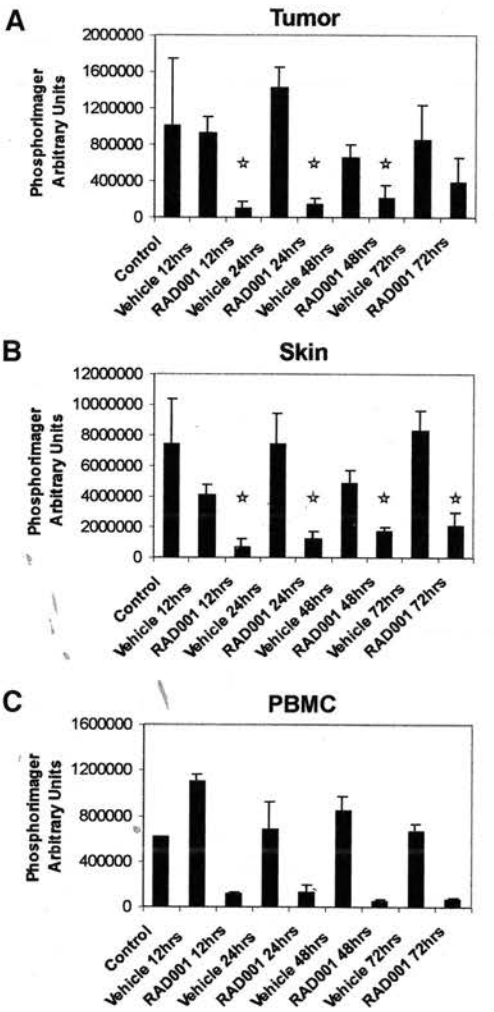

Fig. 3. RAD001 administration (5 mg/kg) causes prolonged inactivation of ribosomal protein S6 kinase 1 in tumors, skin, and PBMCs derived from CA20948 tumor-bearing rats. CA20948 tumor-bearing rats were treated once with 5 mg/kg RAD001 or vehicle (3 rats/group). After 12, 24, 48, and 72 h, tumor and skin samples were individually extracted. Blood obtained from rats within each treatment group was pooled, and peripheral blood mononuclear cells (PBMCs) were isolated and extracted. Assay of ribosomal protein S6 kinase 1 activity was performed using 40S ribosomal subunits as *in vitro* substrate. PhosphorImager quantifications of the S6 kinase assays are presented. *A* (*Tumor*) and *B* (*Skin*): data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C* (*PBMC*): data are means; *error bars* represent the range of duplicate assays.

To further investigate the dose dependency of weekly schedules in terms of effects on mTOR signaling in a surrogate tissue, the duration of S6K1 inactivation in response to a single administration of 0.5 *versus* 5 mg/kg RAD001 was determined in PBMCs derived from three non-tumor-bearing rats (Fig. 4, *A* and *B*). Whereas in vehicle controls, no effect on S6K1 activity could be observed (24 h after administration), a single administration of 5 mg/kg RAD001 resulted in statistically significant, prolonged inactivation of the S6K1 for up to 7 days (99% and 86% inhibition after 24 h and 7 days, respectively; $P < 0.05$). In comparison, 0.5 mg/kg RAD001 caused a significant inhibition of PBMC-derived S6K1 activity 24 h after administration

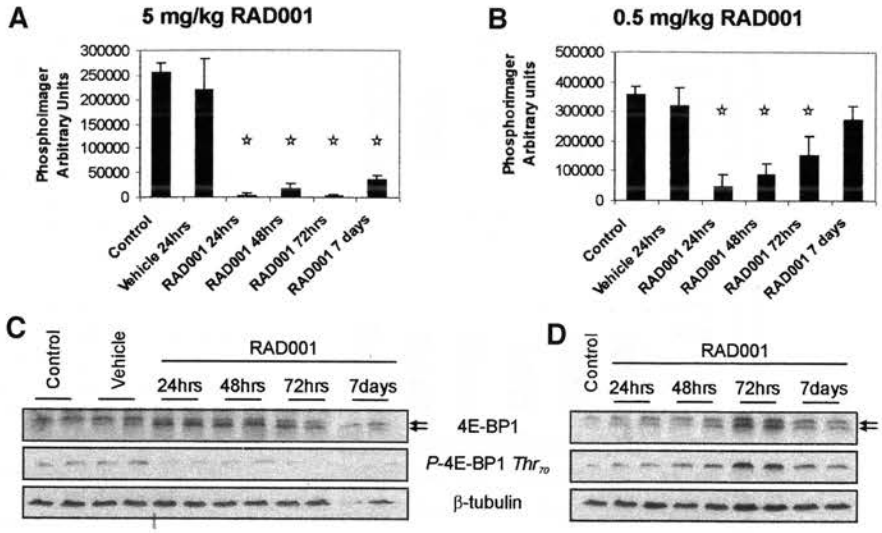

Fig. 4. Dose-dependent effects of RAD001 on ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) in peripheral blood mononuclear cells (PBMCs) obtained from non-tumor-bearing rats. Rats were treated with a single optimal (*A* and *C*) *versus* suboptimal (*B* and *D*) RAD001 dose (5 and 0.5 mg/kg, respectively) or vehicle (3 rats/group). At the times indicated, PBMC samples were collected and individually extracted. *A* and *B*, S6K1 was immunoprecipitated from equal amounts of protein extract, and S6K1 activity was assayed using 40S ribosomal subunits as a substrate. PhosphorImager quantification of the kinase assays are presented (means ± SD of $n = 3$ animals/group). *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C* and *D*, equal amounts of PBMC extracts were resolved by SDS-PAGE, transferred onto a polyvinylidene difluoride membrane, and probed for 4E-BP1 protein, phospho-threonine 70 4E-BP1 (*P-4E-BP1 Thr*$_{70}$), or β-tubulin as a loading control. *Arrows* denote hypophosphorylated (*bottom arrow*) and hyperphosphorylated (*top arrow*) forms of 4E-BP1 protein.

(88% inhibition); however, kinase activity began to recover after 48 h (75% inhibition) and was almost totally recovered after 7 days [23% inhibition; not significant ($P > 0.05$ *versus* controls)]. In contrast to effects on S6K1 activity, no effect on Thr70 phosphorylation or the electrophoretic mobility of 4E-BP1 was observed with the 0.5 mg/kg RAD001 dose, whereas decreased Thr70 phosphorylation and a shift to a lower migrating form were observed with the 5 mg/kg RAD001 dose (Fig. 4, *C* and *D*). The latter effect was maintained for 72 h, with evidence of recovery by 7 days.

The above observations indicate that RAD001 has dose-dependent effects on the mTOR pathway in rat PBMCs. Moreover, long-term effects are associated with a RAD001 dose shown to have significant antitumor efficacy with intermittent treatment schedules. To confirm this hypothesis, a more stringent RAD001 titration was also performed to analyze effects on PBMC-derived S6K1 activity after a single administration of 0.5, 1, 2, or 5 mg/kg RAD001 (Fig. 5). In all cases, inactivation of S6K1 was observed 24 h after RAD001 administration. However, at RAD001 doses that do not elicit a significant antitumor response with weekly schedules (0.5 and 1 mg/kg; see Table 1), evidence of recovery of S6K1 activity was already observed at 72 h (34% and 13% recovery *versus* untreated controls, respectively) and was dramatic at 7 days [73% and 61%, respectively; no significant inhibition of S6K1 ($P > 0.05$ *versus* controls)]. In contrast, at RAD001 doses that do elicit a significant antitumor response with weekly schedules (2 and 5 mg/kg; see Table 1), minimal recovery was observed at 72 h (3% and 1%, respectively) or 7 days [30% and 12%, respectively; significant inhibition of S6K1 ($P < 0.05$ *versus* controls)]. These data confirm that long-term inactivation of PBMC-derived S6K1 correlates with the antitumor efficacy of weekly RAD001 treatment schedules.

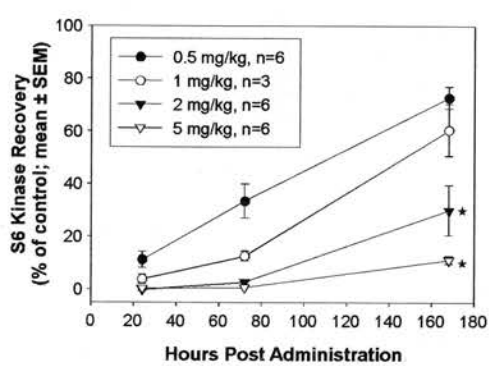

Fig. 5. Association between antitumor efficacy of weekly RAD001 schedules and long-term down-regulation of ribosomal protein S6 kinase 1 (S6K1) activity in rat peripheral blood mononuclear cells (PBMCs). Non-tumor-bearing rats were treated with a single RAD001 dose (0.5, 1, 2, or 5 mg/kg). At the times indicated, PBMC samples were collected and individually extracted and assayed for S6K1 activity. Data are presented as mean percentage recovery of S6K1 activity *versus* untreated control animals ± SEM of $n = 3$ or 6 S6K1 assays from different rat PBMC extracts. All data are derived from two separate experiments, except in the case of 1 mg/kg, where data from a single experiment are presented. *Stars* represent $P < 0.05$ *versus* untreated controls (ANOVA on ranks test).

S6K1 Activity Can Be Reproducibly Detected in Human PBMC Extracts: RAD001 Induces Concentration-Dependent S6K1 Inactivation *Ex Vivo*. To evaluate the potential of using mTOR effectors as biomarkers to evaluate RAD001 treatment schedules, we assessed whether basal S6K1 activity could also be measured in human PBMC extracts obtained from healthy volunteers. Human blood was collected into tubes containing either sodium citrate or EDTA as an anticoagulant, and PBMC extracts were prepared. Subsequent assay of S6K1 activity demonstrated that activity could indeed be detected in non-challenged human PBMCs derived from unrelated donors (Fig. 6*A*). Interestingly, S6K1 activity was reproducibly higher when the blood was initially collected in EDTA as compared with sodium citrate, a phenomenon potentially related to the different chelating properties of these anticoagulants. Using EDTA, a coefficient of variation of 10% was obtained among six assays on PBMC extracts prepared separately from the same blood donor, indicating good reproducibility of preparation (Fig. 6*B*). Accordingly, equivalent S6K1 protein levels were detected in the same extracts by immunoblot analysis (Fig. 6*B*). These results demonstrate that, in analogy with the rat PBMC data, basal S6K1 activity can be detected in human PBMCs. However, unlike control rat PBMC extracts (see Fig. 2*A*), there was no evidence of Thr70 phosphorylation in any of the human PBMC extracts analyzed,[5] an observation correlating with the fact that most of the 4E-BP1 protein was present in the hypophosphorylated/fast migrating state (when compared with 4E-BP1 derived from proliferating human tumor cells; Fig. 7*A, DMSO*). *Ex vivo* treatment of whole blood with 20 nM RAD001 for 30 min did not further increase protein mobility (Fig. 7*A, RAD001*), suggesting that 4E-BP1 is largely active as a translational repressor in human PBMCs. Hence, unlike the situation

[5] A. Boulay, S. Zumstein-Mecker, and H. A. Lane, unpublished data.

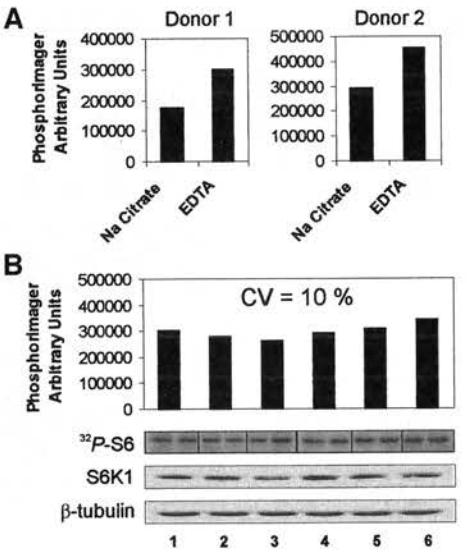

Fig. 6. Detection of ribosomal protein S6 kinase 1 (S6K1) activity in human peripheral blood mononuclear cells (PBMCs). Blood from healthy volunteers was withdrawn at the same time into tubes containing either sodium citrate or EDTA as an anticoagulant. PBMCs were immediately isolated and extracted. *A*, S6K1 was immunoprecipitated from equal amounts of PBMC protein extracts, and activity was assessed using 40S ribosomal subunits as a substrate. PhosphorImager quantifications are presented and represent basal S6K1 activity (means of duplicate assays of a single sample) from two unrelated donors. *B*, blood from a single volunteer was withdrawn into tubes containing EDTA as an anticoagulant and was split into six equal fractions. PBMCs were prepared separately and extracted from each blood fraction, and extracts were simultaneously assayed for S6K1 kinase activity. Phosphorimages (*^{32}P-S6*) and PhosphorImager quantifications (*graph*) of duplicate kinase assays are presented. As internal controls, equal amounts of PBMC protein extracts were analyzed by immunoblot for S6K1 and β-tubulin protein levels.

in rat, this protein may not be applicable as a biomarker for monitoring RAD001-specific effects on mTOR signaling in human PBMCs.

To assess whether human PBMC-derived S6K1 is inactivated in the presence of RAD001, whole blood from two unrelated healthy volunteers was treated *ex vivo* with either DMSO vehicle or increasing concentrations of RAD001 for 30 min, followed by isolation, extraction, and assay of PBMC-derived S6K1 activity (Fig. 7*B*). Treatment with 2 nM RAD001 diminished PBMC-derived S6K1 activity as compared with DMSO vehicle controls (44% and 63% inhibition in donor 1 and 2, respectively). Furthermore, increasing RAD001 concentrations led to almost complete inactivation of S6K1 (≥95% inhibition with ≥20 nM RAD001 in donor 1 and 2). These results demonstrate that RAD001 treatment of human blood *ex vivo* results in a concentration-dependent inactivation of PBMC-derived S6K1, supporting the notion that changes in PBMC-derived S6K1 activity could serve as a biomarker when assessing treatment schedules with rapamycin derivatives such as RAD001 in clinical trials for cancer.

DISCUSSION

The mTOR pathway plays a major role in cell proliferation by coupling cell growth with G_1-S progression. Compounds targeting the mTOR pathway have potential, therefore, for application in cancer treatment modalities (2, 3, 4). In this context, RAD001 potently inhibits the proliferation of numerous tumor cell lines *in vitro* and inhibits the growth of a range of human xenografts in nude mice (2, 27, 43–46).[6] Rapamycin and the rapamycin ester CCI-779 also present antitumor activity in a number of animal models of cancer (2, 24–26, 53, 55–59). However, although human pancreatic tumors have been reported in abstract form to be sensitive to CCI-779 (reviewed in Ref. 2), and mTOR/S6K1 signaling appears to be required for pancreatic cancer cell proliferation (60, 61), the work presented here is the first full publication demonstrating significant antitumor efficacy of a rapamycin derivative in an animal model of pancreatic cancer. Orally administered RAD001 was found to be well tolerated and to elicit antitumor potency equivalent to that of the cytotoxic agent 5-FU. Moreover, similar responses were achieved with daily or weekly RAD001 administrations, indicating that frequent drug administration is unnecessary to maintain an antitumor response. Although weekly rapamycin dosing schedules have been used previously (55, 56), a comparative analysis addressing the efficacy of daily *versus* weekly administration had not been performed. The fact that weekly RAD001 administration produces statistically significant antitumor responses in the CA20948 model is supported by a number of experimental observations. First, *in vitro* pulse treatment with either RAD001 (43) or rapamycin (51) causes prolonged down-regulation of the mTOR pathway in tumor cell lines. Indeed, Hosoi *et al.* (51) postulated that this phenomenon was due to the slow dissociation rate of the rapamycin·FKBP12 complex. Second, prolonged effects of CCI-779 on xenograft tumor growth were evident after cessation of daily treatment schedules (24, 53, 57), and antitumor responses have been

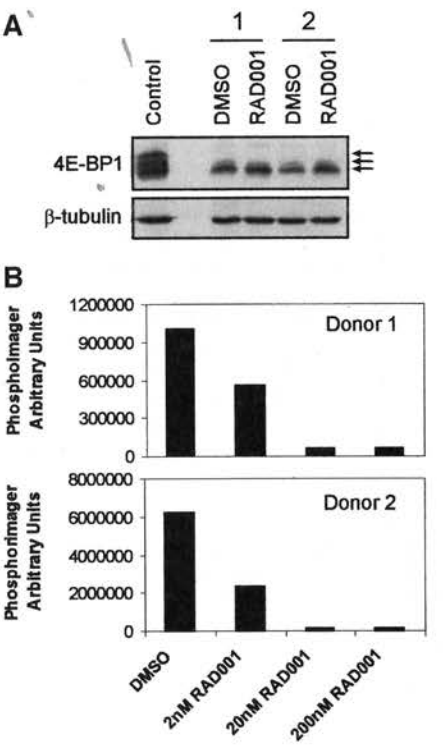

Fig. 7. Effects of *ex vivo* RAD001 treatment on ribosomal protein S6 kinase 1 activity and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) mobility in human PBMCs. *A*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with DMSO vehicle or 20 nM RAD001 for 30 min at room temperature, followed by PBMC isolation and extraction. Equal amounts of PBMC protein extracts were resolved by SDS-PAGE and transferred onto a polyvinylidene difluoride membrane. The membrane was probed for 4E-BP1 protein, with β-tubulin as a loading control. Human lung adenocarcinoma tumor cell lines lysates (*Control*; A549) were included as an example of 4E-BP1 mobility in a highly proliferative human cell population. *B*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with 2, 20, or 200 nM RAD001 or DMSO vehicle for 30 min at room temperature, followed by PBMC isolation and extraction. Ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of PBMC protein extract, and activity was assessed *in vitro* using 40S ribosomal subunits as a substrate. PhosphorImager quantifications of the kinase assay are presented and represent means of duplicate assays of a single sample.

[6] A. Boulay, T. O'Reilly, and H. A. Lane, unpublished data.

reported in Phase I clinical trials with weekly CCI-779 administration (2, 4).

One advantage of administering RAD001 intermittently in oncology is the avoidance of prolonged immunosuppression (1). In this context, the minimal effective dose of RAD001 in stringent rat kidney and heart allotransplantation models is ≥5 mg/kg administered daily (47, 52). Moreover, the immunosuppressive capacity of RAD001 (everolimus in combination with cyclosporin) in transplant patients has been related to maintenance of blood drug trough levels (1, 62), suggesting that constant drug exposure is required to provide clinically relevant immunosuppression. The demonstration that weekly administration of RAD001 (at doses of 2–5 mg/kg) is sufficient to elicit a significant antitumor response indicates that the above premise does not apply to oncology. Indeed, in support of this notion, as compared with daily RAD001 administration (2.5 mg/kg), a 5 mg/kg weekly RAD001 regimen allows a 20-fold higher T-cell-dependent antibody response, as measured by serum IgG antibody titers after immunization of rats with dinitrophenol-coupled keyhole limpet hemocyanogen.[3] Hence, intermittent dosing allows for differentiation between immunosuppressive and antitumor effects, a possibility also suggested from preliminary clinical data (2, 4). The basis of this is presumably related to the biology of T cells as compared with tumor cells. In this respect, rapamycin potently prevents resting T cells from entering the cell cycle in response to interleukin 2 but has little effect on proliferating T cells (63, 64). This may explain why constant drug exposure is required in the immunosuppression setting, as opposed to the antitumor setting where the proliferation of cycling tumor cells is potently inhibited (2, 4) for long periods (51). This possibility is worthy of further investigation.

A limited analysis of the effects of rapamycin derivatives on mTOR effectors in tumor material derived from xenograft models was reported previously (24, 53). Until now, however, a comprehensive analysis had not been performed. Similarly, the possibility that the efficacy of intermittent treatment schedules correlates with long-term effects on the mTOR pathway in tumors and surrogate tissues had not been addressed. This prompted us to profile RAD001-mediated effects on mTOR signaling in CA20948 tumors and normal rat tissues. Mitogen-induced, multisite phosphorylation of the translational suppressor protein 4E-BP1 is known to cause its release from the initiation factor eIF-4E, thereby facilitating formation of the eIF-4F initiation complex and derepression of cap-dependent mRNA translation (2, 5). Indeed, the 4E-BP1 protein has been proposed to be a direct substrate for the mTOR kinase (34, 41, 42). Moreover, rapamycin treatment of cell lines decreases 4E-BP1 phosphorylation, resulting in increased affinity for eIF-4E *in vitro* (2, 5). Consistent with these observations, a single administration of 5 mg/kg RAD001 to three tumor-bearing rats reproducibly inhibited 4E-BP1 phosphorylation in tumors, skin, and PBMCs at 24 h, in accordance with changes in 4E-BP1 electrophoretic mobility and increased 4E-BP1·eIF-4E association. In the same animals, S6K1 signaling was virtually abolished in all tissues. The physiological downstream target of the S6K1 is the S6 40S ribosomal protein (12, 65). Hence, reductions in S6 phosphorylation are expected to parallel S6K1 inactivation, as observed in CA20948 tumor extracts. However, because S6 phosphorylation could not be detected in either skin or PBMC control extracts, no such correlation could be made in these tissues. This failure to detect S6 phosphorylation could reflect a reduced proliferation index as compared with the aggressively growing CA20948 tumors. Strikingly, and in agreement with previous *in vitro* analyses (43, 51), tumors, skin, and PBMC extracts derived from rats treated with a single 5 mg/kg RAD001 dose demonstrated prolonged inactivation of the S6K1 for ≥72 h. Taken together, these data suggest that RAD001-specific effects on 4E-BP1 and S6K1 activity can be reproducibly observed in tumors and surrogate tissues. Moreover, long-term effects of RAD001 on S6K1 activity occur with a dose of RAD001 known to elicit significant antitumor responses with intermittent treatment schedules.

The observation that the mTOR pathway is affected for long periods of time in tumors and PBMCs is consistent with preliminary pharmacokinetic studies performed in CA20948 tumor-bearing rats. Pharmacokinetic measurements after a single RAD001 administration (5 mg/kg, over a 72 h period) demonstrated good bioavailability/efficient tumor penetration (maximal concentrations in blood and tumor, ~200 and ~700 nM, respectively) and prolonged residency [RAD001 half-life, ~20–22 h.[7] Unfortunately, a precise correlation of pharmacokinetic parameters with antiproliferative effects in tumors is difficult in this model because of the inability to determine *in vitro* IC_{50} values with the nonculturable CA20948 line. However, the efficient tumor accumulation and relatively long half-life of RAD001 provide further rationale for the long-term effects observed in this model.

Sequential tumor sampling is difficult in the clinical setting, necessitating some reliance on surrogate tissue to assess pharmacodynamic effects of antitumor agents. For this reason, the possibility of using PBMCs as a source for biomarker analysis when assessing RAD001 treatment schedules was evaluated. Detailed efficacy experiments demonstrated that antitumor response to weekly administration of RAD001 was dose dependent. Moreover, significant antitumor responses were associated with long-term effects on the mTOR pathway in PBMCs. Interestingly, PBMC-derived 4E-BP1 was unaffected by a suboptimal RAD001 dose (0.5 mg/kg), despite transient effects on S6K1 activity. This suggests that S6K1 is a more sensitive marker of RAD001 exposure in PBMCs than 4E-BP1. Indeed, all doses of RAD001 evaluated elicited a dramatic inhibition of PBMC-derived S6K1 after 24 h. However, the rate at which S6K1 activity subsequently recovered differed, with RAD001 doses that were efficacious with weekly schedules causing more profound long-term effects on S6K1 activity (≥7 days). The demonstration that the mTOR pathway is affected in PBMCs for a week after administration of 5 mg/kg RAD001 may be interpreted as being contrary to our observations that weekly treatment with this dose is suboptimal in terms of suppression of T-cell-dependent antigen responses. To reconcile these observations, one has to consider that T- and B-cell proliferative responses to foreign antigen presentation occur mainly in the secondary lymphoid organs (64). Here we assayed S6K1 derived from PBMCs, a source that does not reflect the situation in these organs. We therefore speculate that, using weekly schedules, there is a possibility to recover T-cell responses, a phenomenon that may also reflect the pharmacokinetic characteristics of RAD001.

To most efficiently exploit the pharmacological profile of targeted agents such as RAD001, it is important to carefully monitor the dose given to a cancer patient, especially considering the observation that rapamycin can be less effective as an antitumor agent in animal models if overdosed (59). The ease of human PBMC preparation suggests that this could be a valuable surrogate tissue when establishing treatment regimens for RAD001 in clinical trials for oncology. Based on this premise, S6K1 activity could be reproducibly assayed in PBMC extracts prepared from healthy volunteers, and RAD001 treatment of whole blood *ex vivo* resulted in concentration-dependent inactivation of the kinase. In contrast, despite promising results in tumor extracts derived from xenograft models (53) and suggestions that 4E-BP1 phosphorylation could be used as a confirmatory measure of mTOR inhibition in PBMCs (66), we have shown that 4E-BP1 phosphorylation cannot be detected in human PBMCs. During the

[7] T. O'Reilly and L. McMahon, unpublished data.

revision of this manuscript, others (66, 67) also reported on the potential for PBMC-derived S6K1 activity measurements to aid pharmacodynamic evaluation of rapamycin derivatives. Analysis of cancer patient-derived PBMCs after i.v. administration of 25, 75, and 250 mg CCI-779 demonstrated inactivation of PBMC-derived S6K1 for up to 8 days, with no evidence of dose dependency at the doses used (66–68). Although a limited feasibility study in nine patients indicated an association between time to disease progression and the degree of inhibition of S6K1 24 h after CCI-779 administration, no conclusions were drawn regarding the predictive nature of this biomarker or associated implications of the long-term S6K1 inactivation observed in patients (67). Our data provide a strong experimental rationale for analyzing long-term effects on PBMC-derived S6K1 activity when establishing weekly administration schedules. Indeed, recent Phase I trials with weekly administration of RAD001 in patients with advanced cancer have demonstrated a clear association between RAD001 dose and the recovery of PBMC-derived S6K1 activity over a ≥7-day period (69). The value of these observations in terms of prediction of patient response is now being pursued in clinical trials of RAD001 in oncology.

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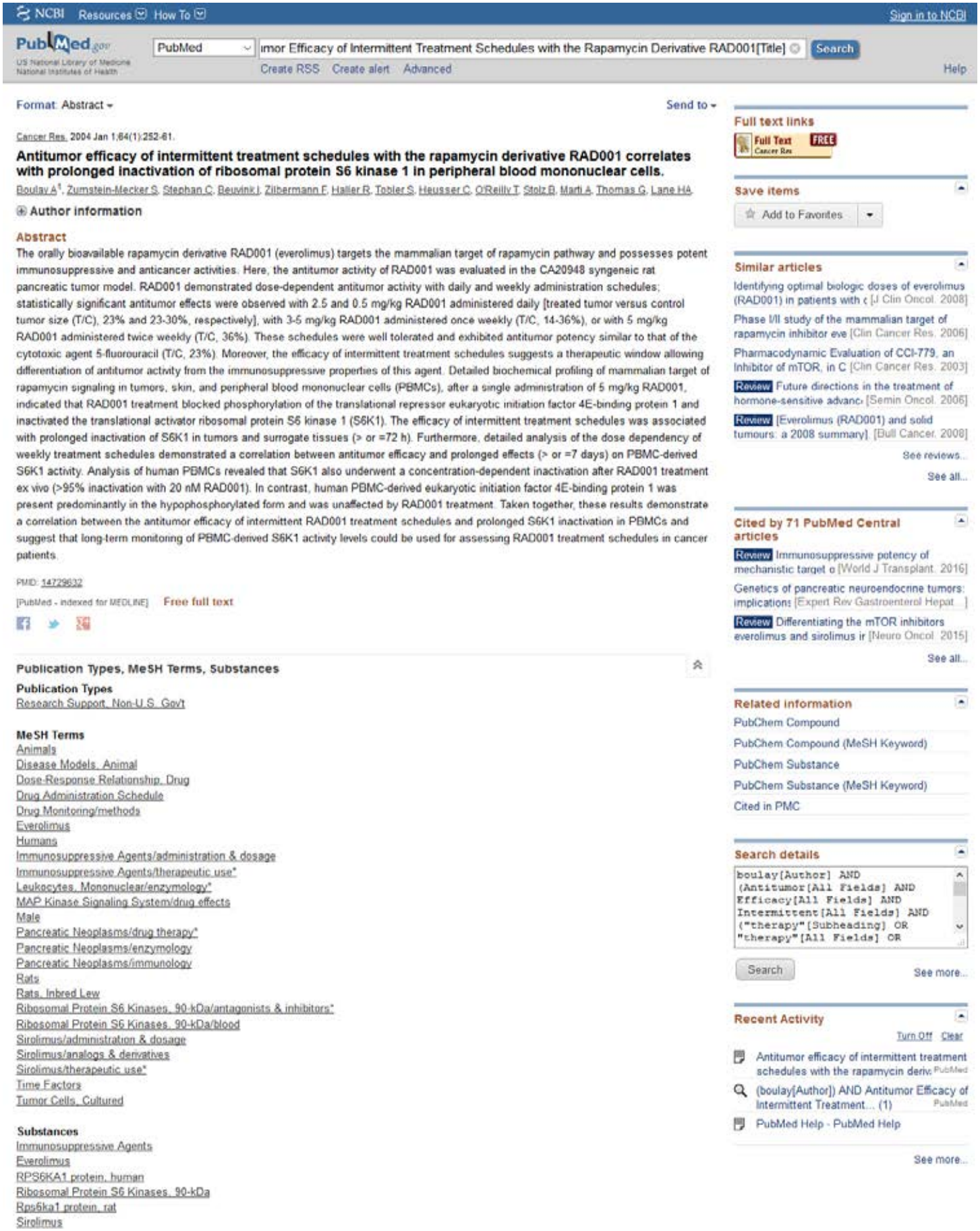
REFERENCES

1. Nashan, B. Early clinical experience with a novel rapamycin derivative. Ther. Drug Monit., *24:* 53–58, 2002.
2. Huang, S., and Houghton, P. J. Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic. Curr. Opin. Investig. Drugs, *3:* 295–304, 2002.
3. Mita, M. M., Mita, A., and Rowinski, E. K. Mammalian target of rapamycin: a new molecular target for breast cancer. Clin. Breast Cancer, *4:* 126–137, 2003.
4. Hidalgo, M., and Rowinsky, E. K. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. Oncogene, *19:* 6680–6686, 2000.
5. Gingras, A. C., Raught, B., and Sonenberg, N. Regulation of translation initiation by FRAP/mTOR. Genes Dev., *15:* 807–826, 2001.
6. Tibbetts, R. S., and Abraham, R. T. PI3K-related kinases: roles in cell-cycle regulation and DNA damage responses. *In*: J. S. Gutkind (eds.), Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases, Vol. 5, pp. 267–301. Totowa, NJ: Humana Press, 2000.
7. Desai, B. N., Myers, B. R., and Schreiber, S. L. FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. Proc. Natl. Acad. Sci. USA, *99:* 4319–4324, 2002.
8. Hara, K., Yonezawa, K., Weng, Q. P., Kozlowski, M. T., Belham, C., and Avruch, J. Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 through a common effector mechanism. J. Biol. Chem., *273:* 14484–14494, 1998.
9. Xu, G., Kwon, G., Marshall, C. A., Lin, T. A., Lawrence, J. C., Jr., and McDaniel, M. L. Branched-chain amino acids are essential in the regulation of PHAS-I and p70 S6 kinase by pancreatic β-cells. A possible role in protein translation and mitogenic signaling. J. Biol. Chem., *273:* 28178–28184, 1998.
10. Iiboshi, Y., Papst, P. J., Kawasome, H., Hosoi, H., Abraham, R. T., Houghton, P. J., and Terada, N. Amino acid-dependent control of p70(s6k). involvement of tRNA aminoacylation in the regulation. J. Biol. Chem., *274:* 1092–1099, 1999.
11. Dennis, P. B., Jaeschke, A., Saitoh, M., Fowler, B., Kozma, S. C., and Thomas, G. Mammalian TOR: a homeostatic ATP sensor. Science (Wash. DC), *294:* 1102–1105, 2001.
12. Dufner, A., and Thomas, G., Ribosomal S6 kinase signaling and the control of translation. Exp. Cell Res., *253:* 100–109, 1999.
13. Hashemolhosseini, S., Nagamine, Y., Morley, S. J., Desrivieres, S., Mercep, L., and Ferrari, S. Rapamycin inhibition of the G_1 to S transition is mediated by effects on cyclin D1 mRNA and protein stability. J. Biol. Chem., *273:* 14424–14429, 1998.
14. West, M. J., Stoneley, M., and Willis, A. E. Translational induction of the c-myc oncogene via activation of the FRAP/TOR signalling pathway. Oncogene, *17:* 769–780, 1998.
15. Peng, T., Golub, T. R., and Sabatini, D. M. The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. Mol. Cell. Biol., *22:* 5575–5584, 2002.
16. Fingar, D. C., Salama, S., Tsou, C., Harlow, E., and Blenis, J. Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. Genes Dev., *16:* 1472–1487, 2002.
17. Scott, P. H., Brunn, G. J., Kohn, A. D., Roth, R. A., and Lawrence, J. C., Jr. Evidence of insulin-stimulated phosphorylation and activation of the mammalian target of rapamycin mediated by a protein kinase B signaling pathway. Proc. Natl. Acad. Sci. USA, *95:* 7772–7777, 1998.
18. Nave, B. T., Ouwens, M., Withers, D. J., Alessi, D. R., and Shepherd, P. R. Mammalian target of rapamycin is a direct target for protein kinase B: identification of a convergence point for opposing effects of insulin and amino-acid deficiency on protein translation. Biochem. J., *344:* 427–431, 1999.
19. Sekulic, A., Hudson, C. C., Homme, J. L., Yin, P., Otterness, D. M., Karnitz, L. M., and Abraham, R. T. A direct linkage between the phosphoinositide 3-kinase-AKT signaling pathway and the mammalian target of rapamycin in mitogen-stimulated and transformed cells. Cancer Res., *60:* 3504–3513, 2000.
20. Inoki, K., Li, Y., Zhu, T., Wu, J., and Guan, K. L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat. Cell Biol., *4:* 648–657, 2002.
21. Potter, C. J., Pedraza, L. G., and Xu, T. Akt regulates growth by directly phosphorylating Tsc2. Nat. Cell Biol., *4:* 658–665, 2002.
22. Garami, A., Zwartkruis, F. J., Nobukuni, T., Joaquin, M., Roccio, M., Stocker, H., Kozma, S. C., Hafen, E., Bos, J. L., and Thomas, G. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mol. Cell, *11:* 1457–1466, 2003.
23. Inoki, K., Li, Y., Xu, T., and Guan, K. L. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes Dev., *17:* 1829–1834, 2003.
24. Neshat, M. S., Mellinghoff, I. K., Tran, C., Stiles, B., Thomas, G., Petersen, R., Frost, P., Gibbons, J. J., Wu, H., and Sawyers, C. L. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc. Natl. Acad. Sci. USA, *98:* 10314–10319, 2001.
25. Podsypanina, K., Lee, R. T., Politis, C., Hennessy, I., Crane, A., Puc, J., Neshat, M., Wang, H., Yang, L., Gibbons, J., Frost, P., Dreisbach, V., Blenis, J., Gaciong, Z., Fisher, P., Sawyers, C., Hedrick-Ellenson, L., and Parsons, R. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in PTEN+/− mice. Proc. Natl. Acad. Sci. USA, *98:* 10320–10325, 2001.
26. Shi, Y., Gera, J., Hu, L., Hsu, J. H., Bookstein, R., Li, W., and Lichtenstein, A. Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779. Cancer Res., *62:* 5027–5034, 2002.
27. Lane, H. A., Boulay, A., Hattenberger, M., Maira, S-M., Thomas, G., Merlo, A., and O'Reilly, T. The orally active rapamycin derivative RAD001 has potential as an antitumor agent with a broad antiproliferative activity: PTEN as a molecular determinant of response. Proc. Am. Assoc. Cancer Res., *44:* 314, 2003.
28. Kim, D. H., Sarbassov, D. D., Ali, S. M., King, J. E., Latek, R. R., Erdjument-Bromage, H., Tempst, P., and Sabatini, D. M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell, *110:* 163–175, 2002.
29. Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J., and Yonezawa, K. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell, *110:* 177–189, 2002.
30. Kim, D. H., Sarbassov dos, D., Ali, S. M., Latek, R. R., Guntur, K. V., Erdjument-Bromage, H., Tempst, P., and Sabatini, D. M. GβL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol. Cell, *11:* 895–904, 2003.
31. Schalm, S. S., and Blenis, J. Identification of a conserved motif required for mTOR signaling. Curr. Biol., *12:* 632–639, 2002.
32. Schalm, S. S., Fingar, D. C., Sabatini, D. M., and Blenis, J. TOS motif-mediated raptor binding regulates 4E-BP1 multisite phosphorylation and function. Curr. Biol., *13:* 797–806, 2003.
33. Nojima, H., Tokunaga, C., Eguchi, S., Oshiro, N., Hidayat, S., Yoshino, K., Hara, K., Tanaka, N., Avruch, J., and Yonezawa, K. The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. J. Biol. Chem., *278:* 15461–15464, 2003.
34. Gingras, A. C., Gygi, S. P., Raught, B., Polakiewicz, R. D., Abraham, R. T., Hoekstra, M. F., Aebersold, R., and Sonenberg, N. Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism. Genes Dev., *13:* 1422–1437, 1999.
35. Mothe-Satney, I., Brunn, G. J., McMahon, L. P., Capaldo, C. T., Abraham, R. T., and Lawrence, J. C., Jr. Mammalian target of rapamycin-dependent phosphorylation of PHAS-I in four (S/T)P sites detected by phospho-specific antibodies. J. Biol. Chem., *275:* 33836–33843, 2000.
36. Jefferies, H. B., Reinhard, C., Kozma, S. C., and Thomas, G. Rapamycin selectively represses translation of the "polypyrimidine tract" mRNA family. Proc. Natl. Acad. Sci. USA, *91:* 4441–4445, 1994.
37. Jefferies, H. B., Fumagalli, S., Dennis, P. B., Reinhard, C., Pearson, R. B., and Thomas, G. Rapamycin suppresses 5′TOP mRNA translation through inhibition of p70s6k. EMBO J., *16:* 3693–3704, 1997.
38. Meyuhas, O. Synthesis of the translational apparatus is regulated at the translational level. Eur. J. Biochem., *267:* 6321–6330, 2000.
39. Pearson, R. B., Dennis, P. B., Han, J. W., Williamson, N. A., Kozma, S. C., Wettenhall, R. E., and Thomas, G. The principal target of rapamycin-induced p70s6k inactivation is a novel phosphorylation site within a conserved hydrophobic domain. EMBO J., *14:* 5279–5287, 1995.

40. Peterson, R. T., Beal, P. A., Comb, M. J., and Schreiber, S. L. FKBP12-rapamycin-associated protein (FRAP) autophosphorylates at serine 2481 under translationally repressive conditions. J. Biol. Chem., *275:* 7416–7423, 2000.
41. Brunn, G. J., Hudson, C. C., Sekulic, A., Williams, J. M., Hosoi, H., Houghton, P. J., Lawrence, J. C., Jr., and Abraham, R. T. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. Science (Wash. DC), *277:* 99–101, 1997.
42. Burnett, P. E., Barrow, R. K., Cohen, N. A., Snyder, S. H., and Sabatini, D. M. RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. Proc. Natl. Acad. Sci. USA, *95:* 1432–1437, 1998.
43. Beuvink, I., O'Reilly, T., Zumstein-Mecker, S., Zilbermann, F., Sedrani, R., Kozma, S. C., Thomas, G., and Lane, H. A. Antitumor activity of RAD001, an orally active rapamycin derivative. Proc. Am. Assoc. Cancer Res., *42:* 366, 2001.
44. O'Reilly, T., Vaxelaire, J., Muller, M., Fiebig, H. H., Hattenberger, M., and Lane, H. A. *In vivo* activity of RAD001, an orally active rapamycin derivative, in experimental tumor models. Proc. Am. Assoc. Cancer Res., *43:* 71, 2002.
45. Majewski, M., Korecka, M., Kossev, P., Li, S., Goldman, J., Moore, J., Silberstein, L. E., Nowell, P. C., Schuler, W., Shaw, L. M., and Wasik, M. A. The immunosuppressive macrolide RAD inhibits growth of human Epstein-Barr virus-transformed B lymphocytes *in vitro* and *in vivo*: a potential approach to prevention and treatment of posttransplant lymphoproliferative disorders. Proc. Natl. Acad. Sci. USA, *97:* 4285–4290, 2000.
46. Majewski, M., Korecka, M., Joergensen, J., Fields, L., Kossev, P., Schuler, W., Shaw, L., and Wasik, M. A. Immunosuppressive TOR kinase inhibitor everolimus (RAD) suppresses growth of cells derived from posttransplant lymphoproliferative disorder at allograft-protecting doses. Transplantation, *75:* 1710–1717, 2003.
47. Schuler, W., Sedrani, R., Cottens, S., Häberlin, B., Schulz, M., Schuurman, H. J., Zenke, G., Zerwes, H. G., and Schreier, M. H. SDZ RAD, a new rapamycin derivative: pharmacological properties *in vitro* and *in vivo*. Transplantation, *64:* 36–42, 1997.
48. Lane, H. A., Beuvink, I., Motoyama, A. B., Daly, J. M., Neve, R. M., and Hynes, N. E. ErbB2 potentiates breast tumor proliferation through modulation of p27(Kip1)-Cdk2 complex formation: receptor overexpression does not determine growth dependency. Mol. Cell. Biol., *20:* 3210–3223, 2000.
49. Olayioye, M. A., Graus-Porta, D., Beerli, R. R., Rohrer, J., Gay, B., and Hynes, N. E. ErbB-1 and ErbB-2 acquire distinct signaling properties dependent upon their dimerization partner. Mol. Cell. Biol., *18:* 5042–5051, 1998.
50. Lane, H. A., and Thomas, G. Purification and properties of mitogen-activated S6 kinase from rat liver and 3T3 cells. Methods Enzymol., *200:* 268–291, 1991.
51. Hosoi, H., Dilling, M. B., Shikata, T., Liu, L. N., Shu, L., Ashmun, R. A., Germain, G. S., Abraham, R. T., and Houghton, P. J. Rapamycin causes poorly reversible inhibition of mTOR and induces p53-independent apoptosis in human rhabdomyosarcoma cells. Cancer Res., *59:* 886–894, 1999.
52. Schuurman, H. J., Cottens, S., Fuchs, S., Joergensen, J., Meerloo, T., Sedrani, R., Tanner, M., Zenke, G., and Schuler, W. SDZ RAD, a new rapamycin derivative: synergism with cyclosporine. Transplantation, *64:* 32–35, 1997.
53. Dudkin, L., Dilling, M. B., Cheshire, P. J., Harwood, F. C., Hollingshead, M., Arbuck, S. G., Travis, R., Sausville, E. A., and Houghton, P. J. Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition. Clin. Cancer Res., *7:* 1758–1764, 2001.
54. Jiang, Y. P., Ballou, L. M., and Lin, R. Z. Rapamycin-insensitive regulation of 4E-BP1 in regenerating rat liver. J. Biol. Chem., *276:* 10943–10951, 2001.
55. Eng, C. P., Sehgal, S. N., and Vezina, C. Activity of rapamycin (AY-22.989) against transplanted tumors. J. Antibiot., *37:* 1231–1237, 1984.
56. Houchens, D. P., Ovejera, A. A., Riblet, S. M., and Slagel, D. E. Human brain tumor xenografts in nude mice as a chemotherapy model. Eur. J. Cancer Clin. Oncol., *19:* 799–805, 1983.
57. Geoerger, B., Kerr, K., Tang, C. B., Fung, K. M., Powell, B., Sutton, L. N., Phillips, P. C., and Janss, A. J. Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy. Cancer Res., *61:* 1527–1532, 2001.
58. Yu, K., Toral-Barza, L., Discafani, C., Zhang, W. G., Skotnicki, J., Frost, P., and Gibbons, J. J. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. Endocr. Relat. Cancer, *8:* 249–258, 2001.
59. Guba, M., von Breitenbuch, P., Steinbauer, M., Koehl, G., Flegel, S., Hornung, M., Bruns, C. J., Zuelke, C., Farkas, S., Anthuber, M., Jauch, K. W., and Geissler, E. K. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat. Med., *8:* 128–135, 2002.
60. Grewe, M., Gansauge, F., Schmid, R. M., Adler, G., and Seufferlein, T. Regulation of cell growth and cyclin D1 expression by the constitutively active FRAP-p70s6K pathway in human pancreatic cancer cells. Cancer Res., *59:* 3581–3587, 1999.
61. Shah, S. A., Potter, M. W., Ricciardi, R., Perugini, R. A., and Callery, M. P. FRAP-p70S6K signaling is required for pancreatic cancer cell proliferation. J. Surg. Res., *97:* 123–130, 2001.
62. Kovarik, J. M., Kaplan, B., Tedesco Silva, H., Kahan, B. D., Dantal, J., Vitko, S., Boger, R., and Rordorf, C. Exposure-response relationships for everolimus in *de novo* kidney transplantation: defining a therapeutic range. Transplantation, *73:* 920–925, 2002.
63. Terada, N., Franklin, R. A., Lucas, J. J., Blenis, J., and Gelfand, E. W. Failure of rapamycin to block proliferation once resting cells have entered the cell cycle despite inactivation of p70 S6 kinase. J. Biol. Chem., *268:* 12062–12068, 1993.
64. Zenke, G., Strittmatter, U., Fuchs, S., Quesniaux, V. F., Brinkmann, V., Schuler, W., Zurini, M., Enz, A., Billich, A., Sanglier, J. J., and Fehr, T. Sanglifehrin A, a novel cyclophilin-binding compound showing immunosuppressive activity with a new mechanism of action. J. Immunol., *166:* 7165–7171, 2001.
65. Chung, J., Kuo, C. J., Crabtree, G. R., and Blenis, J. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. Cell, *69:* 1227–1236, 1992.
66. Harding, M. W. Immunophilins, mTOR, and pharmacodynamic strategies for a targeted cancer therapy. Clin. Cancer Res., *9:* 2882–2886, 2003.
67. Peralba, J. M., deGraffenried, L., Friedrichs, W., Fulcher, L., Grünwald, V., Weiss, G., and Hidalgo, M. Pharmacodynamic evaluation of CCI-779, an inhibitor of mTOR, in cancer patients. Clin. Cancer Res., *9:* 2887–2892, 2003.
68. Stadler, W., Logan, T., Dutcher, J., Hudes, G., Park, Y., Marshall, B., Boni, J., and Dukart, J. A randomized double-blind phase 2 study of intravenous CCI-779 administered weekly to patients with advanced renal cell carcinoma. Proc. Am. Soc. Clin. Oncol., *21:* 10a, 2002.
69. O'Donnell, A., Faivre, S., Judson, I., Delbado, C., Brock, C., Lane, H., Shand, N., Hazell, K., Armand, J-P., and Raymond, E. Phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours. Proc. Am. Soc. Clin. Oncol., *22:* 200, 2003.

Attachment 2e: MEDLINE/PubMed record for Boulay



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Cancer Res. 2004 Jan 1;64(1):252-61.

Antitumor efficacy of intermittent treatment schedules with the rapamycin derivative RAD001 correlates with prolonged inactivation of ribosomal protein S6 kinase 1 in peripheral blood mononuclear cells.

Boulay A[1], Zumstein-Mecker S, Stephan C, Beuvink I, Zilbermann F, Haller R, Tobler S, Heusser C, O'Reilly T, Stolz B, Marti A, Thomas G, Lane HA

Author information

Abstract

The orally bioavailable rapamycin derivative RAD001 (everolimus) targets the mammalian target of rapamycin pathway and possesses potent immunosuppressive and anticancer activities. Here, the antitumor activity of RAD001 was evaluated in the CA20948 syngeneic rat pancreatic tumor model. RAD001 demonstrated dose-dependent antitumor activity with daily and weekly administration schedules; statistically significant antitumor effects were observed with 2.5 and 0.5 mg/kg RAD001 administered daily [treated tumor versus control tumor size (T/C), 23% and 23-30%, respectively], with 3-5 mg/kg RAD001 administered once weekly (T/C, 14-36%), or with 5 mg/kg RAD001 administered twice weekly (T/C, 36%). These schedules were well tolerated and exhibited antitumor potency similar to that of the cytotoxic agent 5-fluorouracil (T/C, 23%). Moreover, the efficacy of intermittent treatment schedules suggests a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical profiling of mammalian target of rapamycin signaling in tumors, skin, and peripheral blood mononuclear cells (PBMCs), after a single administration of 5 mg/kg RAD001, indicated that RAD001 treatment blocked phosphorylation of the translational repressor eukaryotic initiation factor 4E-binding protein 1 and inactivated the translational activator ribosomal protein S6 kinase 1 (S6K1). The efficacy of intermittent treatment schedules was associated with prolonged inactivation of S6K1 in tumors and surrogate tissues (> or =72 h). Furthermore, detailed analysis of the dose dependency of weekly treatment schedules demonstrated a correlation between antitumor efficacy and prolonged effects (> or =7 days) on PBMC-derived S6K1 activity. Analysis of human PBMCs revealed that S6K1 also underwent a concentration-dependent inactivation after RAD001 treatment ex vivo (>95% inactivation with 20 nM RAD001). In contrast, human PBMC-derived eukaryotic initiation factor 4E-binding protein 1 was present predominantly in the hypophosphorylated form and was unaffected by RAD001 treatment. Taken together, these results demonstrate a correlation between the antitumor efficacy of intermittent RAD001 treatment schedules and prolonged S6K1 inactivation in PBMCs and suggest that long-term monitoring of PBMC-derived S6K1 activity levels could be used for assessing RAD001 treatment schedules in cancer patients.

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Immunosuppressive Agents/therapeutic use*
Leukocytes, Mononuclear/enzymology*
MAP Kinase Signaling System/drug effects
Male
Pancreatic Neoplasms/drug therapy*
Pancreatic Neoplasms/enzymology
Pancreatic Neoplasms/immunology
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Rats, Inbred Lew
Ribosomal Protein S6 Kinases, 90-kDa/antagonists & inhibitors*
Ribosomal Protein S6 Kinases, 90-kDa/blood
Sirolimus/administration & dosage
Sirolimus/analogs & derivatives
Sirolimus/therapeutic use*
Time Factors
Tumor Cells, Cultured

Substances
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Experimental Therapeutics, Molecular Targets, and Chemical Biology

Antitumor Efficacy of Intermittent Treatment Schedules with the Rapamycin Derivative RAD001 Correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells

Anne Boulay, Sabine Zumstein-Mecker, Christine Stephan, Iwan Beuvink, Frederic Zilbermann, Roland Haller, Sonja Tobler, Christoph Heusser, Terence O'Reilly, Barbara Stolz, Andreas Marti, George Thomas, Heidi A. Lane

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Abstract

The orally bioavailable rapamycin derivative RAD001 (everolimus) targets the mammalian target of rapamycin pathway and possesses potent immunosuppressive and anticancer activities. Here, the antitumor activity of RAD001 was evaluated in the CA20948 syngeneic rat pancreatic tumor model. RAD001 demonstrated dose-dependent antitumor activity with daily and weekly administration schedules; statistically significant antitumor effects were observed with 2.5 and 0.5 mg/kg RAD001 administered daily [treated tumor *versus* control tumor size (T/C), 23% and 23–30%, respectively], with 3–5 mg/kg RAD001 administered once weekly (T/C, 14–36%), or with 5 mg/kg RAD001 administered twice weekly (T/C, 36%). These schedules were well tolerated and exhibited antitumor potency similar to that of the cytotoxic agent 5-fluorouracil (T/C, 23%). Moreover, the efficacy of intermittent treatment schedules suggests a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical profiling of mammalian target of rapamycin signaling in tumors, skin, and peripheral blood mononuclear cells (PBMCs), after a single administration of 5 mg/kg RAD001, indicated that RAD001 treatment blocked phosphorylation of the translational repressor eukaryotic initiation factor 4E-binding protein 1 and inactivated the translational activator ribosomal protein S6 kinase 1 (S6K1). The efficacy of intermittent treatment schedules was associated with prolonged inactivation of S6K1 in tumors and surrogate tissues (≥72 h). Furthermore, detailed analysis of the dose dependency of weekly treatment schedules demonstrated a correlation between antitumor efficacy and prolonged effects (≥7 days) on PBMC-derived S6K1 activity. Analysis of human PBMCs revealed that S6K1 also underwent a concentration-dependent inactivation after RAD001 treatment *ex vivo* (>95% inactivation with 20 nM RAD001). In contrast, human PBMC-derived

eukaryotic initiation factor 4E-binding protein 1 was present predominantly in the hypophosphorylated form and was unaffected by RAD001 treatment. Taken together, these results demonstrate a correlation between the antitumor efficacy of intermittent RAD001 treatment schedules and prolonged S6K1 inactivation in PBMCs and suggest that long-term monitoring of PBMC-derived S6K1 activity levels could be used for assessing RAD001 treatment schedules in cancer patients.

INTRODUCTION

RAD001 (everolimus), an orally bioavailable derivative of rapamycin, is a macrolide antifungal antibiotic that demonstrates potent antiproliferative effects against a variety of mammalian cell types. Specifically, RAD001 inhibits cytokine-driven lymphocyte proliferation (1), as well as the proliferation of human tumor-derived cells grown either in culture or as tumors in animal models (2, 3). As a result of these properties, RAD001 is being clinically developed both as an immunosuppressant for prevention of allograft rejection (Certican; Ref. 1) and as a novel therapeutic in the fight against human cancer (2, 3, 4).

RAD001, like rapamycin, binds with high affinity to a ubiquitous intracellular receptor, the immunophilin FKBP12. This complex specifically interacts with the mammalian target of rapamycin (mTOR) protein kinase; inhibiting downstream signaling events (5). The mTOR kinase is a member of the phosphoinositide kinase-related kinase family, which consists of high molecular weight serine/threonine kinases involved in cell cycle checkpoint control (6). Several lines of evidence suggest that mTOR acts as a sensor for stress (7) and the availability of amino acids (8, 9, 10) or intracellular ATP (11). In the presence of mitogens and sufficient nutrients, mTOR relays a signal to translational regulators, specifically enhancing the translation of mRNAs encoding proteins essential for cell growth (12) and progression through the G_1 to S transition (13, 14). Consistent with targeting the mTOR pathway, treatment of mammalian cells with rapamycin has been shown to inhibit these signaling events, mimicking a starvation phenotype (15) and leading to growth retardation and accumulation of cells in G_1 phase (16). The mechanism of growth stimulus and nutrient level integration by mTOR is, as yet, not fully understood. However, an increasing body of evidence suggests the involvement of the phosphatidylinositol 3′-kinase/Akt/TSC/Rheb pathway (12, 17, 18, 19, 20, 21, 22, 23). Indeed, it has been suggested that, in tumor cells, the activation status of the Akt pathway may be indicative of responsiveness to rapamycin or its derivatives (24, 25, 26, 27).

mTOR is part of a multisubunit complex that contains the regulatory proteins raptor (28, 29) and GβL (30). The mTOR complex signals to at least two downstream effectors, the translational repressor protein eukaryotic initiation factor 4E (eIF-4E)-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1). These share an evolutionary conserved amino acid motif, the TOS motif, that functions as a docking site for raptor (31, 32, 33). Binding of 4E-BP1 to the translational activator eIF-4E is modulated by mTOR-dependent phosphorylation of specific serine and threonine residues (5). Ser37 and Ser46 are constitutively phosphorylated, acting as priming sites for the mitogen-induced, rapamycin-sensitive phosphorylation of Thr70 and Ser65 (34). After a final phosphorylation event at Ser65, 4E-BP1 dissociates from eIF-4E (35), thereby allowing the reconstitution of a translationally competent initiation factor complex (eIF-4F; Ref. 5). eIF-4F activation results in the translation of a subset of capped mRNA containing highly structured 5′-untranslated regions and encoding proteins involved in G_1- to S-phase progression (13, 14). Mitogen-induced activation of the

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S6K1 is also dependent on mTOR function and has been implicated in the translational regulation of mRNAs possessing a 5′-terminal oligopyrimidine tract (36, 37, 38) . 5′-Terminal oligopyrimidine tract mRNAs are characterized by a stretch of 4–14 pyrimidines located at their extreme 5′ terminus and typically encode ribosomal proteins as well as components of the translational machinery. Activation of S6K1 itself is also tightly regulated by hierarchical phosphorylation events, which are dependent on the activation of various signal transduction pathways and culminate in the phosphorylation of the rapamycin-sensitive site Thr389, an event closely paralleling kinase activation (12 , 39) . Immunopurified mTOR has been shown to autophosphorylate on Ser2481 (40) and to phosphorylate Ser37, Ser46, and Ser65 on 4E-BP1 *in vitro* (11 , 34 , 41 , 42) . However, some of these events have been demonstrated to be resistant to antiproliferative concentrations of rapamycin (40, 41, 42) . It is therefore unclear what role mTOR kinase activity plays *per se* in rapamycin-sensitive signaling events.

Because mTOR couples nutrient/growth factor availability to cell growth and proliferation in a variety of cell types, there is a potential for developing rapamycin derivatives such as RAD001 as novel inhibitors of the deregulated cell growth characteristic of human cancers. Consistent with this, RAD001 inhibits the proliferation of a wide variety of human solid tumor cell lines both *in vitro* in cell culture and *in vivo* in animal xenograft models (2 , 3 , 27 , 43 , 44) . Furthermore, antiproliferative effects of RAD001 in posttransplant lymphoproliferative disorder-like B cell lines have been observed *in vitro* and *in vivo* (45 , 46) . In the present study, we have demonstrated that RAD001 displays significant antitumor activity in the syngeneic CA20948 rat pancreatic tumor model. Equivalent activity was observed with daily and intermittent treatment schedules, suggesting the possibility of a therapeutic window allowing differentiation of antitumor activity from the immunosuppressive properties of this agent. Detailed biochemical analysis of the mTOR effectors 4E-BP1 and S6K1 in tumor, skin, and peripheral blood mononuclear cell (PBMC) extracts obtained from RAD001-treated rats suggests that modulation of 4E-BP1 activity and significant inactivation of S6K1 are associated with antitumor activity. Furthermore, the efficacy observed using intermittent treatment schedules is paralleled by long-term down-regulation of S6K1 activity in all three tissues. We also provide evidence that the duration of S6K1 inactivation in PBMCs correlates with the dose-dependent suppression of tumor growth observed with weekly regimens. Moreover, unlike 4E-BP1 phosphorylation, S6K1 activity can be reproducibly measured in human PBMCs and represents a potentially valuable pharmacodynamic biomarker by which to monitor RAD001 treatment schedules in cancer patients.

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MATERIALS AND METHODS

Drug Preparation.

RAD001 (everolimus) is a derivative of rapamycin [40-O-(2-hydroxyethyl)-rapamycin; Ref. 47] . For animal studies, RAD001 was formulated at 2% (w/v) in a microemulsion vehicle, which was diluted to the appropriate concentration in 5% (w/v) glucose solution just before administration by gavage. For *in vitro* and *ex vivo* analyses, RAD001 was prepared in DMSO before addition to cell culture or human volunteer blood samples.

Antitumor Efficacy Studies and Statistical Analyses.

Male Lewis rats were purchased from Iffa Credo (L'Abresque, France) and allowed food and water *ad libitum*. A suspension of CA20948 tumor cells

(obtained from donor rats because this line is nonculturable *in vitro*) in Ham's F-12 medium supplemented with 10% FCS, 0.1 g/100 ml $NaHCO_3$, 1% penicillin, and 1% fungizone was injected s.c. into the left flank of rats. Treatment of randomized rats started when the tumors reached about 100 mm^3. RAD001 was administered p.o. daily at 0.5 or 2.5 mg/kg (×6/week), twice weekly at 5 mg/kg, or weekly at 0.5, 1, 2, 3, or 5 mg/kg. A volume of vehicle equivalent to the highest dose of RAD001 administered in the experiment was used as a negative control. As a positive control, the cytotoxic agent 5-fluorouracil (5-FU; ICN Pharmaceuticals Inc., Costa Mesa, CA) was administered at a near maximum tolerated dose (15 mg/kg, i.v., 4×/week, 2 days treatment/2 days rest), which gives maximal antitumor effect. Tumors were measured every day or every other day with a caliper, and the volumes were calculated by using the formula of an ellipsoid [$V = \pi/6 (d_1 \times d_2 \times d_3)$, where d_1, d_2, and d_3 represent the three largest diameters]. Animals were also weighed the same day tumors were measured. The animals were sacrificed when either their tumor burden exceeded 25,000 mm^3 or when skin overlaying the tumor exhibited evidence of necrosis. All protocols involving animals were approved by the Veterinäramt of Baselstadt, Switzerland.

Results are presented as mean ± 1 SEM or as percentage of T/C (mean increase of tumor volumes of treated animals divided by the mean increase of tumor volumes of control animals multiplied by 100). The statistical significance of differences between treatment and control groups were determined by ANOVA followed by the Dunnett test. Statistical analyses on body weight were performed by ANOVA followed by Tukey's test, and for comparison between weight at start and end of the experiment for individual animals, the paired *t* test was used. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific).

Rat-Derived and Human Volunteer-Derived Tissue/PBMC Protein Extract Preparation.

CA20948 tumor-bearing rats were given 0.5, 1, 2, or 5 mg/kg RAD001 or an equivalent volume of vehicle. At the indicated times after administration, rats were sacrificed, and tumor and shaved skin samples (for 0.5 and 5 mg/kg RAD001 doses) were dissected and weighed. Samples were rinsed in ice-cold PBS and immediately extracted in ice-cold extraction buffer [50 mM Tris-HCl (pH 8.0), 120 mM NaCl, 20 mM NaF, 1 mM EDTA, 6 mM EGTA, 15 mM PP_i, 30 mM *p*-nitrophenyl phosphate, 1 mM benzamidine, 0.2 mM phenylmethylsulfonyl fluoride, and 0.1% NP40] with a constant ratio of 45 mg tumor/ml extraction buffer and 90 mg skin/ml extraction buffer, using a PT3000 Polytron (probe PT-DA 3012/2S; Kinematica AG) or a hand-held PT2100 Polytron (probe PT-DA 2112/2EC), respectively. Lysates were cleared by centrifugation for 30 min at 12,000 × *g* at 4°C. Supernatants were subsequently aliquoted, snap frozen on dry ice, and stored at −80°C. In the case of skin samples, before further analysis, samples were centrifuged for 20 min at 436,000 × *g* at 4°C to remove the fat fraction.

Blood (for 0.5, 1, 2, and 5 mg/kg RAD001 doses) from tumor-bearing and non-tumor-bearing rats was withdrawn into syringes containing EDTA [0.5% (w/v) final] and then placed into an ice-cold tube and mixed. Unless otherwise stated, the blood from individual animals within the same treatment group was analyzed separately. The blood was immediately centrifuged for 20 min at 430 × *g* at 4°C. The PBMCs, deposited at the interface between the RBCs and the plasma, were collected and pelleted by centrifugation for 5 min at 3000 × *g* at 4°C. PBMCs were washed with 10 ml of ice-cold PBS and then repelleted by centrifugation for 5 min at 3000 × *g* at 4°C. Cell pellets were

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resuspended in ice-cold extraction buffer containing 1% NP40 at the fixed ratio of 500 μl extraction buffer/10 ml initial blood volume. The cells were sheared by vigorous pipetting and then centrifuged for 30 min at 12,000 × *g* at 4°C. Supernatants were aliquoted, snap frozen on dry ice, and stored at −80°C.

Human blood from healthy volunteers was collected under medical supervision into tubes containing either sodium citrate (BD Vacutainer 9NC; BD Vacutainer Systems, Plymouth, United Kingdom) or EDTA (BD Vacutainer K3E) as an anticoagulant. The blood was either immediately processed or, for *ex vivo* treatments, treated with 2, 20, and 200 nM RAD001 or DMSO vehicle for 30 min at room temperature. Human PBMCs were isolated and extracted as described for rat PBMCs.

A549 Cell Culture and Protein Extract Preparation.

A549 human lung carcinoma cells (CCL185) were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 medium (Amimed, Allschwil, Switzerland) supplemented with 10% FCS, 2 mM L-glutamine, and 100 μg/ml penicillin/streptomycin at 37°C and 5% CO_2. Cell lysates were prepared as described previously **(48)** .

Immunoblot Analysis.

Cell lysates (30–40 μg) were electrophoretically resolved on denaturing SDS polyacrylamide gels (SDS-PAGE), transferred to polyvinylidene difluoride (Millipore Corp., Bedford, MA), and probed with the following primary antibodies: anti-S6 (provided by J. Mestan; Oncology Research, Novartis Pharma AG, Basel, Switzerland); anti-4E-BP1 (kindly provided by N. Sonenberg; McGill University, Montreal, Quebec, Canada); anti-eIF-4E (kindly provided by S. J. Morley; University of Sussex, Brighton, United Kingdom); anti-phospho-4E-BP1 Thr70, anti-S6K1, and anti-phospho-S6 Ser240/Ser244 (all from Cell Signaling Technology Inc., Beverly, MA); and anti-β-tubulin (Tub2.1; Sigma, St. Louis, MO). "Decorated" proteins were revealed using horseradish peroxidase-conjugated antimouse or antirabbit immunoglobulins in conjunction with the enhanced chemiluminescence procedure (Amersham Pharmacia Biotech Inc., Buckinghamshire, United Kingdom).

Affinity Purification of 4E-BP1·eIF-4E Complexes with 7-Methyl-GTP-Sepharose.

Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 500 μl in ice-cold extraction buffer and adjusted to a final NP40 concentration of 0.1%. The 4E-BP1·eIF-4E complexes were affinity purified with 20 μl of 7-methyl-GTP-Sepharose beads (Amersham Pharmacia Biotech Inc., Piscataway, NJ) by gentle rotation for 2.5 h at 4°C. Proteins retained on the beads were washed twice with extraction buffer in the absence of NP40 and resuspended in 15 μl of Laemmli buffer. Denatured samples were subjected to 15% SDS-PAGE and transferred to polyvinylidene difluoride membranes. Membranes were first immunoblotted for 4E-BP1 protein, followed by stripping as described previously **(49)** and reprobing for eIF-4E protein (see above).

40S *Ribosomal S6 Kinase Assay.*

Rat tumor (1 mg), skin (0.7 mg), or PBMC (0.25 mg) extracts were diluted to a final volume of 1 ml (tumor and skin) or 500 μl (PBMC) with ice-cold extraction buffer and adjusted to a final NP40 concentration of 1%. Human-derived PBMC extracts (0.8–1 mg) were diluted to a final volume of 750 μl with ice-cold extraction buffer (final NP40 concentration, 1%). In some

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experiments, human-derived PBMC extracts were first precleared with 20 μl of 50% protein A-Sepharose (Amersham Pharmacia Biotech, Uppsala, Sweden) by rotating for 20 min at 4°C. S6K1 was immunoprecipitated from all extracts by addition of 2.5 μl of the M5 S6K1-specific polyclonal antibody and incubation on ice for 1 h, followed by retrieval of immunocomplexes with 20 μl of 50% protein A-Sepharose. S6K1 activity was measured using rat liver 40*S* ribosomal subunits as a specific substrate, as described previously **(50)** , except that *p*-nitrophenyl phosphate was omitted in the reaction mixture. Phosphorylated S6 was resolved by 12.5% SDS-PAGE and analyzed using a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). [γ-^{32}P]phosphate incorporation into S6 was quantified using ImageQuant (Molecular Dynamics). Where appropriate, the statistical significance of differences between treatment groups and untreated control groups was determined using ANOVA or ANOVA on ranks followed by the Dunnett test. The level of significance was set at $P < 0.05$. Statistical calculations were performed using SigmaStat 2.03 (Jandel Scientific). Coefficient of variation is defined as SD divided by the mean and multiplied by 100.

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RESULTS

Intermittent RAD001 Treatment Schedules Display Antitumor Efficacy.

Short-term exposure to rapamycin *in vitro* has long-term antiproliferative effects on tumor cell lines **(51)** , suggesting that intermittent treatment schedules may retain antitumor activity. Furthermore, daily oral administration of RAD001 is effective in rat models of autoimmune disease and allotransplantation **(47 , 52)** , whereas we have found that weekly (5 mg/kg) RAD001 dosing schedules have reduced immunosuppressive properties in rats as compared with daily treatment (2.5 mg/kg): 66 ± 18% and 98 ± 1% inhibition of IgG antibody response after dinitrophenol-coupled keyhole limpet hemocyanogen immunization, respectively. 3 With these observations in mind, we evaluated whether RAD001 treatment schedules, with potentially reduced immunosuppressive properties, could elicit antitumor responses. Daily *versus* intermittent RAD001 administration schedules were compared using the s.c. CA20948 rat pancreatic tumor model. Vehicle was used as a negative control, and the cytotoxic agent 5-FU was used as a positive control (Fig. 1 ⇓ ; Table 1 ⇓ , Experiment 1). RAD001 treatment at 0.5 or 2.5 mg/kg/day, six times a week, resulted in antitumor activity characterized by statistically significant inhibition of tumor growth as compared with vehicle controls [treated tumor *versus* control tumor size (T/C), 30% and 23%, respectively; $P < 0.05$ after 10 days of treatment; Fig. 1*A* ⇓ ; Table 1 ⇓ , Experiment 1]. Statistically significant tumor growth suppression was also observed after intermittent administration of 5 mg/kg RAD001 twice a week (T/C, 36%) or once a week (T/C, 36%). Moreover, all RAD001 treatment schedules suppressed tumor growth to a similar extent as the cytotoxic 5-FU (T/C, 23%). Continued treatment with RAD001 after vehicle controls were sacrificed due to tumor burden led to a prolonged low tumor growth rate with all treatment schedules, resulting in similar tumor burden after 17 days of treatment as compared with 5-FU (Fig. 1*A*) ⇓ . For all treatment schedules, RAD001 was well tolerated, with no significant body weight loss or mortalities observed (Fig. 1*B* ⇓ ; Table 1 ⇓ , Experiment 1). These results demonstrate that RAD001 is a well-tolerated antitumor agent in a rat model of pancreatic cancer and indicate a potential for intermittent administration schedules that may allow dissociation of antitumor from immunosuppressive effects.

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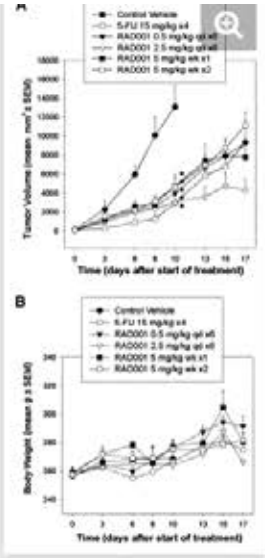

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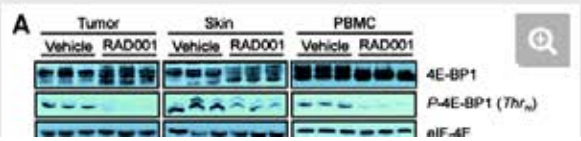
Suppression of tumor growth by daily and intermittent dosing schedules of RAD001. Tumors were established in male Lewis rats by s.c. injection of CA20948 tumor suspension obtained from donor rats. Treatments started on day 4 after inoculation. Formulated RAD001 was diluted in a 5% glucose solution and administered p.o. daily at a dose of 0.5 or 2.5 mg/kg (*qd* ×6, 6 times/week) or once (*wk* ×1) or twice (*wk* ×2) weekly at 5 mg/kg RAD001. Vehicle and 5-fluorouracil (*5-FU* ×4; 4 times/week) were administered as negative and positive controls, respectively. Tumor volumes were measured (*A*), and rats were weighed (*B*) as described in "Materials and Methods." Vehicle control-treated rats were sacrificed on day 10 due to tumor burden. Data are means ± SEM (n = 7–8 animals/group). *Stars* represent $P < 0.05$ *versus* vehicle controls.

Table 1 View inline | View popup

Effect of daily and intermittent RAD001 administration on CA20948 rat pancreatic tumor-bearing rats

RAD001 Modulates 4E-BP1 and S6K1 Activity in Tumor, Skin, and PBMCs Obtained from CA20948 Pancreatic Tumor-Bearing Rats

To investigate RAD001-specific effects on mTOR signaling *in vivo*, three CA20948 tumor-bearing rats were treated with vehicle or a single efficacious dose of RAD001 (5 mg/kg). Rats were sacrificed 24 h later, and protein extracts were prepared from tumors, skin, and PBMCs. By immunoblot analysis, mTOR could be detected in tumor and PBMC extracts; however, neither mTOR expression nor phosphorylation on Ser2448 was modified on RAD001 treatment. 4 In contrast, 4E-BP1 exhibited a decrease in Thr70 phosphorylation in tumor, skin, and PBMC extracts (Fig. 2*A*) 8 , a phenomenon associated with changes in 4E-BP1 electrophoretic mobility, particularly striking in PBMCs. This observation is consistent with previous work demonstrating dephosphorylation of 4E-BP1 on Thr70 in tumors derived from mouse xenograft models after five daily treatments with an ester of rapamycin CCI-779 (1 h after last administration; Ref. 53). Interestingly, the phosphorylation of another rapamycin-sensitive residue (Ser65; Refs. 5 , 34 , and 35) was unaffected by RAD001 treatment, 4 indicating that RAD001-insensitive phosphorylation of this site can occur as reported previously (54) .



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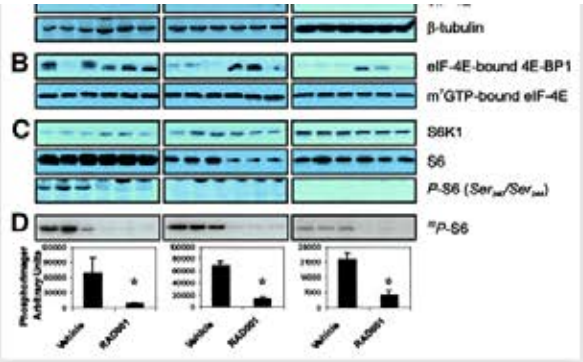

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RAD001 administration inhibits mammalian target of rapamycin signaling in CA20948 tumor-bearing rats. S.c. CA20948 tumor-bearing rats received a single administration of an efficacious dose of RAD001 (5 mg/kg) or vehicle and were sacrificed 24 h after administration (3 rats/group). Tumors, skin, and PBMCs were individually prepared and extracted as described in "Materials and Methods." Results from individual rats are presented. *A* and *C*, total protein was subjected to electrophoresis followed by immunoblot analysis. Membranes were probed for eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and phospho-threonine 70 4E-BP1 [*P-4E-BP1 (Thr$_{70}$)*] levels, with eukaryotic initiation factor 4E (eIF-4E) and β-tubulin levels acting as loading controls (*A*) or ribosomal protein S6 kinase 1 protein, S6 40*S* ribosomal protein, and phospho-serine 240/244 S6 [*P-S6 (Ser$_{240}$/Ser$_{244}$)*] levels (*C*). *B*, the level of 4E-BP1 bound to eIF-4E was measured by purification of 4E-BP1·eIF-4E complexes on 7-methyl-GTP-Sepharose, as described in "Materials and Methods," followed by immunoblot analysis. *D*, ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of total protein extract, and activity was measured by *in vitro* kinase assay using 40*S* ribosomal subunits as a specific substrate, as described in "Materials and Methods." Phosphorimages (*32P-S6*) and PhosphorImager quantifications of the kinase assay are presented. Data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* vehicle-treated controls (Dunnett test).

To determine whether the decreased phosphorylation state of 4E-BP1 resulted in a change in functionality, the eIF-4E binding activity of 4E-BP1 was assessed using an *in vitro* 7-methyl-GTP-binding assay (Fig. 2*B*) . Whereas similar levels of eIF-4E were recovered in the control- and RAD001-treated extracts, in two animals increased eIF-4E·4E-BP1 complex formation was clearly observed in skin and PBMC samples after RAD001 treatment. In tumor samples, two electrophoretically distinct forms of 4E-BP1 protein were bound to eIF-4E in vehicle control-treated rats (Fig. 2*B*) . After RAD001 treatment, only the lower migrating form was found bound to eIF-4E, with an associated loss of the upper band consistent with reduced 4E-BP1 phosphorylation levels (Fig. 2*A*) . A similar 4E-BP1 doublet with eIF-4E binding activity has been observed previously in proliferating cells/tissue (29 , 54) and presumably reflects differential 4E-BP1 phosphorylation states within the proliferating tumor.

To further assess the effect of RAD001 administration on the mTOR pathway, S6K1 protein and activity levels were also analyzed (Fig. 2, *C* and *D*) . Whereas S6K1 protein levels were unaffected by RAD001 treatment (Fig. 2*C*) , *in vitro* kinase assay using 40*S* ribosomal subunits as a substrate revealed a statistically significant reduction in S6K1 activity in all extracts [Fig. 2*D* ; 83% (tumors), 80% (skin), and 75% (PBMC), all $P < 0.05$ *versus* vehicle-treated controls]. This reduction in S6K1 activity was associated with the dramatic dephosphorylation of its physiological substrate, 40*S* ribosomal protein S6, in tumor extracts (Fig. 2*C*) . A similar reduction was not observed in skin and PBMC extracts because these tissues exhibited no detectable S6 phosphorylation in control animals. Interestingly, a reduction in S6 protein expression was observed in RAD001-treated skin, but not in tumor or PBMC extracts. A similar phenomenon has been reported previously in tumors after treatment of mice bearing human prostate cancer xenografts with CCI-779 (24) . Moreover, the translation of

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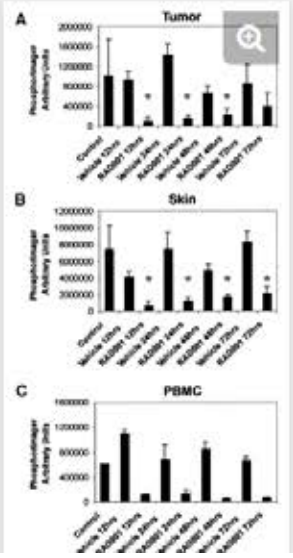
S6 (as a 5′-terminal oligopyrimidine tract mRNA) has been shown to be specifically inhibited by rapamycin in 3T3 cells (36) . It is not known why, in this model, RAD001 treatment only has effects on S6 expression in skin; however, differential downstream effects of mTOR pathway inhibition, depending on the tissue source, are a plausible possibility (54) . Taken together, these data demonstrate that both 4E-BP1 and S6K1 pathways are affected in tumors, skin, and PBMC samples obtained from CA20948 tumor-bearing rats after a single administration of an efficacious dose of RAD001.

Prolonged Inactivation of S6K1 in Tumors, Skin, and PBMCs Correlates with the Efficacy of Intermittent RAD001 Treatment Schedules.

To investigate whether the antitumor efficacy of intermittent RAD001 treatment schedules is associated with prolonged effects on the mTOR pathway, CA20948 tumor-bearing rats were treated with a single dose of RAD001 (5 mg/kg) or vehicle, and tumor, skin, and PBMC extracts were prepared 12, 24, 48, or 72 h after administration. Because S6K1 was significantly inactivated 24 h after a single RAD001 administration in all tissues analyzed (Fig. 2*D*) , long-term effects on mTOR function were assessed using the 40*S* kinase assay (Fig. 3) . Tumor and skin extracts were obtained from each of 3 rats/treatment group, whereas PBMC extracts were obtained from pooled blood from each treatment group. A dramatic reduction in S6K1 activity was already observed in tumors, skin, and PBMCs 12 h after RAD001 administration (91%, 91%, and 82% inhibition, respectively; all $P < 0.05$ *versus* untreated controls; Fig. 3). In contrast, treatment with vehicle did not significantly modulate S6K1 activity as compared with untreated controls (Fig. 3) . Moreover, RAD001 treatment resulted in the sustained inactivation of S6K1 in all tissues. In tumors, statistically significant inhibition of S6K1 was maintained up to 48 h after administration, with some evidence of recovery after 72 h (80% and 62% inhibition at 48 and 72 h, respectively; Fig. 3*A*). In comparison, S6K1 derived from skin samples remained significantly inhibited for at least 72 h (72% inhibition at 72 h; Fig. 3*B*). Although a statistical analysis could not be performed on the pooled PBMC samples, S6K1 activity was also dramatically inhibited for up to 72 h in these samples (82% inhibition at 72 h, Fig. 3*C*). Thus, consistent with the antitumor efficacy of intermittent 5 mg/kg RAD001 treatment schedules in CA20948 tumor-bearing rats, a single administration of 5 mg/kg RAD001 resulted in long-term inactivation of S6K1 in tumors, skin, and PBMCs.



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RAD001 administration (5 mg/kg) causes prolonged inactivation of ribosomal protein S6 kinase 1 in tumors, skin, and PBMCs derived from CA20948 tumor-bearing rats. CA20948 tumor-bearing rats were treated once with 5 mg/kg RAD001 or vehicle (3 rats/group). After 12, 24, 48, and 72 h, tumor and skin samples were individually extracted. Blood obtained from rats within each treatment group was pooled, and peripheral blood mononuclear cells (PBMCs) were isolated and extracted. Assay of ribosomal protein S6 kinase 1 activity was performed using 40S ribosomal subunits as *in vitro* substrate. Phosphorimager quantifications of the S6 kinase assays are presented. *A* (*Tumor*) and *B* (*Skin*): data are means ± SD of $n = 3$ animals/group. *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C* (*PBMC*): data are means; *error bars* represent the range of duplicate assays.

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The Antitumor Efficacy of Intermittent RAD001 Treatment Schedules Is Dose Dependent: Correlation Between Efficacy and Prolonged Effects on mTOR Effectors in Rat PBMCs

Following the observation that intermittent RAD001 (5 mg/kg) treatment schedules significantly inhibited tumor growth, we explored the effect of RAD001 dose on the efficacy of weekly treatment schedules (Table 1, Experiments 2 and 3). As expected, 5 mg/kg/week RAD001 significantly suppressed CA20948 tumor growth as compared with vehicle controls (T/C, 14% and 24% at 7 and 8 days, respectively; $P < 0.05$). In contrast, although 0.5 mg/kg RAD001 caused a significant inhibition of tumor growth when administered daily (T/C, 23%), weekly administration of the same dose did not significantly affect tumor growth (T/C, 48%; $P > 0.05$). This apparent dose dependency of weekly RAD001 schedules was confirmed by a more stringent analysis comprising doses between 5 and 0.5 mg/kg (Table 1, Experiment 3). Statistically significant antitumor responses were observed with 3 and 2 mg/kg RAD001 (T/C, 36% and 32%, respectively), but not with 1 mg/kg (T/C, 45%). Interestingly, 3 mg/week elicited a similar antitumor response (T/C, 36%) as 0.5 mg/kg/day (×6/week; T/C, 30% and 23%). Because both these schedules involve administration of 3 mg/kg RAD001 per week, these data indicate that, with the same total RAD001 exposure, intermittent dosing schedules can elicit equivalent antitumor responses as daily schedules.

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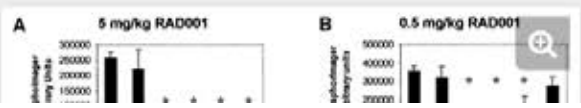
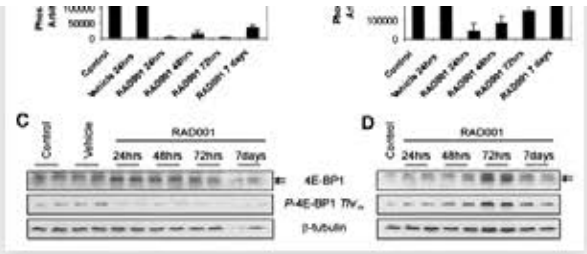
To further investigate the dose dependency of weekly schedules in terms of effects on mTOR signaling in a surrogate tissue, the duration of S6K1 inactivation in response to a single administration of 0.5 *versus* 5 mg/kg RAD001 was determined in PBMCs derived from three non-tumor-bearing rats (Fig. 4, *A* and *B*). Whereas in vehicle controls, no effect on S6K1 activity could be observed (24 h after administration), a single administration of 5 mg/kg RAD001 resulted in statistically significant, prolonged inactivation of the S6K1 for up to 7 days (99% and 86% inhibition after 24 h and 7 days, respectively; $P < 0.05$). In comparison, 0.5 mg/kg RAD001 caused a significant inhibition of PBMC-derived S6K1 activity 24 h after administration (88% inhibition); however, kinase activity began to recover after 48 h (75% inhibition) and was almost totally recovered after 7 days [23% inhibition; not significant ($P > 0.05$ *versus* controls)]. In contrast to effects on S6K1 activity, no effect on Thr70 phosphorylation or the electrophoretic mobility of 4E-BP1 was observed with the 0.5 mg/kg RAD001 dose, whereas decreased Thr70 phosphorylation and a shift to a lower migrating form were observed with the 5 mg/kg RAD001 dose (Fig. 4, *C* and *D*). The latter effect was maintained for 72 h, with evidence of recovery by 7 days.





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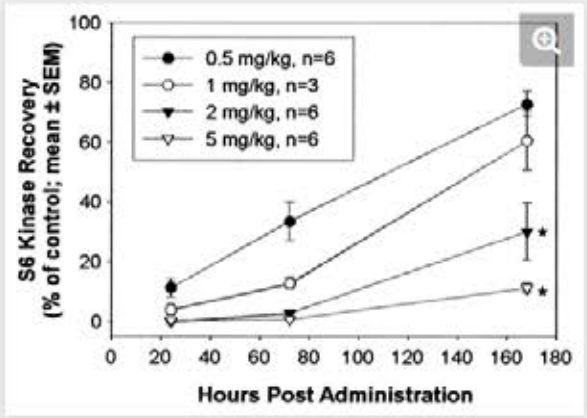
Dose-dependent effects of RAD001 on ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) in peripheral blood mononuclear cells (PBMCs) obtained from non-tumor-bearing rats. Rats were treated with a single optimal (*A* and *C*) *versus* suboptimal (*B* and *D*) RAD001 dose (5 and 0.5 mg/kg, respectively) or vehicle (3 rats/group). At the times indicated, PBMC samples were collected and individually extracted. *A* and *B*, S6K1 was immunoprecipitated from equal amounts of protein extract, and S6K1 activity was assayed using 40S ribosomal subunits as a substrate. Phosphorimager quantification of the kinase assays are presented (means ± SD of $n = 3$ animals/group). *Stars* represent $P < 0.05$ *versus* untreated controls (Dunnett test). *C* and *D*, equal amounts of PBMC extracts were resolved by SDS-PAGE, transferred onto a polyvinylidene difluoride membrane, and probed for 4E-BP1 protein, phospho-threonine 70 4E-BP1 (*P-4E-BP1 Thr*$_{70}$), or β-tubulin as a loading control. *Arrows* denote hypophosphorylated (*bottom arrow*) and hyperphosphorylated (*top arrow*) forms of 4E-BP1 protein.

The above observations indicate that RAD001 has dose-dependent effects on the mTOR pathway in rat PBMCs. Moreover, long-term effects are associated with a RAD001 dose shown to have significant antitumor efficacy with intermittent treatment schedules. To confirm this hypothesis, a more stringent RAD001 titration was also performed to analyze effects on PBMC-derived S6K1 activity after a single administration of 0.5, 1, 2, or 5 mg/kg RAD001 (Fig. 5) . In all cases, inactivation of S6K1 was observed 24 h after RAD001 administration. However, at RAD001 doses that do not elicit a significant antitumor response with weekly schedules (0.5 and 1 mg/kg; see Table 1), evidence of recovery of S6K1 activity was already observed at 72 h (34% and 13% recovery *versus* untreated controls, respectively) and was dramatic at 7 days [73% and 61%, respectively; no significant inhibition of S6K1 ($P > 0.05$ *versus* controls)]. In contrast, at RAD001 doses that do elicit a significant antitumor response with weekly schedules (2 and 5 mg/kg; see Table 1), minimal recovery was observed at 72 h (3% and 1%, respectively) or 7 days [30% and 12%, respectively; significant inhibition of S6K1 ($P < 0.05$ *versus* controls)]. These data confirm that long-term inactivation of PBMC-derived S6K1 correlates with the antitumor efficacy of weekly RAD001 treatment schedules.



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Association between antitumor efficacy of weekly RAD001 schedules and long-term

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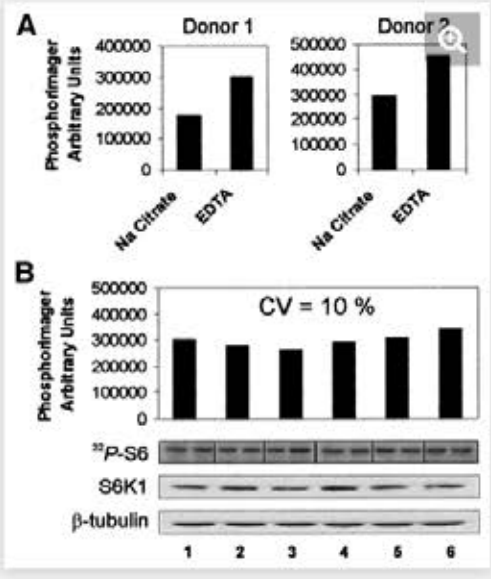
down-regulation of ribosomal protein S6 kinase 1 (S6K1) activity in rat peripheral blood mononuclear cells (PBMCs). Non-tumor-bearing rats were treated with a single RAD001 dose (0.5, 1, 2, or 5 mg/kg). At the times indicated, PBMC samples were collected and individually extracted and assayed for S6K1 activity. Data are presented as mean percentage recovery of S6K1 activity *versus* untreated control animals ± SEM of $n = 3$ or 6 S6K1 assays from different rat PBMC extracts. All data are derived from two separate experiments, except in the case of 1 mg/kg, where data from a single experiment are presented. *Stars* represent $P < 0.05$ *versus* untreated controls (ANOVA on ranks test).

S6K1 Activity Can Be Reproducibly Detected in Human PBMC Extracts: RAD001 Induces Concentration-Dependent S6K1 Inactivation ***Ex Vivo.***

To evaluate the potential of using mTOR effectors as biomarkers to evaluate RAD001 treatment schedules, we assessed whether basal S6K1 activity could also be measured in human PBMC extracts obtained from healthy volunteers. Human blood was collected into tubes containing either sodium citrate or EDTA as an anticoagulant, and PBMC extracts were prepared. Subsequent assay of S6K1 activity demonstrated that activity could indeed be detected in nonchallenged human PBMCs derived from unrelated donors (Fig. 6*A*). Interestingly, S6K1 activity was reproducibly higher when the blood was initially collected in EDTA as compared with sodium citrate, a phenomenon potentially related to the different chelating properties of these anticoagulants. Using EDTA, a coefficient of variation of 10% was obtained among six assays on PBMC extracts prepared separately from the same blood donor, indicating good reproducibility of preparation (Fig. 6*B*). Accordingly, equivalent S6K1 protein levels were detected in the same extracts by immunoblot analysis (Fig. 6*B*). These results demonstrate that, in analogy with the rat PBMC data, basal S6K1 activity can be detected in human PBMCs. However, unlike control rat PBMC extracts (see Fig. 2*A*), there was no evidence of Thr70 phosphorylation in any of the human PBMC extracts analyzed, 5 an observation correlating with the fact that most of the 4E-BP1 protein was present in the hypophosphorylated/fast migrating state (when compared with 4E-BP1 derived from proliferating human tumor cells; Fig. 7*A*, *DMSO*). *Ex vivo* treatment of whole blood with 20 nM RAD001 for 30 min did not further increase protein mobility (Fig. 7*A*, *RAD001*), suggesting that 4E-BP1 is largely active as a translational repressor in human PBMCs. Hence, unlike the situation in rat, this protein may not be applicable as a biomarker for monitoring RAD001-specific effects on mTOR signaling in human PBMCs.



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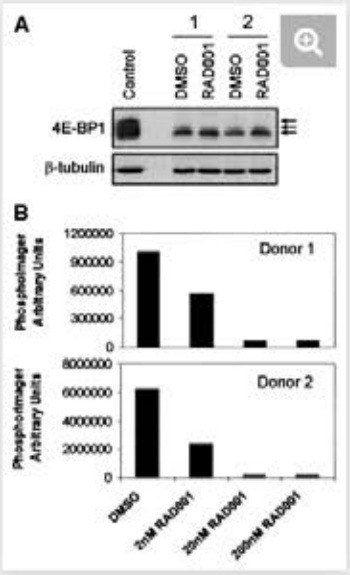
Detection of ribosomal protein S6 kinase 1 (S6K1) activity in human peripheral blood mononuclear cells (PBMCs). Blood from healthy volunteers was withdrawn at the same time into tubes containing either sodium citrate or EDTA as an anticoagulant. PBMCs were immediately isolated and extracted. *A*, S6K1 was immunoprecipitated from equal amounts of PBMC protein extracts, and activity was assessed using 40S ribosomal subunits as a substrate. Phosphorimager quantifications are presented and represent basal S6K1 activity (means of duplicate assays of a single sample) from two unrelated donors. *B*, blood from a single volunteer was withdrawn into tubes containing EDTA as an anticoagulant and was split into six equal fractions. PBMCs were prepared separately and extracted from each blood fraction, and extracts were simultaneously assayed for S6K1 kinase activity. Phosphorimages (*32P-S6*) and Phosphorimager quantifications (*graph*) of duplicate kinase assays are presented. As internal controls, equal amounts of PBMC protein extracts were analyzed by immunoblot for S6K1 and β-tubulin protein levels.



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Effects of *ex vivo* RAD001 treatment on ribosomal protein S6 kinase 1 activity and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) mobility in human PBMCs. *A*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with DMSO vehicle or 20 nM RAD001 for 30 min at room temperature, followed by PBMC isolation and extraction. Equal amounts of PBMC protein extracts were resolved by SDS-PAGE and transferred onto a polyvinylidene difluoride membrane. The membrane was probed for 4E-BP1 protein, with β-tubulin as a loading control. Human lung adenocarcinoma tumor cell lines lysates (*Control*; A549) were included as an example of 4E-BP1 mobility in a highly proliferative human cell population. *B*, blood was collected from two unrelated donors using EDTA as an anticoagulant and treated *ex vivo* with 2, 20, or 200 nM RAD001 or DMSO vehicle for 30 min at room temperature, followed by PBMC isolation and extraction. Ribosomal protein S6 kinase 1 was immunoprecipitated from equal amounts of PBMC protein extract, and activity was assessed *in vitro* using 40S ribosomal subunits as a substrate. Phosphorimager quantifications of the kinase assay are presented and represent means of duplicate assays of a single sample.

To assess whether human PBMC-derived S6K1 is inactivated in the presence of RAD001, whole blood from two unrelated healthy volunteers was treated *ex vivo* with either DMSO vehicle or increasing concentrations of RAD001 for 30 min, followed by isolation, extraction, and assay of PBMC-derived S6K1 activity (Fig. 7*B*). Treatment with 2 nM RAD001 diminished PBMC-derived S6K1 activity as compared with DMSO vehicle controls (44% and 63% inhibition in donor 1 and 2, respectively). Furthermore, increasing RAD001 concentrations led to almost complete inactivation of S6K1 (≥95% inhibition with ≥20 nM RAD001 in donor 1 and 2). These results demonstrate that RAD001 treatment of human blood *ex vivo* results in a concentration-dependent inactivation of PBMC-derived S6K1, supporting the notion that changes in PBMC-derived S6K1 activity could serve as a biomarker when assessing treatment schedules with rapamycin

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derivatives such as RAD001 in clinical trials for cancer.

DISCUSSION

The mTOR pathway plays a major role in cell proliferation by coupling cell growth with G_1-S progression. Compounds targeting the mTOR pathway have potential, therefore, for application in cancer treatment modalities (2 , 3 , 4) . In this context, RAD001 potently inhibits the proliferation of numerous tumor cell lines *in vitro* and inhibits the growth of a range of human xenografts in nude mice (2 , 27 , 43, 44, 45, 46) . 6 Rapamycin and the rapamycin ester CCI-779 also present antitumor activity in a number of animal models of cancer (2 , 24, 25, 26 , 53 , 55, 56, 57, 58, 59) . However, although human pancreatic tumors have been reported in abstract form to be sensitive to CCI-779 (reviewed in Ref. 2), and mTOR/S6K1 signaling appears to be required for pancreatic cancer cell proliferation (60 , 61) , the work presented here is the first full publication demonstrating significant antitumor efficacy of a rapamycin derivative in an animal model of pancreatic cancer. Orally administered RAD001 was found to be well tolerated and to elicit antitumor potency equivalent to that of the cytotoxic agent 5-FU. Moreover, similar responses were achieved with daily or weekly RAD001 administrations, indicating that frequent drug administration is unnecessary to maintain an antitumor response. Although weekly rapamycin dosing schedules have been used previously (55 , 56) , a comparative analysis addressing the efficacy of daily *versus* weekly administration had not been performed. The fact that weekly RAD001 administration produces statistically significant antitumor responses in the CA20948 model is supported by a number of experimental observations. First, *in vitro* pulse treatment with either RAD001 (43) or rapamycin (51) causes prolonged down-regulation of the mTOR pathway in tumor cell lines. Indeed, Hosoi *et al.* (51) postulated that this phenomenon was due to the slow dissociation rate of the rapamycin·FKBP12 complex. Second, prolonged effects of CCI-779 on xenograft tumor growth were evident after cessation of daily treatment schedules (24 , 53 , 57) , and antitumor responses have been reported in Phase I clinical trials with weekly CCI-779 administration (2 , 4) .

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One advantage of administering RAD001 intermittently in oncology is the avoidance of prolonged immunosuppression (1) . In this context, the minimal effective dose of RAD001 in stringent rat kidney and heart allotransplantation models is ≥5 mg/kg administered daily (47 , 52) . Moreover, the immunosuppressive capacity of RAD001 (everolimus in combination with cyclosporin) in transplant patients has been related to maintenance of blood drug trough levels (1 , 62) , suggesting that constant drug exposure is required to provide clinically relevant immunosuppression. The demonstration that weekly administration of RAD001 (at doses of 2–5 mg/kg) is sufficient to elicit a significant antitumor response indicates that the above premise does not apply to oncology. Indeed, in support of this notion, as compared with daily RAD001 administration (2.5 mg/kg), a 5 mg/kg weekly RAD001 regimen allows a 20-fold higher T-cell-dependent antibody response, as measured by serum IgG antibody titers after immunization of rats with dinitrophenol-coupled keyhole limpet hemocyanogen. 3 Hence, intermittent dosing allows for differentiation between immunosuppressive and antitumor effects, a possibility also suggested from preliminary clinical data (2 , 4) . The basis of this is presumably related to the biology of T cells as compared with tumor cells. In this respect, rapamycin potently prevents resting T cells from entering the cell cycle in response to interleukin 2 but has little effect on proliferating T cells (63 , 64) . This may explain why constant drug exposure is required in the immunosuppression setting, as

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opposed to the antitumor setting where the proliferation of cycling tumor cells is potently inhibited (2 , 4) for long periods (51) . This possibility is worthy of further investigation.

A limited analysis of the effects of rapamycin derivatives on mTOR effectors in tumor material derived from xenograft models was reported previously (24 , 53) . Until now, however, a comprehensive analysis had not been performed. Similarly, the possibility that the efficacy of intermittent treatment schedules correlates with long-term effects on the mTOR pathway in tumors and surrogate tissues had not been addressed. This prompted us to profile RAD001-mediated effects on mTOR signaling in CA20948 tumors and normal rat tissues. Mitogen-induced, multisite phosphorylation of the translational suppressor protein 4E-BP1 is known to cause its release from the initiation factor eIF-4E, thereby facilitating formation of the eIF-4F initiation complex and derepression of cap-dependent mRNA translation (2 , 5) . Indeed, the 4E-BP1 protein has been proposed to be a direct substrate for the mTOR kinase (34 , 41 , 42) . Moreover, rapamycin treatment of cell lines decreases 4E-BP1 phosphorylation, resulting in increased affinity for eIF-4E *in vitro* (2 , 5) . Consistent with these observations, a single administration of 5 mg/kg RAD001 to three tumor-bearing rats reproducibly inhibited 4E-BP1 phosphorylation in tumors, skin, and PBMCs at 24 h, in accordance with changes in 4E-BP1 electrophoretic mobility and increased 4E-BP1·eIF-4E association. In the same animals, S6K1 signaling was virtually abolished in all tissues. The physiological downstream target of the S6K1 is the S6 40S ribosomal protein (12 , 65) . Hence, reductions in S6 phosphorylation are expected to parallel S6K1 inactivation, as observed in CA20948 tumor extracts. However, because S6 phosphorylation could not be detected in either skin or PBMC control extracts, no such correlation could be made in these tissues. This failure to detect S6 phosphorylation could reflect a reduced proliferation index as compared with the aggressively growing CA20948 tumors. Strikingly, and in agreement with previous *in vitro* analyses (43 , 51) , tumors, skin, and PBMC extracts derived from rats treated with a single 5 mg/kg RAD001 dose demonstrated prolonged inactivation of the S6K1 for ≥72 h. Taken together, these data suggest that RAD001-specific effects on 4E-BP1 and S6K1 activity can be reproducibly observed in tumors and surrogate tissues. Moreover, long-term effects of RAD001 on S6K1 activity occur with a dose of RAD001 known to elicit significant antitumor responses with intermittent treatment schedules.

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The observation that the mTOR pathway is affected for long periods of time in tumors and PBMCs is consistent with preliminary pharmacokinetic studies performed in CA20948 tumor-bearing rats. Pharmacokinetic measurements after a single RAD001 administration (5 mg/kg, over a 72 h period) demonstrated good bioavailability/efficient tumor penetration (maximal concentrations in blood and tumor, ~200 and ~700 nM, respectively) and prolonged residency [RAD001 half-life, ~20–22h. 7 Unfortunately, a precise correlation of pharmacokinetic parameters with antiproliferative effects in tumors is difficult in this model because of the inability to determine *in vitro* IC_{50} values with the nonculturable CA20948 line. However, the efficient tumor accumulation and relatively long half-life of RAD001 provide further rationale for the long-term effects observed in this model.

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Sequential tumor sampling is difficult in the clinical setting, necessitating some reliance on surrogate tissue to assess pharmacodynamic effects of antitumor agents. For this reason, the possibility of using PBMCs as a source for biomarker analysis when assessing RAD001 treatment schedules was evaluated. Detailed efficacy experiments demonstrated that antitumor response to weekly administration of RAD001 was dose dependent

Moreover, significant antitumor responses were associated with long-term effects on the mTOR pathway in PBMCs. Interestingly, PBMC-derived 4E-BP1 was unaffected by a suboptimal RAD001 dose (0.5 mg/kg), despite transient effects on S6K1 activity. This suggests that S6K1 is a more sensitive marker of RAD001 exposure in PBMCs than 4E-BP1. Indeed, all doses of RAD001 evaluated elicited a dramatic inhibition of PBMC-derived S6K1 after 24 h. However, the rate at which S6K1 activity subsequently recovered differed, with RAD001 doses that were efficacious with weekly schedules causing more profound long-term effects on S6K1 activity (≥7 days). The demonstration that the mTOR pathway is affected in PBMCs for a week after administration of 5 mg/kg RAD001 may be interpreted as being contrary to our observations that weekly treatment with this dose is suboptimal in terms of suppression of T-cell-dependent antigen responses. To reconcile these observations, one has to consider that T- and B-cell proliferative responses to foreign antigen presentation occur mainly in the secondary lymphoid organs **(64)** . Here we assayed S6K1 derived from PBMCs, a source that does not reflect the situation in these organs. We therefore speculate that, using weekly schedules, there is a possibility to recover T-cell responses, a phenomenon that may also reflect the pharmacokinetic characteristics of RAD001.

To most efficiently exploit the pharmacological profile of targeted agents such as RAD001, it is important to carefully monitor the dose given to a cancer patient, especially considering the observation that rapamycin can be less effective as an antitumor agent in animal models if overdosed **(59)** . The ease of human PBMC preparation suggests that this could be a valuable surrogate tissue when establishing treatment regimens for RAD001 in clinical trials for oncology. Based on this premise, S6K1 activity could be reproducibly assayed in PBMC extracts prepared from healthy volunteers, and RAD001 treatment of whole blood *ex vivo* resulted in concentration-dependent inactivation of the kinase. In contrast, despite promising results in tumor extracts derived from xenograft models **(53)** and suggestions that 4E-BP1 phosphorylation could be used as a confirmatory measure of mTOR inhibition in PBMCs **(66)** , we have shown that 4E-BP1 phosphorylation cannot be detected in human PBMCs. During the revision of this manuscript, others **(66 , 67)** also reported on the potential for PBMC-derived S6K1 activity measurements to aid pharmacodynamic evaluation of rapamycin derivatives. Analysis of cancer patient-derived PBMCs after i.v. administration of 25, 75, and 250 mg CCI-779 demonstrated inactivation of PBMC-derived S6K1 for up to 8 days, with no evidence of dose dependency at the doses used **(66**, **67**, **68)** . Although a limited feasibility study in nine patients indicated an association between time to disease progression and the degree of inhibition of S6K1 24 h after CCI-779 administration, no conclusions were drawn regarding the predictive nature of this biomarker or associated implications of the long-term S6K1 inactivation observed in patients **(67)** . Our data provide a strong experimental rationale for analyzing long-term effects on PBMC-derived S6K1 activity when establishing weekly administration schedules. Indeed, recent Phase I trials with weekly administration of RAD001 in patients with advanced cancer have demonstrated a clear association between RAD001 dose and the recovery of PBMC-derived S6K1 activity over a ≥7-day period **(69)** . The value of these observations in terms of prediction of patient response is now being pursued in clinical trials of RAD001 in oncology.

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- 3 T. O'Reilly, H. A. Lane, and C. Heusser, unpublished data.
- 4 A. Boulay and H. A. Lane, unpublished data.
- 5 A. Boulay, S. Zumstein-Mecker, and H. A. Lane, unpublished data.
- 6 A. Boulay, T. O'Reilly, and H. A. Lane, unpublished data.
- 7 T. O'Reilly and L. McMahon, unpublished data.
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References

1. Nashan B. Early clinical experience with a novel rapamycin derivative. *Ther. Drug Monit.*, **24**: 53-58, 2002. CrossRef Medline
2. Huang S., Houghton P. J. Inhibitors of mammalian target of rapamycin as novel antitumor agents: from bench to clinic. *Curr. Opin. Investig. Drugs*, **3**: 295-304, 2002. Medline
3. Mita M. M., Mita A., Rowinski E. K. Mammalian target of rapamycin: a new molecular target for breast cancer. *Clin. Breast Cancer*, **4**: 126-137, 2003. CrossRef Medline
4. Hidalgo M., Rowinsky E. K. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. *Oncogene*, **19**: 6680-6686, 2000. CrossRef Medline
5. Gingras A. C., Raught B., Sonenberg N. Regulation of translation initiation by FRAP/mTOR. *Genes Dev.*, **15**: 807-826, 2001. FREE Full Text
6. Tibbetts R. S., Abraham R. T. PI3K-related kinases: roles in cell-cycle regulation and DNA damage responses Gutkind J. S. eds. . *Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases*, **Vol. 5**:

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267-301, Humana Press Totowa, NJ 2000. CrossRef

7. Desai B. N., Myers B. R., Schreiber S. L. FKBP12-rapamycin-associated protein associates with mitochondria and senses osmotic stress via mitochondrial dysfunction. *Proc. Natl. Acad. Sci. USA*, **99**: 4319-4324, 2002. Abstract/FREE Full Text

8. Hara K., Yonezawa K., Weng Q. P., Kozlowski M. T., Belham C., Avruch J. Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 through a common effector mechanism. *J. Biol. Chem.*, **273**: 14484-14494, 1998. Abstract/FREE Full Text

9. Xu G., Kwon G., Marshall C. A., Lin T. A., Lawrence J. C., Jr., McDaniel M. L. Branched-chain amino acids are essential in the regulation of PHAS-I and p70 S6 kinase by pancreatic β-cells. A possible role in protein translation and mitogenic signaling. *J. Biol. Chem.*, **273**: 28178-28184, 1998. Abstract/FREE Full Text

10. Iiboshi Y., Papst P. J., Kawasome H., Hosoi H., Abraham R. T., Houghton P. J., Terada N. Amino acid-dependent control of p70(s6k). involvement of tRNA aminoacylation in the regulation. *J. Biol. Chem.*, **274**: 1092-1099, 1999. Abstract/FREE Full Text

11. Dennis P. B., Jaeschke A., Saitoh M., Fowler B., Kozma S. C., Thomas G. Mammalian TOR: a homeostatic ATP sensor. *Science (Wash. DC)*, **294**: 1102-1105, 2001. Abstract/FREE Full Text

12. Dufner A., Thomas G. Ribosomal S6 kinase signaling and the control of translation. *Exp. Cell Res.*, **253**: 100-109, 1999. CrossRef Medline

13. Hashemolhosseini S., Nagamine Y., Morley S. J., Desrivieres S., Mercep L., Ferrari S. Rapamycin inhibition of the G_1 to S transition is mediated by effects on cyclin D1 mRNA and protein stability. *J. Biol. Chem.*, **273**: 14424-14429, 1998. Abstract/FREE Full Text

14. West M. J., Stoneley M., Willis A. E. Translational induction of the c-myc oncogene via activation of the FRAP/TOR signalling pathway. *Oncogene*, **17**: 769-780, 1998. CrossRef Medline

15. Peng T., Golub T. R., Sabatini D. M. The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. *Mol. Cell. Biol.*, **22**: 5575-5584, 2002. Abstract/FREE Full Text

16. Fingar D. C., Salama S., Tsou C., Harlow E., Blenis J. Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. *Genes Dev.*, **16**: 1472-1487, 2002. Abstract/FREE Full Text

17. Scott P. H., Brunn G. J., Kohn A. D., Roth R. A., Lawrence J. C., Jr. Evidence of insulin-stimulated phosphorylation and activation of the mammalian target of rapamycin mediated by a protein kinase B signaling pathway. *Proc. Natl. Acad. Sci. USA*, **95**: 7772-7777, 1998. Abstract/FREE Full Text

18. Nave B. T., Ouwens M., Withers D. J., Alessi D. R., Shepherd P. R. Mammalian target of rapamycin is a direct target for protein kinase B: identification of a convergence point for opposing effects of insulin and amino-acid deficiency on protein translation. *Biochem. J.*, **344**: 427-431, 1999.

19. Sekulic A., Hudson C. C., Homme J. L., Yin P., Otterness D. M., Karnitz L. M., Abraham R. T. A direct linkage between the phosphoinositide 3-kinase-AKT signaling pathway and the mammalian target of rapamycin in mitogen-stimulated and transformed cells. *Cancer Res.*, **60**: 3504-3513, 2000. Abstract/FREE Full Text

20. Inoki K., Li Y., Zhu T., Wu J., Guan K. L. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nat. Cell Biol.*, **4**: 648-657, 2002. CrossRef Medline

21. Potter C. J., Pedraza L. G., Xu T. Akt regulates growth by directly phosphorylating Tsc2. *Nat. Cell Biol.*, **4**: 658-665, 2002. CrossRef Medline

22. Garami A., Zwartkruis F. J., Nobukuni T., Joaquin M., Roccio M., Stocker H., Kozma S. C., Hafen E., Bos J. L., Thomas G. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. *Mol. Cell*, **11**: 1457-1466, 2003. CrossRef Medline

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activity and regulates mTOR signaling. *Genes Dev.*, **17**: 1829-1834, 2003. Abstract/FREE Full Text

24. Neshat M. S., Mellinghoff I. K., Tran C., Stiles B., Thomas G., Petersen R., Frost P., Gibbons J. J., Wu H., Sawyers C. L. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. *Proc. Natl. Acad. Sci. USA*, **98**: 10314-10319, 2001. Abstract/FREE Full Text

25. Podsypanina K., Lee R. T., Politis C., Hennessy I., Crane A., Puc J., Neshat M., Wang H., Yang L., Gibbons J., Frost P., Dreisbach V., Blenis J., Gaciong Z., Fisher P., Sawyers C., Hedrick-Ellenson L., Parsons R. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in PTEN+/− mice. *Proc. Natl. Acad. Sci. USA*, **98**: 10320-10325, 2001. Abstract/FREE Full Text

26. Shi Y., Gera J., Hu L., Hsu J. H., Bookstein R., Li W., Lichtenstein A. Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779. *Cancer Res.*, **62**: 5027-5034, 2002. Abstract/FREE Full Text

27. Lane H. A., Boulay A., Hattenberger M., Maira S-M., Thomas G., Merlo A., O'Reilly T. The orally active rapamycin derivative RAD001 has potential as an antitumor agent with a broad antiproliferative activity: PTEN as a molecular determinant of response. *Proc. Am. Assoc. Cancer Res.*, **44**: 314 2003.

28. Kim D. H., Sarbassov D. D., Ali S. M., King J. E., Latek R. R., Erdjument-Bromage H., Tempst P., Sabatini D. M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell*, **110**: 163-175, 2002. CrossRef Medline

29. Hara K., Maruki Y., Long X., Yoshino K., Oshiro N., Hidayat S., Tokunaga C., Avruch J., Yonezawa K. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell*, **110**: 177-189, 2002. CrossRef Medline

30. Kim D. H., Sarbassov dos D., Ali S. M., Latek R. R., Guntur K. V., Erdjument-Bromage H., Tempst P., Sabatini D. M. GβL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. *Mol. Cell*, **11**: 895-904, 2003. CrossRef Medline

31. Schalm S. S., Blenis J. Identification of a conserved motif required for mTOR signaling. *Curr. Biol.*, **12**: 632-639, 2002. CrossRef Medline

32. Schalm S. S., Fingar D. C., Sabatini D. M., Blenis J. TOS motif-mediated raptor binding regulates 4E-BP1 multisite phosphorylation and function. *Curr. Biol.*, **13**: 797-806, 2003. CrossRef Medline

33. Nojima H., Tokunaga C., Eguchi S., Oshiro N., Hidayat S., Yoshino K., Hara K., Tanaka N., Avruch J., Yonezawa K. The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif. *J. Biol. Chem.*, **278**: 15461-15464, 2003. Abstract/FREE Full Text

34. Gingras A. C., Gygi S. P., Raught B., Polakiewicz R. D., Abraham R. T., Hoekstra M. F., Aebersold R., Sonenberg N. Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism. *Genes Dev.*, **13**: 1422-1437, 1999. Abstract/FREE Full Text

35. Mothe-Satney I., Brunn G. J., McMahon L. P., Capaldo C. T., Abraham R. T., Lawrence J. C., Jr. Mammalian target of rapamycin-dependent phosphorylation of PHAS-I in four (S/T)P sites detected by phospho-specific antibodies. *J. Biol. Chem.*, **275**: 33836-33843, 2000. Abstract/FREE Full Text

36. Jefferies H. B., Reinhard C., Kozma S. C., Thomas G. Rapamycin selectively represses translation of the "polypyrimidine tract" mRNA family. *Proc. Natl. Acad. Sci. USA*, **91**: 4441-4445, 1994. Abstract/FREE Full Text

37. Jefferies H. B., Fumagalli S., Dennis P. B., Reinhard C., Pearson R. B., Thomas G. Rapamycin suppresses 5'TOP mRNA translation through inhibition of p70s6k. *EMBO J.*, **16**: 3693-3704, 1997. Abstract

38. Meyuhas O. Synthesis of the translational apparatus is regulated at the translational level. *Eur. J. Biochem.*, **267**: 6321-6330, 2000. CrossRef Medline

39. Pearson R. B., Dennis P. B., Han J. W., Williamson N. A., Kozma S. C., Wettenhall R. E., Thomas G. The principal target of rapamycin-induced p70s6k inactivation is a novel phosphorylation site within a conserved hydrophobic domain

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EMBO J., **14**: 5279-5287, 1995. Medline

40. Peterson R. T., Beal P. A., Comb M. J., Schreiber S. L. FKBP12-rapamycin-associated protein (FRAP) autophosphorylates at serine 2481 under translationally repressive conditions. *J. Biol. Chem.*, **275**: 7416-7423, 2000. Abstract/FREE Full Text

41. Brunn G. J., Hudson C. C., Sekulic A., Williams J. M., Hosoi H., Houghton P. J., Lawrence J. C., Jr., Abraham R. T. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. *Science (Wash. DC)*, **277**: 99-101, 1997. Abstract/FREE Full Text

42. Burnett P. E., Barrow R. K., Cohen N. A., Snyder S. H., Sabatini D. M. RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. *Proc. Natl. Acad. Sci. USA*, **95**: 1432-1437, 1998. Abstract/FREE Full Text

43. Beuvink I., O'Reilly T., Zumstein-Mecker S., Zilbermann F., Sedrani R., Kozma S. C., Thomas G., Lane H. A. Antitumor activity of RAD001, an orally active rapamycin derivative. *Proc. Am. Assoc. Cancer Res.*, **42**: 366 2001.

44. O'Reilly T., Vaxelaire J., Muller M., Fiebig H. H., Hattenberger M., Lane H. A. *In vivo* activity of RAD001, an orally active rapamycin derivative, in experimental tumor models. *Proc. Am. Assoc. Cancer Res.*, **43**: 71 2002.

45. Majewski M., Korecka M., Kossev P., Li S., Goldman J., Moore J., Silberstein L. E., Nowell P. C., Schuler W., Shaw L. M., Wasik M. A. The immunosuppressive macrolide RAD inhibits growth of human Epstein-Barr virus-transformed B lymphocytes *in vitro* and *in vivo*: a potential approach to prevention and treatment of posttransplant lymphoproliferative disorders. *Proc. Natl. Acad. Sci. USA*, **97**: 4285-4290, 2000. Abstract/FREE Full Text

46. Majewski M., Korecka M., Joergensen J., Fields L., Kossev P., Schuler W., Shaw L., Wasik M. A. Immunosuppressive TOR kinase inhibitor everolimus (RAD) suppresses growth of cells derived from posttransplant lymphoproliferative disorder at allograft-protecting doses. *Transplantation*, **75**: 1710-1717, 2003. CrossRef Medline

47. Schuler W., Sedrani R., Cottens S., Häberlin B., Schulz M., Schuurman H. J., Zenke G., Zerwes H. G., Schreier M. H. SDZ RAD, a new rapamycin derivative: pharmacological properties *in vitro* and *in vivo*. *Transplantation*, **64**: 36-42, 1997. CrossRef Medline

48. Lane H. A., Beuvink I., Motoyama A. B., Daly J. M., Neve R. M., Hynes N. E. ErbB2 potentiates breast tumor proliferation through modulation of p27(Kip1)-Cdk2 complex formation: receptor overexpression does not determine growth dependency. *Mol. Cell. Biol.*, **20**: 3210-3223, 2000. Abstract/FREE Full Text

49. Olayioye M. A., Graus-Porta D., Beerli R. R., Rohrer J., Gay B., Hynes N. E. ErbB-1 and ErbB-2 acquire distinct signaling properties dependent upon their dimerization partner. *Mol. Cell. Biol.*, **18**: 5042-5051, 1998. Abstract/FREE Full Text

50. Lane H. A., Thomas G. Purification and properties of mitogen-activated S6 kinase from rat liver and 3T3 cells. *Methods Enzymol.*, **200**: 268-291, 1991. CrossRef Medline

51. Hosoi H., Dilling M. B., Shikata T., Liu L. N., Shu L., Ashmun R. A., Germain G. S., Abraham R. T., Houghton P. J. Rapamycin causes poorly reversible inhibition of mTOR and induces p53-independent apoptosis in human rhabdomyosarcoma cells. *Cancer Res.*, **59**: 886-894, 1999. Abstract/FREE Full Text

52. Schuurman H. J., Cottens S., Fuchs S., Joergensen J., Meerloo T., Sedrani R., Tanner M., Zenke G., Schuler W. SDZ RAD, a new rapamycin derivative: synergism with cyclosporine. *Transplantation*, **64**: 32-35, 1997. CrossRef Medline

53. Dudkin L., Dilling M. B., Cheshire P. J., Harwood F. C., Hollingshead M., Arbuck S. G., Travis R., Sausville E. A., Houghton P. J. Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition. *Clin. Cancer Res.*, **7**: 1758-1764, 2001. Abstract/FREE Full Text

54. Jiang Y. P., Ballou L. M., Lin R. Z. Rapamycin-insensitive regulation of 4E-BP1 in regenerating rat liver. *J. Biol. Chem.*, **276**: 10943-10951, 2001. Abstract/FREE Full Text

55. Eng C. P., Sehgal S. N., Vezina C. Activity of rapamycin (AY-22,989) against transplanted tumors. *J. Antibiot.*, **37**: 1231-1237, 1984. CrossRef Medline

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56. Houchens D. P., Ovejera A. A., Riblet S. M., Slagel D. E. Human brain tumor xenografts in nude mice as a chemotherapy model. *Eur. J. Cancer Clin. Oncol.*, **19**: 799-805, 1983. CrossRef Medline

57. Geoerger B., Kerr K., Tang C. B., Fung K. M., Powell B., Sutton L. N., Phillips P. C., Janss A. J. Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy. *Cancer Res.*, **61**: 1527-1532, 2001. Abstract/FREE Full Text

58. Yu K., Toral-Barza L., Discafani C., Zhang W. G., Skotnicki J., Frost P., Gibbons J. J. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. *Endocr. Relat. Cancer*, **8**: 249-258, 2001. Abstract

59. Guba M., von Breitenbuch P., Steinbauer M., Koehl G., Flegel S., Hornung M., Bruns C. J., Zuelke C., Farkas S., Anthuber M., Jauch K. W., Geissler E. K. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat. Med.*, **8**: 128-135, 2002. CrossRef Medline

60. Grewe M., Gansauge F., Schmid R. M., Adler G., Seufferlein T. Regulation of cell growth and cyclin D1 expression by the constitutively active FRAP-p70s6K pathway in human pancreatic cancer cells. *Cancer Res.*, **59**: 3581-3587, 1999. Abstract/FREE Full Text

61. Shah S. A., Potter M. W., Ricciardi R., Perugini R. A., Callery M. P. FRAP-p70S6K signaling is required for pancreatic cancer cell proliferation. *J. Surg. Res.*, **97**: 123-130, 2001. CrossRef Medline

62. Kovarik J. M., Kaplan B., Tedesco Silva H., Kahan B. D., Dantal J., Vitko S., Boger R., Rordorf C. Exposure-response relationships for everolimus in de *novo* kidney transplantation: defining a therapeutic range. *Transplantation*, **73**: 920-925, 2002. CrossRef Medline

63. Terada N., Franklin R. A., Lucas J. J., Blenis J., Gelfand E. W. Failure of rapamycin to block proliferation once resting cells have entered the cell cycle despite inactivation of p70 S6 kinase. *J. Biol. Chem.*, **268**: 12062-12068, 1993. Abstract/FREE Full Text

64. Zenke G., Strittmatter U., Fuchs S., Quesniaux V. F., Brinkmann V., Schuler W., Zurini M., Enz A., Billich A., Sanglier J. J., Fehr T. Sanglifehrin A, a novel cyclophilin-binding compound showing immunosuppressive activity with a new mechanism of action. *J. Immunol.*, **166**: 7165-7171, 2001. Abstract/FREE Full Text

65. Chung J., Kuo C. J., Crabtree G. R., Blenis J. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. *Cell*, **69**: 1227-1236, 1992. CrossRef Medline

66. Harding M. W. Immunophilins, mTOR, and pharmacodynamic strategies for a targeted cancer therapy. *Clin. Cancer Res.*, **9**: 2882-2886, 2003. FREE Full Text

67. Peralba J. M., deGraffenried L., Friedrichs W., Fulcher L., Grünwald V., Weiss G., Hidalgo M. Pharmacodynamic evaluation of CCI-779, an inhibitor of mTOR, in cancer patients. *Clin. Cancer Res.*, **9**: 2887-2892, 2003. Abstract/FREE Full Text

68. Stadler W., Logan T., Dutcher J., Hudes G., Park Y., Marshall B., Boni J., Dukart J. A randomized double-blind phase 2 study of intravenous CCI-779 administered weekly to patients with advanced renal cell carcinoma. *Proc. Am. Soc. Clin. Oncol.*, **21**: 10a 2002.

69. O'Donnell A., Faivre S., Judson I., Delbado C., Brock C., Lane H., Shand N., Hazell K., Armand J-P., Raymond E. Phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours. *Proc. Am. Soc. Clin. Oncol.*, **22**: 200 2003.

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Contents

Letter from the President

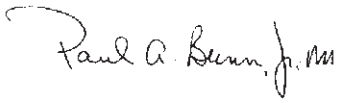
Dear Colleagues,

On behalf of the American Society of Clinical Oncology's Board of Directors, I invite you to attend the Thirty-Ninth ASCO Annual Meeting, the premier event of our year, to be held in Chicago, Illinois, on May 31-June 3, 2003. As oncologists, our priority is the patient with cancer, and this year's Meeting reflects our commitment to advancing excellence in the care of patients and to offering our patients compassion as well as care. You will note that this year's Meeting has a patient theme, and we have planned several special sessions and events to represent this theme. More information on these activities will be available onsite at the Meeting.

As with the Preliminary Program Announcement, the contents of the Final Program Announcement are organized in two ways to help you evaluate the Meeting program. You can review the program according to the daily schedule or according to 23 primary tracks, or series of educational and scientific sessions in disease-specific or discipline-related topics. The Final Program Announcement also includes new information—details on the Plenary Session and other scientific sessions. Nearly 2,100 abstracts, representing the latest advances in cancer research, will be presented in oral and poster sessions.

Please review this Final Program Announcement to learn more about ASCO's Thirty-Ninth Annual Meeting and the four Educational Symposia offered on Friday, May 30, before the official start of the Meeting. I hope you plan to attend the best Meeting we have ever designed, and I encourage you to register as soon as possible to ensure your place in limited-attendance sessions. I look forward to seeing you in Chicago.

Sincerely,



Paul A. Bunn, Jr., MD
ASCO 2002-2003 President

Commitment Care Compassion
Honoring People with Cancer

INTRODUCTION TO THE 2003 ANNUAL MEETING

The 2003 ASCO Annual Meeting is structured to serve the respective interests of the Society's multidisciplinary membership, with education focused on medical, surgical, and radiation oncology. Again this year, both educational and scientific sessions have been combined to form tracks, or series of focused learning opportunities on disease-specific topics and oncology-related subjects. The primary tracks include

- Breast Cancer
- Cancer Prevention/Epidemiology
- Central Nervous System Tumors
- Clinical Trials
- Developmental Therapeutics
- Ethics
- Fellows and Junior Faculty Program
- Gastrointestinal (Colorectal and Noncolorectal) Cancer
- Genitourinary Cancer
- Geriatric Oncology
- Gynecologic Cancer
- Head and Neck Cancer
- Health Services Research
- Hematologic Malignancies
- Lung Cancer
- Melanoma
- Patient Care
- Pediatric Cancer
- Practice Management and Professional Issues
- Sarcoma/Bone and Soft Tissue Cancers
- Surgical Oncology and Management
- Transplantation
- Tumor Biology/Human Genetics

This program announcement features the Annual Meeting program presented in two ways: according to the daily schedule (page 8) and according to primary track (page 19). Because many sessions can be categorized according to more than one track, prospective attendees are encouraged to review the sessions offered in other tracks to ensure that they find all the sessions in their preferred area of interest.

NEEDS STATEMENT

The clinical practice of oncology continues to be a rapidly evolving discipline. Changes in the understanding of pathophysiology, diagnosis, and management, together with newly approved drugs and therapies and their indications relevant to oncology practice, create a need for continuing education.

OVERALL GOAL

The goal of the 2003 ASCO Annual Meeting is to foster communication among cancer-related medical subspecialties and the exchange of a wide range of ideas related to cancer. ASCO's objectives are to advance the education of physicians and other professionals in the care of patients with cancer, support the development of clinical cancer researchers, and facilitate the delivery of high-quality health care to patients with cancer.

TARGET AUDIENCE

The Annual Meeting is targeted to U.S. and international physicians, academicians, clinical researchers, nurses, pharmacists, and other health-care professionals involved in multidisciplinary clinical cancer care.

ACCREDITATION STATEMENT

The American Society of Clinical Oncology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION

The American Society of Clinical Oncology designates this educational activity for a maximum of 29.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

New This Year: One hundred sessions in the 2003 ASCO Annual Meeting program are certified for pharmacy and/or nursing continuing education credit. Sessions certified for such credit are identified by a statement with the description of the session.

Professional Education Services Group is accredited by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Provider number 829. Continuing Education Statements of Credit will be distributed by mail four weeks after successful completion of a CE workbook and a separate program evaluation form.

Professional Education Services Group is accredited by the American Nurses Credentialing Center's Commission on Accreditation as a provider of continuing education in nursing. Selected sessions in this activity are designated for nursing credit.

EDUCATIONAL SYMPOSIA

In addition to the Annual Meeting, ASCO offers certified continuing medical education activities through the Society's Educational Symposia. The symposia held in conjunction with the 2003 Annual Meeting are described on page 50.

CANCELLATION STATEMENT

The American Society of Clinical Oncology reserves the right to cancel this activity because of unforeseen circumstances. In the event of such cancellation, the full registration fee will be returned to each registrant.

EQUAL OPPORTUNITY STATEMENT

Events and activities of the American Society of Clinical Oncology are available without regard to race, color, sex, national origin, disability, age, or veteran status as provided by law and in accordance with the Society's respect for personal dignity.

Descriptions of Session Types

The 2003 Annual Meeting, developed by Cancer Education Committee and the Scientific Program Committee, is made up of the following types of sessions.

SPECIAL SESSIONS

Special Sessions include Award Lectures as well as symposia recommended by other oncology-related organizations and developed in conjunction with ASCO, the Cancer Education Committee, and the ASCO Board of Directors as being of particular interest, importance, and relevance to Meeting attendees.

INTEGRATED EDUCATION SESSIONS

Integrated Education Sessions provide a forum for translational science in oncology, combining the presentation of selected abstracts on a specific topic with didactic lectures. Experts in the field place the studies in the appropriate context based on the strength of the evidence and critically discuss the conclusions in terms of their applicability to clinical practice.

EDUCATION SESSIONS

Education Sessions offer multidisciplinary explorations of focused topics in clinical oncology. Particular care was taken to ensure that these sessions are integrated in terms of such issues as surgical, radiation, and geriatric oncology; symptom management; health services research; international perspectives; and pathology, as appropriate.

FELLOWS AND JUNIOR FACULTY EDUCATION SESSIONS

Fellows and Junior Faculty Education Sessions are moderated by recognized leaders in oncology and focus on topics targeted specifically to the career development needs of fellows, junior faculty, and beginning practitioners.

SCIENTIFIC SYMPOSIA

Scientific Symposia provide perspectives on translational and cutting-edge research, with an emphasis on clinical relevance.

ORAL ABSTRACT PRESENTATION SESSIONS

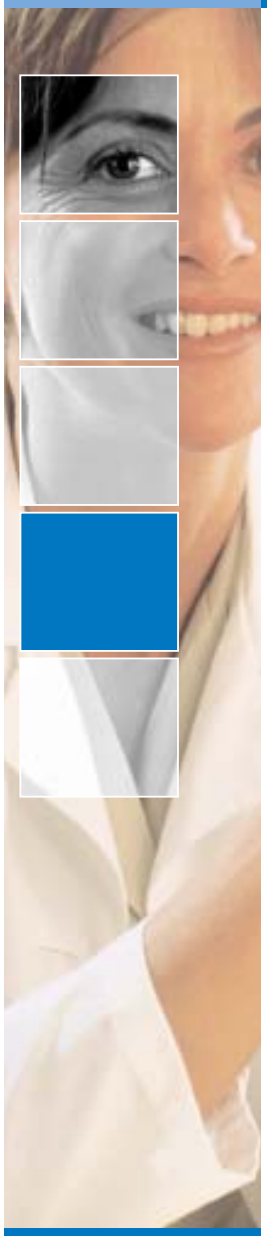
Oral Abstract Presentation Sessions include 10-minute didactic presentations of selected abstracts of scientific research in clinical trials by topical area. Experts in the field serve as Discussants to place research findings into perspective.

POSTER DISCUSSION SESSIONS

Poster Discussion Sessions highlight selected abstracts of clinical research in poster format. The posters are grouped by topic or by the questions posed as a result of the research findings. During the time the posters are on display, attendees may ask questions of the authors regarding the displayed information. The discussion portion of the session (one hour) provides expert commentary on research findings in context.

GENERAL POSTER SESSIONS

General Poster Sessions include selected abstracts of clinical research in poster format. The posters are grouped by topic and during their display, attendees may ask questions of the authors regarding the displayed information.



Ticketed Sessions

Ticketed sessions require additional registration. Each ticketed session has a code that should be entered on the Individual Registration Form. Early registration is encouraged, as attendance in these sessions is limited. Registration fees for these sessions vary (see page 66).

MEET THE PROFESSOR SESSIONS

Meet the Professor Sessions provide open discussion between recognized experts and session attendees, with an opportunity for attendees to obtain answers to specific questions. Attendees may register for only two Meet the Professor Sessions.

This year, Meet the Professor Sessions have been classified according to several types, each providing a different forum tailored for specific educational objectives. The title of each session provides a reference to one of the new classifications, as described here.

- Expert Opinion: The format is a combination of didactic introduction by an expert and interactive group discussion.
- Controversies: Both sides of a controversial issue are presented, with a discussion of the background and supporting evidence for each perspective.
- Emerging Concepts: The session provides an opportunity for attendees to gain a deeper understanding of an emerging concept..
- Research Seminar: The format provides a forum for high-level scientific discussion of a specific research issue.
- Method: The session enables participants to explore how they can implement methods or procedures into their research or practice.

FELLOWS AND JUNIOR FACULTY MEET THE PROFESSOR SESSIONS

Fellows and Junior Faculty Meet the Professor Sessions provide an informal environment for fellows, junior faculty, and beginning practitioners to participate in discussion targeted to their knowledge level.

CLINICAL PROBLEMS IN ONCOLOGY SESSIONS

Clinical Problems in Oncology Sessions combine the use of case-based panel discussion with interactive, keypad technology for audience participation. Attendees may register for only one Clinical Problems in Oncology Session.

Times and speakers are subject to change. Updated information will be available on www.ASCO.org.

Plenary Session

MONDAY, JUNE 2, 2003
1:00 PM – 3:30 PM

CHAIRS

Paul A. Bunn, Jr., MD—Co-Chair
ASCO President

S. Gail Eckhardt, MD—Co-Chair
Chair, ASCO Scientific Program Committee

ABSTRACT 1

Emerging Science
Prospective Validation of Gene Expression Profiling-Based Prediction of Complete Pathologic Response to Neoadjuvant Paclitaxel/FAC Chemotherapy in Breast Cancer

Presenting Author: Lajos Pusztai, MD, PhD
M.D. Anderson Cancer Center

Discussant: Larry Norton, MD
Memorial Sloan-Kettering Cancer Center

ABSTRACT 2

A Randomized Trial of Direct Decompressive Surgical Resection in the Treatment of Spinal Cord Compression Caused by Metastasis

Presenting Author: Roy Patchell, MD
University of Kentucky

Discussant: William Shapiro, MD
St. Joseph's Hospital and Medical Center

ABSTRACT 3

Whole Abdominal Radiotherapy versus Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Randomized Phase III Trial of the Gynecologic Oncology Group

Presenting Author: Marcus E. Randall, MD
Indiana University School of Medicine

Discussant: Gilliam Thomas, MD
GlaxoSmithKline

ABSTRACTS 4 AND 5

Surveillance of "High Risk" Women with Proven or Suspected Familial (Hereditary) Breast Cancer: First Mid-Term Results of a Multi-Modality Clinical Screening Trial

Presenting Author: Christiane K. Kuhl, MD, PhD
University of Bonn

MRI Screening for Breast Cancer in Women with High Familial and Genetic Risk: First Results of the Dutch MRI Screening Study (MRISC)

Presenting Author: Mieke Kriege, MS
Erasmus MC, University Medical Center Rotterdam

Discussant: Elizabeth Morris, MD
Memorial Sloan-Kettering Cancer Center

ABSTRACT 6

Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): Cisplatin-Based Chemotherapy (CT) vs No CT in 1867 Patients (PTS) with Resected Non-Small-Cell Lung Cancer

Presenting Author: Thierry Le Chevalier, MD
Institut Gustave Roussy

Discussant: David H. Johnson, MD
Vanderbilt-Ingram Cancer Center

DAILY SCHEDULE

ASCO FINAL PROGRAM

On the following pages, the educational and scientific programs of the 2003 Annual Meeting are presented according to the daily schedule, beginning with the ASCO Educational Symposia offered on the day before the official start of the Meeting. Refer to the page numbers given here to find faculty information, additional times the session may be offered, continuing medical education (CME) credit hours, nursing contact hours, pharmacy contact hours, and other sessions that have been categorized within the same primary track.

Friday, May 30, 2003

PAGE

11:30 AM – 4:00 PM

EDUCATIONAL SYMPOSIUM

12:00 PM – 4:00 PM

EDUCATIONAL SYMPOSIA

Saturday, May 31, 2003

7:45 AM – 9:00 AM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

PAGE

SCIENTIFIC SYMPOSIUM

7:45 AM – 9:15 AM

INTEGRATED EDUCATION SESSION

7:45 AM – 9:45 AM

POSTER DISCUSSION SESSION

7:45 AM – 10:45 AM

ORAL ABSTRACT SESSION

9:00 AM – 1:00 PM

GENERAL POSTER SESSIONS

9:15 AM – 12:00 PM

SPECIAL SESSION

12:30 PM – 1:45 PM

EDUCATION SESSION

PAGE

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

SPECIAL SESSION

12:45 PM – 2:00 PM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

12:45 PM – 2:15 PM

INTEGRATED EDUCATION SESSION

12:45 PM – 3:45 PM

ORAL ABSTRACT SESSION

PAGE

1:00 PM – 4:00 PM

ORAL PRESENTATION

1:00 PM – 5:00 PM

ORAL PRESENTATION

POSTER DISCUSSION SESSIONS

1:30 PM – 5:30 PM

POSTER DISCUSSION SESSIONS

GENERAL POSTER SESSION

2:00 PM – 3:30 PM

SPECIAL SESSION

2:00 PM – 5:30 PM

GENERAL POSTER SESSIONS

2:15 PM – 3:30 PM

CLINICAL PROBLEMS IN ONCOLOGY

Additional registration is required for this ticketed session type.

DAILY SCHEDULE

SATURDAY (CONTINUED)

PAGE

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

2:30 PM – 3:45 PM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

4:00 PM – 5:15 PM

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

PAGE

4:00 PM – 5:30 PM

SPECIAL SESSION

4:15 PM – 5:45 PM

SPECIAL SESSIONS

4:15 PM – 5:30 PM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

4:30 PM – 5:45 PM

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

Sunday, June 1, 2003

7:45 AM – 9:00 AM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

PAGE

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

7:45 AM – 10:45 AM

ORAL ABSTRACT SESSIONS

7:45 AM – 11:45 AM

ORAL ABSTRACT SESSION

8:00 AM – 10:30 AM

ORAL ABSTRACT SESSION

8:00 AM – 12:00 PM

POSTER DISCUSSION SESSIONS

8:00 AM – 12:15 PM

POSTER DISCUSSION SESSIONS

PAGE

9:00 AM – 10:30 AM

SPECIAL SESSION

9:00 AM – 1:00 PM

GENERAL POSTER SESSIONS

9:15 AM – 10:30 AM

EDUCATION SESSION

SCIENTIFIC SYMPOSIUM

9:30 AM – 10:45 AM

EDUCATION SESSIONS

FELLOWS EDUCATION SESSION

FELLOWS MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

9:30 AM – 11:00 AM

EDUCATION SESSION

DAILY SCHEDULE

SUNDAY (CONTINUED)

DAILY SCHEDULE

SUNDAY (CONTINUED)

PAGE

2:45 PM – 4:00 PM

CLINICAL PROBLEMS IN ONCOLOGY
Additional registration is required for this ticketed session type.

EDUCATION SESSION

FELLOWS MEET THE PROFESSOR SESSION
Additional registration is required for this ticketed session type.

MEET THE PROFESSOR SESSIONS
Additional registration is required for this ticketed session type.

2:45 PM – 5:45 PM

ORAL ABSTRACT SESSION

3:45 PM – 5:15 PM

SPECIAL SESSION

4:15 PM – 5:45 PM

SPECIAL SESSION

PAGE

4:30 PM – 5:45 PM

EDUCATION SESSION

FELLOWS EDUCATION SESSION

FELLOWS MEET THE PROFESSOR SESSION
Additional registration is required for this ticketed session type.

MEET THE PROFESSOR SESSIONS
Additional registration is required for this ticketed session type.

Monday, June 2, 2003

7:45 AM – 9:00 AM

EDUCATION SESSIONS

FELLOWS MEET THE PROFESSOR SESSION
Additional registration is required for this ticketed session type.

PAGE

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

SCIENTIFIC SYMPOSIA

7:45 AM – 9:15 AM

INTEGRATED EDUCATION SESSION

SPECIAL SESSION

7:45 AM – 10:45 AM

ORAL ABSTRACT SESSIONS

8:00 AM – 11:00 AM

ORAL ABSTRACT SESSION

PAGE

8:00 AM – 12:00 PM

POSTER DISCUSSION SESSIONS

8:00 AM – 12:15 PM

POSTER DISCUSSION SESSIONS

9:00 AM – 1:00 PM

GENERAL POSTER SESSIONS

9:30 AM – 10:45 AM

CLINICAL PROBLEMS IN ONCOLOGY

Additional registration is required for this ticketed session type.

EDUCATION SESSIONS

FELLOWS MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

DAILY SCHEDULE

MONDAY (CONTINUED)

PAGE

INTEGRATED EDUCATION SESSION

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

SPECIAL SESSION

11:00 AM – 12:00 PM

11:00 AM – 12:15 PM

EDUCATION SESSION

11:15 AM – 12:30 PM

INTEGRATED EDUCATION SESSION

CLINICAL PROBLEMS IN ONCOLOGY

Additional registration is required for this ticketed session type.

EDUCATION SESSIONS

PAGE

FELLOWS MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

SPECIAL SESSION

11:30 AM – 12:45 PM

MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

1:00 PM – 3:30 PM

PLENARY SESSION

PAGE

4:00 PM – 5:15 PM

CLINICAL PROBLEMS IN ONCOLOGY

Additional registration is required for this ticketed session type.

EDUCATION SESSIONS

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

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4:00 PM – 5:30 PM

INTEGRATED EDUCATION SESSIONS

SPECIAL SESSION

Tuesday, June 3, 2003

7:45 AM – 9:00 AM

CLINICAL PROBLEMS IN ONCOLOGY

Additional registration is required for this ticketed session type.

EDUCATION SESSIONS

FELLOWS MEET THE PROFESSOR SESSION

Additional registration is required for this ticketed session type.

MEET THE PROFESSOR SESSIONS

Additional registration is required for this ticketed session type.

DAILY SCHEDULE

TUESDAY (CONTINUED)

PROGRAM BY TRACK

BREAST CANCER

Evolution of Breast Cancer Management Over 30 Years Through Randomized Clinical Trials

CME credits: 0.5

Sunday, June 1
1:00 PM – 1:30 PM

Umberto Veronesi, MD
European Institute of Oncology

After this session, attendees should be able to
- Identify the results of clinical trials involving breast surgery options
- Describe the role of sentinel node in improving breast cancer staging and multidisciplinary management
- Discuss the emerging role of intraoperative breast radiation

Role of Molecular and Genetics Markers in Breast Cancer Treatment Decisions

CME credits: 1.5

Monday, June 2
7:45 AM – 9:15 AM

C. Kent Osborne, MD—Chair
Baylor College of Medicine

After this session, attendees should be able to
- Discuss key biologic pathways in breast cancer
- Describe the standard markers in use today
- Identify new molecular profiling techniques used to estimate prognosis or treatment response

Adjuvant Therapy for Breast Cancer

CME credits and pharmacy contact hours: 1.25

Sunday, June 1
9:30 AM – 10:45 AM

Monday, June 2
9:30 AM – 10:45 AM

Larry Norton, MD—Chair
Memorial Sloan-Kettering Cancer Center

I. Craig Henderson, MD
University of California at San Francisco

Hyman B. Muss, MD
University of Vermont

Charles L. Vogel, MD, FACP
Cancer Research Network

After this session, attendees should be able to
- Identify the optimal use of anthracyclines in adjuvant therapy for breast cancer
- Discuss the current use of taxanes in adjuvant therapy for breast cancer
- Evaluate other options for adjuvant therapy

Controversies in Metastatic Breast Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1
7:45 AM – 9:00 AM

Monday, June 2
7:45 AM – 9:00 AM

Gabriel N. Hortobagyi, MD, FACP—Chair
M.D. Anderson Cancer Center

Alan S. Coates, MD
The Cancer Council Australia

Lori J. Goldstein, MD
Fox Chase Cancer Center

After this session, attendees should be able to
- Describe the appropriate use of single-agent sequential therapies
- Discuss the optimal use of combination therapies
- Outline when drug holidays and no therapy are appropriate
- Explain the effects of various strategies on quality of life

Ductal Carcinoma in Situ: Dilemmas in Practice

CME credits: 1.25

Sunday, June 1
11:15 AM – 12:30 PM

Tuesday, June 3
7:45 AM – 9:00 AM

Sandra M. Swain, MD—Chair
National Cancer Institute

Craig Allred, MD
Baylor College of Medicine

Lori J. Pierce, MD
University of Michigan Medical School

After this session, attendees should be able to
- Discuss molecular markers, including estrogen receptors
- Explain local therapy, breast conservation, the role of magnetic resonance imaging, and margins
- Interpret results of follow-up randomized studies in which radiotherapy is compared with no radiotherapy

New Issues in the Staging of Breast Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2
9:30 AM – 10:45 AM

Tuesday, June 3
9:30 AM – 10:45 AM

Robert W. Carlson, MD—Chair
Stanford University

Bruce L. Daniel, MD
Stanford University

Richard L. Theriault, DO, MBA
M.D. Anderson Cancer Center

After this session, attendees should be able to
- Discuss the new American Joint Commission on Cancer Breast Cancer Staging System to develop treatment options for early stage breast cancer
- Appraise the scientific data regarding the implications of detectable micrometastasis in assigning prognosis and developing treatment options
- Identify appropriate patients for breast magnetic resonance imaging and/or positron emission tomography for diagnostic and treatment planning purposes

Risk Assessment, Screening, and Management of BRCA1 and BRCA2 Mutation Carriers

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2 4:00 PM – 5:15 PM
Tuesday, June 3 11:15 AM – 12:30 PM

Judy E. Garber, MD—Chair
Dana-Farber Cancer Institute

Lynn C. Hartmann, MD
Mayo Clinic Cancer Center

Ellen Warner, MD
Toronto Sunnybrook Regional Cancer Centre

After this session, attendees should be able to

- Identify individuals and families in whom a heritable mutation in BRCA1 or BRCA2 might underlie the pattern of cancer observed
- Estimate the risk of breast and ovarian cancers conferred by mutations in BRCA1 and BRCA2 and some of the factors that might influence those risks
- Discuss current data on the efficacy and limitations of the available surveillance modalities for breast and ovarian cancer in mutation carriers and current recommendations on when and how often these techniques should be recommended
- Evaluate data on the efficacy of risk-reducing surgeries for breast and ovarian cancers and some of the issues in breast reconstruction

Controversies: Anthracycline versus Nonanthracycline Adjuvant Therapy for Breast Cancer

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M01A) 7:45 AM – 9:00 AM
Monday, June 2 (M01B) 7:45 AM – 9:00 AM

Edith A. Perez, MD
Mayo Clinic

After this session, attendees should be able to

- Evaluate data on the background and evidence for anthracycline and nonanthracycline adjuvant regimens
- Describe the relative impact of anthracycline versus nonanthracycline adjuvant therapies
- Determine patient populations that could be most appropriate for management with different regimens
- Discuss translational (laboratory and clinical) studies to help elucidate predictive markers of response to anthracycline adjuvant therapy

Emerging Concepts: Brachytherapy

CME credits: 1.25

Saturday, May 31 (M02A) 7:45 AM – 9:00 AM
Monday, June 2 (M02B) 7:45 AM – 9:00 AM

Robert R. Kuske, MD
Ochsner Clinic

After this session, attendees should be able to

- Define the biologic basis and scientific rationale for accelerated partial breast irradiation (APBI)
- Discuss the target volume of wide-volume breast brachytherapy
- Define the evolution of clinical data supporting APBI (completed phase II and planned phase III trials)
- Describe four different methods of catheter insertion for breast brachytherapy

Emerging Concepts: Ductal Lavage in Breast Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M04A) 12:30 PM – 1:45 PM
Monday, June 2 (M04B) 11:15 AM – 12:30 PM

Carol J. Fabian, MD
University of Kansas Medical Center

After this session, attendees should be able to

- Discuss the rationale for using breast tissue sampling by ductal lavage and random fine-needle aspiration for short-term risk assessment and intermediate response endpoints in chemoprevention trials
- Identify strengths and weakenesses of both tissue sampling approaches
- Summarize the preliminary results on the potential for ductal lavage as an early detection tool

Expert Opinion: Evolving Issues in Breast Cancer Pathology for Clinicians

CME credits: 1.25

Saturday, May 31 (M03A) 12:30 PM – 1:45 PM
Monday, June 2 (M03B) 11:15 AM – 12:30 PM

Syed Hoda, MD
New York Presbyterian Hospital-Weill Cornell Medical Center

Anne Moore, MD
New York Presbyterian Hospital-Weill Cornell Medical Center

After this session, attendees should be able to

- Define the optimal way for pathologists and clinicians to communicate about a patient's pathology report, using breast cancer as a model
- Apply new knowledge about sentinel node and bone marrow micrometastases to patient care
- Interpret reports based on immunohistochemical analysis or fluorescent in situ hybridization (HER-2/*neu*, hormone receptors, e-cadherin)
- Discuss the applicability of molecular pathology (microarray analysis)

Expert Opinion: Adjuvant Treatment for Breast Cancer—The Importance of Incremental Gains

CME credits: 1.25

Saturday, May 31 (M06A) 2:15 PM – 3:30 PM
Monday, June 2 (M06B) 4:00 PM – 5:15 PM

Martin D. Abeloff, MD
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

After this session, attendees should be able to

- Discuss the overall role of adjuvant therapy in the management of breast cancer

- Identify the magnitude of gains achieved with adjuvant therapy
- Define the limitations of adjuvant therapy
- Discuss the potential for future gains

Expert Opinion: Neoadjuvant Therapy for Early Breast Cancer

CME credits: 1.25

Saturday, May 31 (M05A) 2:15 PM – 3:30 PM
Monday, June 2 (M05B) 4:00 PM – 5:15 PM

Terry P. Mamounas, MD
Aultman Cancer Center

After this session, attendees should be able to

- Define the evolving role of neoadjuvant therapy for operable breast cancer
- Summarize results from randomized clinical trials of neoadjuvant therapy
- Discuss surgical issues in patients receiving neoadjuvant therapy
- Describe future research efforts with neoadjuvant therapy

Selecting Adjuvant Endocrine Therapy

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (CPO01A) 11:15 AM – 12:30 PM
Monday, June 2 (CPO01B) 11:15 AM – 12:30 PM

Hyman B. Muss, MD—Chair
University of Vermont

Heikki Joensuu, MD
Helsinki University Central Hospital

Kathleen I. Pritchard, MD, FRCPC
Toronto-Sunnybrook Regional Cancer Centre

After this session, attendees should be able to

- Evaluate patients for risk of recurrence
- Define adjuvant endocrine options for premenopausal and postmenopausal patients

Early Breast Cancer

CME credits: 4.0

Saturday, May 31
1:00 PM – 5:00 PM

Advanced Breast Cancer

CME credits: 4.0

Sunday, June 1
1:30 PM – 5:30 PM

Early Breast Cancer

CME credits: 1.0

Sunday, June 1
8:00 AM – 12:00 PM

Advanced Breast Cancer

CME credits: 1.0

Monday, June 2
8:00 AM – 12:00 PM

Breast Cancer

Saturday, May 31
9:00 AM – 1:00 PM

CANCER PREVENTION/ EPIDEMIOLOGY

ASCO/European Society for Medical Oncology Joint Symposium: Screening and Prevention—Today's Understanding of Mammography, Spiral Computerized Tomography, and Prostate-Specific Antigen

CME credits and pharmacy contact hours: 2.0
Nursing contact hours: 2.4

Sunday, June 1
1:00 PM – 3:00 PM

Paul A. Bunn, Jr., MD—Co-Chair
University of Colorado Cancer Center

Heinz Ludwig, MD—Co-Chair
Wilhelminenspital

E. David Crawford, MD
University of Colorado Health Sciences Center

I. Craig Henderson, MD
University of California at San Francisco

Ugo Pastorino, MD
Istituto Europeo Di Oncologi

Edward F. Patz, Jr., MD
Duke University

Fritz H. Schroeder, MD
Erasmus University

Christopher Williams, MD
Cochrane Cancer Network

After this session, attendees should be able to

- Define the state-of-the-art options in the cancer prevention and screening techniques discussed
- Interpret differences in factors associated with the current choice of techniques
- Explain the benefits and challenges of screening techniques relevant to appropriate clinical situations

Breast Cancer Risk Assessment and Prevention Strategies for Practicing Oncologists

CME credits and pharmacy contact hours: 1.5
Nursing contact hours: 1.8

Sunday, June 1
4:15 PM – 5:45 PM

Scott M. Lippman, MD—Co-Chair
M.D. Anderson Cancer Center

Robin T. Zon, MD—Co-Chair
Michiana Hematology-Oncology, P.C.

Craig Allred, MD
Baylor College of Medicine

Monica Morrow, MD
Northwestern Memorial Hospital and Medical School

Victor G. Vogel, MD
Magee-Womens Hospital

After this session, attendees should be able to

- Describe the histopathology and molecular pathology of premalignant disease
- Discuss new sampling techniques for detection of premalignant disease
- Apply surgical prevention and/or chemoprevention to high-risk groups, including special populations

Tobacco Control: Novel Approaches for Smoking Cessation and Chemoprevention

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1
7:45 AM – 9:00 AM

Tuesday, June 3
7:45 AM – 9:00 AM

Paul F. Engstrom, MD—Chair
Fox Chase Cancer Center

Ethan Dmitrovsky, MD
Dartmouth Medical School

Carolyn M. Dresler, MD
Harvard University

Ellen R. Gritz, PhD
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Discuss and implement behavioral interventions that work for patients with cancer who continue to smoke
- Identify the genetic basis for nicotine addiction and implement effective pharmacologic interventions for patients with cancer
- Interpret and critically analyze chemoprevention trial methodologies for people at risk for smoking-associated cancer

Controversies: Lung Cancer Screening and Prevention

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M10A)
4:30 PM – 5:45 PM

Monday, June 2 (M10B)
11:15 AM – 12:30 PM

Waun Ki Hong, MD
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Define susceptibility to the development of lung cancer
- Identify molecular markers
- Discuss defects of signal transduction pathways
- Describe reversal of lung carcinogenesis with chemoprevention

Controversies: Screening with Mammography and Magnetic Resonance Imaging

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M07A)
7:45 AM – 9:00 AM

Monday, June 2 (M07B)
9:30 AM – 10:45 AM

Barnett S. Kramer, MD, MPH
National Institutes of Health

After this session, attendees should be able to

- Discuss the controversies surrounding screening mammography
- Assess the benefits and risks of screening for breast cancer
- Interpret recent data on screening magnetic resonance imaging for women with low sensitivity to mammography, including women with inherited risk of breast cancer

Expert Opinion: Colon Cancer Screening and Prevention

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M09A)
4:30 PM – 5:45 PM

Monday, June 2 (M09B)
11:15 AM – 12:30 PM

Bernard Levin, MD
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Evaluate novel screening methods
- Describe chemopreventive approaches
- Identify possible molecular targets for action of chemopreventive agents

Expert Opinion: Treatment of Premalignant Disease

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M08A)
7:45 AM – 9:00 AM

Monday, June 2 (M08B)
9:30 AM – 10:45 AM

Ernest Hawk, MD
National Cancer Institute

After this session, attendees should be able to

- Describe the process of carcinogenesis, its natural history, and its relevance to clinical oncology practice
- Explain premalignant disease as a marker of cancer risk and a focus of intervention
- Evaluate the risks and benefits of available and emerging interventions for the treatment of premalignant disease

The Road to Cancer: Genetic Susceptibility, Genetic Changes, and Environmental Interactions

CME credits: 1.25

Monday, June 2
7:45 AM – 9:00 AM

Tuesday, June 3
11:00 AM – 12:15 PM

Sanford D. Markowitz, MD, PhD—Chair
Case Western Reserve University

Stephen B. Gruber, MD, PhD
University of Michigan

David Sidransky, MD
Johns Hopkins University

After this session, attendees should be able to

- Describe susceptibility genes
- Discuss the uses of genetic and molecular markers in screening for malignancy
- Evaluate data on gene and environment interactions and the implication to reduce risk

Cancer Prevention

CME credits: 2.0

Sunday, June 1
2:00 PM – 4:00 PM

Cancer Prevention

Monday, June 2
9:00 AM – 1:00 PM

CENTRAL NERVOUS SYSTEM TUMORS

Update on Therapeutic Approaches to Brain Tumors

CME credits: 1.25

Saturday, May 31
7:45 AM – 9:00 AM

Monday, June 2
7:45 AM – 9:00 AM

Lisa M. DeAngelis, MD—Chair
Memorial Sloan-Kettering Cancer Center

Paul Kleihues, MD
International Agency for Research on Cancer

Edward G. Shaw, MD
Wake Forest University School of Medicine

Roger Stupp, MD
Lausanne University Hospital (CHUV)

After this session, attendees should be able to

- Discuss the current use of molecular classification of gliomas
- Explain the latest and optimal treatment for patients with malignant gliomas
- Describe current approaches to low-grade gliomas

Research Seminar: Current Animal Models and Basic Biology of Gliomas

CME credits: 1.25

Sunday, June 1 (M11A)
7:45 AM – 9:00 AM

Monday, June 2 (M11B)
9:30 AM – 10:45 AM

Eric Holland, MD, PhD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Define the molecular and histologic characteristics of gliomas
- Identify the important signal transduction abnormalities that lead to glioma formation in mouse models
- Describe the issues surrounding the parallels between differentiation and gliomagenesis, and the potential cell of origin for gliomas
- Discuss the uses of mouse models for cancer

Central Nervous System Tumors

CME credits: 3.0

Saturday, May 31
1:00 PM – 4:00 PM

Central Nervous System Tumors

CME credits: 1.0

Sunday, June 1
8:00 AM – 12:00 PM

Central Nervous System Tumors

Sunday, June 1
2:00 PM – 5:30 PM

CLINICAL TRIALS

New High-Priority Phase III Trials: A Discussion on Rationale and Participation

CME credits: 1.25

Monday, June 2
11:15 AM – 12:30 PM

Robert L. Comis, MD—Chair
Coalition of National Cancer Cooperative Group

After this session, attendees should be able to

- Identify and discuss the newest high-priority clinical trials from the Cooperative Groups
- Outline the scientific rationale for these trials
- Discuss strategies and resources available for oncologists to effectively participate in these trials

Oversight of Clinical Research

CME credits: 1.5

Saturday, May 31
4:15 PM – 5:45 PM

Lowell E. Schnipper, MD—Chair
Beth Israel Deaconess Medical Center

Ezekiel J. Emanuel, MD, PhD
Warren G. Magnuson Clinical Center

Rebecca D. Pentz, PhD
Emory University School of Medicine

Jeremy Sugarman, MD, MPH, MA
Duke University Medical Center

After this session, attendees should be able to

- Discuss key federal requirements for the protection of research participants
- Describe the role of the institutional review board in the protection of research participants
- Identify the key elements of the informed consent process
- Define the roles and responsibilities of investigators to ensure safe and ethical research
- Outline ASCO's policy recommendations for the oversight of clinical research

Developmental Therapeutics: Successes and Failures of Clinical Trials of Targeted Compounds

CME credits and pharmacy contact hours: 1.25

Saturday, May 31
2:30 PM – 3:45 PM

Monday, June 2
9:30 AM – 10:45 AM

S. Gail Eckhardt, MD—Chair
University of Colorado Health Sciences Center

Elizabeth A. Eisenhauer, MD
National Cancer Institute of Canada

Richard Pazdur, MD
U.S. Food and Drug Administration

After this session, attendees should be able to

- Define the clinical scenarios for which the incorporation of biologic assays may be important and identify the types of assays utilized
- Describe novel early clinical trial designs of targeted agents and assess their efficacy
- Outline and evaluate the success of regulatory strategies that have been used for approval

Expert Opinion: Regulatory Issues in the Design of Clinical Trials

CME credits and pharmacy contact hours: 1.25

Sunday, June 1 (M17A)
7:45 AM – 9:00 AM

Monday, June 2 (M17B)
7:45 AM – 9:00 AM

Richard Pazdur, MD
U.S. Food and Drug Administration

After this session, attendees should be able to

- Describe the basis for approval of a new drug application
- Define the criteria for selecting clinical trial endpoints for registration trials
- Discuss the differences between accelerated approval, priority review, and fast-track designation
- Describe the regulatory mechanisms for patient access to unapproved agents

Expert Opinion: The European Influence on Clinical Trials in Oncology

CME credits: 1.25

Saturday, May 31 (M12A)
7:45 AM – 9:00 AM

Sunday, June 1 (M12B)
1:00 PM – 2:15 PM

Allan T. Van Oosterom, MD, PhD
Universitaire Ziekenhuizer Leuven

After this session, attendees should be able to

- Define the major differences in the approach and performance of studies in Europe and the United States
- Describe the mechanisms underlying these differences, such as health organization and supporting system
- Discuss the comparison of the clinical trial systems in Europe and in the United States and the lessons that can be learned from both systems

Methods: Concepts of Clinical Trials

CME credits: 1.25

Saturday, May 31 (M13A)
7:45 AM – 9:00 AM

Sunday, June 1 (M13B)
1:00 PM – 2:15 PM

Sylvan B. Green, MD
Arizona Cancer Center

After this session, attendees should be able to

- Describe the rationale for randomized trials, effects of chance and bias, and the roles of large simple trials and factorial designs
- Define type I and type II errors (false-positive and false-negative results) and the meaning of statistical significance
- Outline clinical trial "phases" and choices of treatment groups
- Discuss aspects of the analysis of phase III clinical trials, such as the intention-to-treat principle

Methods: Endpoints in Clinical Trials

CME credits: 1.25

Saturday, May 31 (M15A)
12:30 PM – 1:45 PM

Sunday, June 1 (M15B)
2:45 PM – 4:00 PM

Ian Tannock, MD, PhD
Princess Margaret Hospital and University of Toronto

After this session, attendees should be able to

- Discuss the appropriateness and use of different endpoints in clinical trials, including classical endpoints such as survival and newer endpoints such as quality of life

Methods: Getting Involved in Cooperative Group Trials

CME credits: 1.25

Sunday, June 1 (M16A)
7:45 AM – 9:00 AM

Monday, June 2 (M16B)
11:15 AM – 12:30 PM

Gini Fleming, MD
University of Chicago

Alan P. Lyss, MD
Missouri Baptist Cancer Center

After this session, attendees should be able to

- Describe ways oncologists can become involved in the clinical trial process

Methods: Increasing Participation of Oncologists in Surgical Clinical Trials

CME credits: 1.25

Sunday, June 1 (M66A)
9:30 AM – 10:45 AM

Monday, June 2 (M66B)
7:45 AM – 9:00 AM

Samuel A. Wells, MD
Duke University Medical Center

After this session, attendees should be able to

- Discuss reasons that oncologists have not participated in surgical clinical trials
- Describe the unique aspects of surgical clinical trials and outline why they should be of interest to every oncologist
- Define ways to increase participation in clinical trials

Methods: Phase I and II Trials

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M14A)
12:30 PM – 1:45 PM

Sunday, June 1 (M14B)
2:45 PM – 4:00 PM

Janice P. Dutcher, MD
Our Lady of Mercy Medical Center

After this session, attendees should be able to

- Define the goals and differences of phase I and II clinical trials
- Apply skills to plan such clinical trials
- Discuss the role of pharmacokinetics in these clinical trials
- Describe the role of laboratory correlates

DEVELOPMENTAL THERAPEUTICS

Pharmacology and Drug Development

CME credits and pharmacy contact hours: 4.0
Nursing contact hours: 4.8

Friday, May 30 (ES01)
11:30 AM – 4:00 PM

Richard Pazdur, MD—Co-Chair
U.S. Food and Drug Administration

Mark J. Ratain, MD—Co-Chair
University of Chicago

See page 50 for complete description.

Opening Ceremony

Saturday, May 31
9:15 AM – 12:00 PM

Paul A. Bunn, Jr., MD—Chair
University of Colorado Cancer Center

Karnofsky Memorial Award Lecture

CME credits and pharmacy contact hours: 1.0

Brian J. Druker, MD
Howard Hughes Medical Institute

After this session, attendees should be able to

- Describe the rationale for developing imatinib as a therapeutic agent for chronic myelogenous leukemia and gastrointestinal stromal tumors
- Summarize the current data on the use of imatinib
- Identify other tumors for which imatinib may be useful
- Discuss how the imatinib paradigm may be applied to other cancers

Viral-Mediated Cancers

CME credits: 1.5
Nursing contact hours: 1.8

Saturday, May 31
4:15 PM – 5:45 PM

Richard F. Ambinder, MD—Chair
Johns Hopkins University

Maura L. Gillison, MD, PhD
Johns Hopkins University

Lee Ratner, MD, PhD
Washington University Medical School

After this session, attendees should be able to

- Discuss human papillomavirus and its relationship to head and neck cancer
- Describe the relationship of Epstein-Barr virus to lymphoid and epithelial cancers
- Identify human T-cell leukemia virus type I and its relationship to adult T-cell lymphoma

Antiangiogenic Therapy at a Crossroads: Clinical Trial Results and Future Directions

CME credits: 1.5

Saturday, May 31
7:45 AM – 9:15 AM

Lee M. Ellis, MD—Co-Chair
M.D. Anderson Cancer Center

Lee S. Rosen, MD—Co-Chair
Cancer Institute Medical Group

After this session, attendees should be able to

- Evaluate results of clinical trials on antiangiogenic therapy for patients with metastatic disease
- Determine the appropriate use of such therapy
- Identify the adverse effects of this therapy

The Epidermal Growth Factor As a Therapeutic Target

CME credits and pharmacy contact hours: 1.5

Monday, June 2
9:30 AM – 10:45 AM

Carlos L. Arteaga, MD—Co-Chair
Vanderbilt University School of Medicine

Jose Baselga, MD—Co-Chair
Vall d'Hebron University Hospital

After this session, attendees should be able to

- Describe what is now known about the epidermal growth factor receptor signaling pathway
- Identify the therapeutic agents currently available to target this pathway
- Discuss clinical settings in which these agents could be used as single agents or as part of combination regimens

Methods: The U.S. Food and Drug Administration Drug Review Process

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M67A)
12:30 PM – 1:45 PM

Monday, June 2 (M67B)
4:00 PM – 5:15 PM

Richard Pazdur, MD
U.S. Food and Drug Administration

After this session, attendees should be able to

- Describe the Food and Drug Administration review process for a new drug application
- Define the differences between an accelerated approval process and a standard review process
- Describe differences between priority reviews, accelerated approval, and fast-track designation

Vaccines and Cellular Therapies Targeting Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Monday, June 2
7:45 AM – 9:00 AM

Tuesday, June 3
7:45 AM – 9:00 AM

H. Kim Lyerly, MD—Chair
Duke University Medical Center

Michael R. Bishop, MD
National Institutes of Health

Nora Disis, MD
University of Washington

Elizabeth M. Jaffee, MD
The Johns Hopkins University School of Medicine

After this session, attendees should be able to

- Discuss the current molecular and cellular biology associated with immune recognition of tumor cells
- Identify components of phase I cancer vaccine trials that differ substantially from those of standard chemotherapeutic agents

DEVELOPMENTAL THERAPEUTICS *(continued)*

- Describe the mechanisms by which a patient's immune system may have decreased function
- Discuss peptide and protein-based, cellular-based, and gene therapy-based vaccine strategies, as well as cellular-based adoptive immunotherapy strategies
- Define the role of nonmyeloablative transplant in facilitating adoptive immunotherapy

Developmental Therapeutics: Pharmacogenomics and Cancer Therapy

CME credits: 3.0

Sunday, June 1
11:15 AM – 2:15 PM

Developmental Therapeutics: Immunotherapy

CME credits: 3.0

Sunday, June 1
7:45 AM – 10:45 AM

Developmental Therapeutics: Molecular Therapeutics

CME credits: 3.0

Sunday, June 1
2:45 PM – 5:45 PM

Developmental Therapeutics: Cytotoxic Chemotherapy

CME credits: 1.0

Saturday, May 31
1:00 PM – 5:00 PM

Developmental Therapeutics: Immunotherapy

CME credits: 1.0

Monday, June 2
8:00 AM – 12:15 PM

(Audioguide available during this session.)

Developmental Therapeutics: Molecular Therapeutics

CME credits: 1.0

Tuesday, June 3
8:00 AM – 12:00 PM

Developmental Therapeutics: Cytotoxic Chemotherapy

Monday, June 2
9:00 AM – 1:00 PM

Developmental Therapeutics: Immunotherapy

Monday, June 2
9:00 AM – 1:00 PM

Develpmental Therapeutics: Molecular Therapeutics

Monday, June 2
9:00 AM – 1:00 PM

ETHICS

Expert Opinion: Physicians Coping with Loss

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Monday, June 2 (M18A)
9:30 AM – 10:45 AM

Tuesday, June 3 (M18B)
11:15 AM – 12:30 PM

Daniel Sulmasy, OFM, MD, PhD
St. Vincent's Hospital

After this session, attendees should be able to

- Describe the universal struggle of coping with loss
- Apply coping strategies to deal with a sense of loss

FELLOWS AND JUNIOR FACULTY PROGRAM

Treatment of Breast, Prostate, and Colorectal Cancers: Historical Perspectives, Current State of the Art, and New Targets

CME credits: 4.0

Friday, May 30 (ES04)
12:00 PM – 4:00 PM

Marvin J. Stone, MD—Chair
Baylor University Medical Center

See page 53 for complete description.

Design and Interpretation of Randomized Trials

CME credits: 1.25

Saturday, May 31
12:45 PM – 2:00 PM

Sylvan B. Green, MD—Chair
Arizona Cancer Center

Stephen L. George, PhD
Duke University Medical Center

After this session, attendees should be able to

- Describe the philosophy and rationale for randomized trials
- Explain the meaning of statistical significance and the basis of intention-to-treat analyses
- Define the nature and use of factorial designs
- Discuss aspects of the analysis of randomized clinical trials, such as interim monitoring and subset analyses

How to Write a Grant

CME credits: 1.25

Saturday, May 31
7:45 AM – 9:00 AM

Timothy J. Eberlein, MD—Chair
Washington University School of Medicine

After this session, attendees should be able to

- Design a hypothesis-driven grant proposal
- Respond appropriately to critique of the proposal
- Collaborate with other researchers involved in the proposal

How to Write an Outstanding Scientific Manuscript

CME credits: 1.25

Sunday, June 1
7:45 AM – 9:00 AM

Daniel G. Haller, MD—Chair
University of Pennsylvania Cancer Center

After this session, attendees should be able to
- Define the key aspects of manuscript preparation
- Determine the optimal presentation format
- Select the best journal for submission

Oncology Careers in Private Practice or Industry: How to Choose the Best Setting for You

CME credits: 1.25

Sunday, June 1
1:00 PM – 2:15 PM

R. Steven Paulson, MD—Chair
Texas Oncology PA

Richard Gaynor, MD
Eli Lilly and Company

James L. Wade III, MD, FACP
Cancer Care Specialists of Central Illinois

After this session, attendees should be able to
- Identify the appropriate questions to ask when interviewing or investigating a practice opportunity
- Discuss economic issues and Medicare reimbursement
- Explain how to participate in clinical trials as a private practicioner
- Discuss the differences in working in industry compared with practice
- Explain differences in large groups versus small groups
- Describe professionally managed practices and physician-run practices

Philosophy of Targeted Therapy for Hematologic Malignancies

CME credits: 1.25

Sunday, June 1
9:30 AM – 10:45 AM

Myron S. Czuczman, MD—Co-Chair
Roswell Park Cancer Institute

Parameswaran Venugopal, MD—Co-Chair
Rush University Medical Center

After this session, attendees should be able to
- Describe the mechanisms of action of various biologic agents used in the treatment of hematologic malignancies
- Discuss clinical trials in which biologic agents are used alone or in combination with chemotherapy for the treatment of lymphoma

Strategies for Successful Careers in Academic Oncology

CME credits: 1.25

Saturday, May 31
2:30 PM – 3:45 PM

Margaret A. Tempero, MD—Chair
University of California at San Francisco Cancer Center

Lee M. Ellis, MD
M.D. Anderson Cancer Center

Mace Rothenberg, MD
Vanderbilt-Ingram Cancer Center

After this session, attendees should be able to
- Describe the various opportunities in academic medicine
- Discuss the advantages and disadvantages of an academic career in surgical, radiation, and medical oncology
- Identify the various pathways to a "successful" career in academic oncology

The Role of Industry in Clinical Trials

CME credits: 1.25

Sunday, June 1
4:30 PM – 5:45 PM

Susan G. Arbuck, MD—Co-Chair
Aventis Pharmaceuticals

David R. Parkinson, MD—Co-Chair
Novartis Pharmaceutical Corporation

Susan Hellmann, MD
Genentech

After this session, attendees should be able to
- Identify career opportunities and career paths for medical oncologists interested in drug development in the biotechnology and pharmaceutical industries
- Describe the role of industry in clinical trials

Writing a Protocol and Getting It Approved

CME credits: 1.25

Saturday, May 31
4:15 PM – 5:30 PM

Donna Neuberg, ScD—Chair
Dana-Farber Cancer Institute

Larry D. Cripe, MD
Indiana University

Jonathan W. Friedberg, MD
University of Rochester

After this session, attendees should be able to
- State a clear scientific hypothesis to be addressed by a clinical trial
- Identify the needed components of the protocol team, including nursing, pharmacy, and biostatistics representatives; laboratory assessment; and outcomes, as necessary
- Explain an unambiguous protocol document that specifies the design and implementation of the study
- Develop a strategy for smooth and successful approval by local and federal authorities

Cancer Treatment of Older Patients

CME credits: 1.25

Monday, June 2 (FM10)
11:15 AM – 12:30 PM

John M. Bennett, MD
University of Rochester School of Medicine

After this session, attendees should be able to
- Define obstacles to care for older patients with cancer
- Explain age-related biologic differences in certain cancers

- Identify treatment strategies for this population
- Discuss geriatric assessment tools

Cognitive Issues and Quality-of-Life Endpoints in Clinical Trials

CME credits: 1.25

Sunday, June 1 (FM02)
9:30 AM – 10:45 AM

Ian Tannock, MD, PhD
Princess Margaret Hospital and University of Toronto

After this session, attendees should be able to

- Describe the design of clinical trials with cognitive issues and quality-of-life endpoints
- Evaluate tools for measurement of quality of life
- Determine the cognitive effects of chemotherapy

Communication with Patients and Families

CME credits: 1.25

Monday, June 2 (FM09)
9:30 AM – 10:45 AM

Janet L. Abrahm, MD
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Develop approaches to difficult conversations
- Describe how much can be learned in a 15-minute visit
- Identify strategies for self-preservation

Discussion of the ASCO Plenary Session

CME credits: 1.25

Tuesday, June 3 (FM04)
7:45 AM – 9:00 AM

Larry Norton, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Discuss the abstracts presented at the 2003 ASCO Plenary Session
- Apply the concepts and outcomes of the presented studies to current research and/or practice

Esophagogastric Cancer: Chemo-radiotherapy, Surgery, or Both? New Answers to an Old Question

CME credits: 1.25

Monday, June 2 (FM08)
7:45 AM – 9:00 AM

David P. Kelsen, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Discuss the standard-of-care options, as well as current research initiatives, for the treatment of patients with localized and potentially curable esophagogastric cancers
- Interpret data from recent clinical trials regarding the use of surgery alone (including different types of operations), chemoradiation therapy as a nonoperative approach, and the role of the combination of all three modalities in increasing the cure rate
- Discuss newer staging and molecular analyses to predict which patients are at high risk for poor outcome
- Identify patients early in the course of treatment who may benefit from alternative therapies

Molecular Biology and Targeted Therapies in Lung Cancer

CME credits: 1.25

Sunday, June 1 (FM01)
11:15 AM – 12:30 PM

Karen Kelly, MD
University of Colorado Health Sciences Center

After this session, attendees should be able to

- Decribe the current molecular pathway of lung carcinogenesis
- Identify the most promising molecular targets for therapeutic development
- Discuss the relevant clinical data on targeted therapies in the treatment of lung cancer

New Approaches to Hormone-Responsive Breast Cancer

CME credits: 1.25

Sunday, June 1 (FM06)
2:45 PM – 4:00 PM

John E. Pippen, Jr., MD, FACP
Baylor University Medical Center

After this session, attendees should be able to

- Discuss the role of endocrine therapy in the adjuvant setting
- Define the role and sequencing of endocrine agents in managing metastatic breast cancer
- Identify the interplay between the molecular features of a cancer and the likelihood of endocrine responsiveness

Pancreatic Cancer: Pursuing Targets That Are and Are Not There

CME credits: 1.25

Sunday, June 1 (FM05)
1:00 PM – 2:15 PM

Daniel D. Von Hoff, MD
Arizona Cancer Center

After this session, attendees should be able to

- Describe the current state of treatment for patients with advanced pancreatic cancer
- Discuss the scope of important ongoing clinical trials in this disease
- Define molecular approaches to identify and exploit molecular targets that do and do not exist in patients with pancreatic cancer

Pharmacology in Clinical Trials

CME credits: 1.25

Sunday, June 1 (FM03)
11:15 AM – 12:30 PM

Merrill J. Egorin, MD
University of Pittsburgh Cancer Institute

After this session, attendees should be able to

- Describe the differences between pharmacokinetics and pharmacodynamics

- Identify issues related to sample timing and matrix
- Define how to calculate sample size for a drug-drug interaction study
- Discuss concerns relevant to pharmacology studies or chronic orally based drugs that have not been relevant in studies of intermittent intravenous therapy

What's New in Genitourinary Cancer: Highlights of the 2003 Annual Meeting

CME credits: 1.25

Sunday, June 1 (FM07)
4:30 PM – 5:45 PM

Donald L. Trump, MD
Roswell Park Cancer Institute

After this session, attendees should be able to

- Discuss controversies in the management of prostate, bladder, and kidney cancers

GASTROINTESTINAL (COLORECTAL AND NONCOLORECTAL) CANCER

International Symposium: Gastric Cancer

CME credits and pharmacy contact hours: 2.0
Nursing contact hours: 2.4

Tuesday, June 3
7:45 AM – 9:45 AM

John Eu-Li Wong, MD—Chair
National University Hospital/ University of Singapore

Pelayo Correa, MD
Louisiana State University Medical Center

Yoshiaki Ito, MD
Institute of Molecular and Cell Biology, Singapore

John S. MacDonald, MD
St. Vincent's Comprehensive Cancer Center

Mitsuru Sasako, MD
National Cancer Center Hospital, Tokyo

Cornelis J. H. van de Velde, MD
Leids Universitair Medisch Centrum

After this session, attendees should be able to

- Define the role of RUNX-3 as a critical tumor suppressor gene in gastric carcinogenesis
- Determine the uses of Helicobacter pylori therapy and antioxidants as chemoprevention strategies
- Discuss the controversy regarding the role of extended lymph node dissection
- Describe the role of adjuvant chemotherapy and adjuvant chemoradiotherapy in resected gastric cancer and the role of chemotherapy in metastatic disease

Gastrointestinal Stromal Tumors: Current Management and Future Challenges

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31
2:30 PM – 3:45 PM

Sunday, June 1
1:00 PM – 2:15 PM

Charles D. Blanke, MD, FACP—Chair
Oregon Health & Science University

Jonathan A. Fletcher, MD
Brigham and Women's Hospital

Lars-Gunnar Kindblom, MD
Goteborg University

After this session, attendees should be able to

- Describe the epidemiology and pathologic characterization of gastrointestinal stromal tumors
- Define current therapeutic options for early stage and advanced disease
- Identify the options for management of imatinib-refractory disease

Localized Pancreatic Cancer: One, Two, or Three Modalities?

CME credits and pharmacy contact hours: 1.25

Monday, June 2
4:00 PM – 5:15 PM

Tuesday, June 3
10:15 AM – 11:30 AM

Peter W. T. Pisters, MD—Chair
M.D. Anderson Cancer Center

Ross A. Abrams, MD
Johns Hopkins University School of Medicine

Vincent J. Picozzi, MD
Virginia Mason Medical Center

After this session, attendees should be able to

- Outline the approach for optimal pretreatment staging of disease for patients with suspected pancreatic cancer
- Describe the outcomes for patients who have treatment for pancreatic adenocarcinoma with pancreatectomy alone, pancreatectomy with postoperative chemoradiation, and pancreatectomy with postoperative chemotherapy
- Discuss the limitations of the existing phase III trials conducted in this patient population
- Outline the present controversy on the optimal treatment of localized pancreatic cancer and integrate this information into the approach to patients with localized pancreatic cancer

Multidisciplinary Approach to Operable Esophageal Cancer

CME credits: 1.25

Monday, June 2
7:45 AM – 9:00 AM

Monday, June 2
4:00 PM – 5:15 PM

David Cunningham, MD, FRCP—Chair
The Royal Marsden Hospital

Leonard L. Gunderson, MD
Mayo Clinic Cancer Center, Scottsdale

Joe B. Putnam, Jr., MD, FACS
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Determine the appropriate preoperative staging investigations in esophageal cancer
- Discuss the role of surgery, types of surgical procedures, and surgical outcomes
- Identify the appropriate use of chemoradiation
- Define the possible role for perioperative chemotherapy

Multimodality Management of Local-Regional Colorectal Cancer

CME credits: 1.25

Saturday, May 31
12:45 PM – 2:00 PM

Sunday, June 1
7:45 AM – 9:00 AM

Leonard Saltz, MD—Chair
Memorial Sloan-Kettering Cancer Center

Alfred M. Cohen, MD, FACS
University of Kentucky, Markey Cancer Center

Carolyn Corlies Compton, MD, PhD
McGill University

Joel E. Tepper, MD
University of North Carolina School of Medicine

After this session, attendees should be able to

- Discuss issues of tumor staging and surgical options
- Determine appropriate selection of patients for adjuvant and neoadjuvant treatments
- Identify optimal chemotherapy and/or radiation-chemotherapy regimens
- Summarize ongoing and recently completed clinical trials, with careful clarification of standard compared with investigational treatment options

Surgical and Ablative Management of Metastatic Colorectal Cancer: What Are the Limits?

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31
2:30 PM – 3:45 PM

Monday, June 2
7:45 AM – 9:00 AM

Yuman Fong, MD—Chair
Memorial Sloan-Kettering Cancer Center

Anton J. Bilchik, MD, PhD, FACS
John Wayne Cancer Institute

Gerald Dodd, MD
University of Texas at San Antonio

After this session, attendees should be able to

- Evaluate data for benefit of hepatic resection and ablative therapies
- Discuss the limitations of these techniques
- Describe how to appropriately select patients for these interventions

Systemic Treatment of Advanced Colorectal Cancer: Where Are We Now and Where Are We Going?

CME credits and pharmacy contact hours: 1.25

Sunday, June 1
9:30 AM – 11:00 AM

Richard M. Goldberg, MD—Chair
Mayo Clinic

David J. Kerr, MD, DSc, FRCP, MA
Oxford University

Neal J. Meropol, MD
Fox Chase Cancer Center

After this session, attendees should be able to

- Discuss studies involving irinotecan and oxaliplatin-based combinations
- Describe the data on the use of new agents (antiangiogenic agents, epidermal growth factor receptor inhibitors, and Cox-2 inhibitors)

Controversies: Are We Overtreating Some Patients with Rectal Cancer?

CME credits and pharmacy contact hours: 1.25

Sunday, June 1 (M19A)
7:45 AM – 9:00 AM

Tuesday, June 3 (M19B)
9:30 AM – 10:45 AM

David A. Rothenberger, MD
University of Minnesota

After this session, attendees should be able to

- Identify appropriate patients as candidates for local excision of rectal cancer
- Determine the molecular markers that may predict recurrence following local excision
- Define the role of preoperative or postoperative chemoradiation therapy for patients who have local excision

Controversies: Defining the Role of Hepatic Arterial Infusion Chemotherapy for Patients with Metastatic Colorectal Cancer

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M20A)
2:15 PM – 3:30 PM

Sunday, June 1 (M20B)
11:15 AM – 12:30 PM

Alan P. Venook, MD
University of California at San Francisco

After this session, attendees should be able to

- Define the role of hepatic arterial infusion chemotherapy for patients with metastatic colorectal cancer to the liver
- Discuss the role of hepatic arterial infusion chemotherapy after hepatic resection/ablation of metastases

Expert Opinion: Interventions in the Management of Hepatic Tumors

CME credits: 1.25

Saturday, May 31 (M23A)
2:15 PM – 3:30 PM

Sunday, June 1 (M23B)
11:15 AM – 12:30 PM

John M. Daly, MD
Temple University School of Medicine

After this session, attendees should be able to

- Discuss alternative methods for local therapy of hepatocellular cancer and metastatic hepatic tumors, using radiofrequency ablation and surgical resection
- Define tumor size and location

Research Seminar: Angiogenesis Inhibition in Gastrointestinal Malignancies

CME credits: 1.25

Sunday, June 1 (M21A) 7:45 AM – 9:00 AM
Tuesday, June 3 (M21B) 7:45 AM – 9:00 AM

Lee M. Ellis, MD
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Describe the biology of angiogenesis
- Identify targets for therapeutic intervention
- Interpret clinical data on antiangiogenic treatments
- Discuss future directions

Research Seminar: Molecular Markers of Chemotherapy Resistance and Sensitivity in Gastrointestinal Malignancies: How Close Are We?

CME credits: 1.25

Sunday, June 1 (M22A) 7:45 AM – 9:00 AM
Tuesday, June 3 (M22B) 7:45 AM – 9:00 AM

Robert B. Diasio, MD
University of Alabama at Birmingham

After this session, attendees should be able to

- Define the difference between predictive molecular markers and prognostic molecular markers
- Discuss the methods used to assess molecular markers
- Determine which markers appear to predict efficacy for gastrointestinal malignancies

Debate on Pelvic Radiotherapy for Rectal Cancer: American versus European Approach

CME credits: 1.25

Saturday, May 31(CPO02A) 2:15 PM – 3:30 PM
Monday, June 2(CPO02B) 9:30 AM – 10:45 AM

Bruce D. Minsky, MD—Co-Chair
Memorial Sloan-Kettering Cancer Center

Cornelius J. H. van de Velde, MD, PhD, FRCS
Leids Universitair Medisch Centrum

After this session, attendees should be able to

- Discuss the rationale of adjuvant therapy for rectal cancer
- Define the impact of surgery on the type of adjuvant therapy
- Explain the differences between radiotherapy techniques
- Interpret the benefits and risks of radiation and chemotherapy

Gastrointestinal (Colorectal) Cancer

CME credits: 4.0

Sunday, June 1
1:00 PM – 5:00 PM

Gastrointestinal (Noncolorectal) Cancer

CME credits: 3.0

Monday, June 2
8:00 AM – 11:00 AM

Gastrointestinal Cancer 1

CME credits: 1.0

Saturday, May 31
1:30 PM – 5:30 PM

Gastrointestinal Cancer 2

CME credits: 1.0

Tuesday, June 3
8:00 AM – 12:00 PM

Gastrointestinal Cancer

Sunday, June 1
9:00 AM – 1:00 PM

Biology and Clinical Management of Bone Metastases in Prostate Cancer

CME credits: 1.5

Monday, June 2 11:15 AM – 12:30 PM
Tuesday, June 3 9:15 AM – 10:45 AM

Christopher Sweeney, MBBS—Chair
Indiana University

Matthew Smith, MD, PhD
Massachusetts General Hospital

After this session, attendees should be able to

- Implement appropriate therapy for patients with metastatic bone disease
- Discuss advances in the management of bone metastases in prostate cancer

Controversies in the Management of Testis Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 4:15 PM – 5:30 PM
Monday, June 2 11:00 AM-12:15 PM

Lawrence H. Einhorn, MD—Chair
Indiana University School of Medicine, Indiana Cancer Pavilion

Sophie D. Fossa, MD
The Norwegian Radium Hospital

Richard Foster, MD
Indiana University School of Medicine

After this session, attendees should be able to

- Identify late toxicity associated with radiotherapy or chemotherapy
- Determine optimal radiation for seminoma
- Distinguish between various treatment options for clinical stage I disease
- Discuss treatment strategies for relapsed germ cell tumors

Multidisciplinary Management of Locally Advanced Bladder Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31
4:15 PM – 5:30 PM

Monday, June 2
11:15 AM – 12:30 PM

Dean F. Bajorin, MD—Chair
Memorial Sloan-Kettering Cancer Center

Michael S. Cookson, MD
Vanderbilt University Medical Center

Anthony L. Zietman, MD
Massachusetts General Hospital

After this session, attendees should be able to

- Discuss the patient selection process and multidisciplinary management paradigms that involve radiation therapy for bladder preservation in patients with muscle-invasive bladder cancer
- Describe data on survival with an intact bladder, overall survival, and quality-of-life assessments in trials pursuing bladder preservation strategies
- Define the surgical management of muscle-invasive disease, including types of urinary diversions, and the process of patient selection for surgical options
- Discuss the controversies surrounding the role of traditional and extended lymphadenectomy in radical cystectomy
- Evaluate clinical trial data on neoadjuvant and adjuvant chemotherapy for muscle-invasive disease
- Define the emerging methodologies predicting relapse after cystectomy for muscle-invasive disease (expression of molecular markers and detection of minimal residual disease)
- Discuss ongoing trials evaluating chemotherapy and immunotherapy

Controversies: Management of Patients with Clinically Evident Androgen-Independent Metastatic Prostate Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M25A)
7:45 AM – 9:00 AM

Sunday, June 1 (M25B)
11:15 AM – 12:30 PM

Eric J. Small, MD
University of California at San Francisco

After this session, attendees should be able to

- Define the current status of chemotherapy in the management of advanced disease
- Discuss the role of second-line hormonal therapy
- Identify emerging issues of bisphosphonate use in this setting

Controversies: Management of Rising PSA Syndrome

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M24A)
7:45 AM – 9:00 AM

Sunday, June 1 (M24B)
11:15 AM – 12:30 PM

Robert Dreicer, MD
Cleveland Clinic Foundation

After this session, attendees should be able to

- Review the natural history of rising PSA following definitive therapy and androgen-independent prostate cancer biochemically defined
- Discuss controversies regarding the role of early versus delayed hormonal therapy
- Describe potential novel strategies for the management of biochemical failure
- Suggest strategies for patient management in settings in which there are no data to drive interventions

Expert Opinion: Integrating Hormonal Therapy with External-Beam Radiation and Brachytherapy for Prostate Cancer

CME credits and pharmacy contact hours: 1.25

Monday, June 2 (M26A)
4:00 PM – 5:15 PM

Tuesday, June 3 (M26B)
7:45 AM – 9:00 AM

Mack Roach III, MD
University of California at San Francisco

After this session, attendees should be able to

- Describe the current status of conformal radiotherapy and brachytherapy
- Define the role of concomitant hormonal therapy
- Identify important toxicity issues
- Discuss follow-up issues, such as "PSA bounce"

Expert Opinion: Locally Advanced and Advanced Renal Cell Carcinoma: Management Strategies

CME credits and pharmacy contact hours: 1.25

Monday, June 2 (M27A)
4:00 PM – 5:15 PM

Tuesday, June 3 (M27B)
7:45 AM – 9:00 AM

Robert A. Figlin, MD, FACP
University of California at Los Angeles

After this session, attendees should be able to

- Define the role of integrating nephrectomy with systemic therapy for patients with metastatic disease
- Identify the current status of biologic response-modifier therapies
- Explain the potential of new agents in the management of advanced disease
- Discuss important differences in histologic subtypes of disease

Genitourinary (Nonprostate) Cancer

CME credits: 3.0

Monday, June 2
7:45 AM – 10:45 AM

Genitourinary (Prostate) Cancer

CME credits: 3.0

Saturday, May 31
12:45 PM – 3:45 PM

GYNECOLOGIC CANCER

Genitourinary (Nonprostate) Cancer
CME credits: 1.0

Sunday, June 1
2:15 PM – 5:45 PM

Genitourinary (Prostate) Cancer
CME credits: 1.0

Tuesday, June 3
8:00 AM – 12:00 PM

Genitourinary Cancer

Sunday, June 1
9:00 AM – 1:00 PM

GERIATRIC ONCOLOGY

Expert Opinion: Adjuvant Therapy for Women Older than 70 Years with Breast Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M28A)
4:00 PM – 5:15 PM

Sunday, June 1 (M28B)
11:15 AM – 12:30 PM

James N. Ingle, MD
Mayo Clinic

After this session, attendees should be able to

- Evaluate data on adjuvant therapy for older women
- Determine appropriate patient selection for such therapy
- Discuss new trials of adjuvant therapy for this population

Genetics and the Prevention of Ovarian Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31
2:30 PM – 3:45 PM

Monday, June 2
9:30 AM – 10:45 AM

Stephen C. Rubin, MD—Chair
University of Pennsylvania

David A. Fishman, MD
Northwestern University Medical School

Thomas C. Hamilton, PhD
Fox Chase Cancer Center

After this session, attendees should be able to

- Discuss recent advances in the molecular biology of ovarian cancer and their impact on screening and prevention
- Describe the current status of strategies for the prevention of ovarian cancer

Initial Therapy for Advanced Ovarian Cancer: Controversies and Future Directions

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31
12:45 PM – 2:00 PM

Monday, June 2
7:45 AM – 9:00 AM

Elizabeth A. Eisenhauer, MD—Chair
National Cancer Institute of Canada

David R. Spriggs, MD
Memorial Sloan-Kettering Cancer Center

Ignace B. Vergote, MD, PhD
University Hospital Leuven

After this session, attendees should be able to

- Discuss controversies regarding intraperitoneal therapy for ovarian cancer
- Define the role of surgery in ovarian cancer therapy
- Explain optimum initial chemotherapy and the status of ongoing or recently completed clinical trials
- Identify novel agents that will be part of future trials in the initial therapy for ovarian cancer

Controversies: Surgical Issues in Ovarian Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M29A)
4:00 PM – 5:15 PM

Monday, June 2 (M29B)
11:15 AM – 12:30 PM

William J. Hoskins, MD
Curtis and Elizabeth Anderson Cancer Institute

After this session, attendees should be able to

- Describe the theoretical benefit of maximum surgical cytoreduction of epithelial ovarian cancer and discuss the published evidence supporting its use
- Summarize the data showing the potential benefits and risks of palliative surgery for patients with recurrent ovarian cancer
- Differentiate which patients with recurrent ovarian cancer may or may not benefit from secondary surgical cytoreduction

Gynecologic Cancer: Advances in Management

CME credits: 3.0

Sunday, June 1
12:30 PM – 3:30 PM

Gynecologic Cancer
CME credits: 1.0

Sunday, June 1
1:00 PM – 5:00 PM

Gynecologic Cancer

Monday, June 2
9:00 AM – 1:00 PM

HEAD AND NECK CANCER

Head and Neck Cancer Debate: Does Induction Chemotherapy Remain a Worthy Approach?

CME credits and pharmacy contact hours: 1.25

Sunday, June 1
9:30 AM – 10:45 AM

Monday, June 2
11:15 AM – 12:30 PM

Paul M. Harari, MD—Chair
University of Wisconsin

Danny Rischin, MD, MBBS, FRACP
Peter MacCallum Cancer Institute

Everett E. Vokes, MD
University of Chicago

After this session, attendees should be able to

- Explain the evolution and rationale for investigating induction chemotherapy in head and neck cancer
- Describe the design and results of clinical trials incorporating induction chemotherapy
- Discuss the justification for future testing of this approach

Head and Neck Cancer: Which Treatment Approach Best Serves Your Patient?

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1
11:00 AM – 12:15 PM

Monday, June 2
4:00 PM – 5:15 PM

David J. Adelstein, MD—Chair
Cleveland Clinic Foundation

Jacques Bernier, MD, PhD
Oncology Institute of Southern Switzerland

Marcy A. List, PhD
University of Chicago Cancer Research Center

John A. Ridge, MD, PhD, FACS
Fox Chase Cancer Center

After this session, attendees should be able to

- Define the role and indications for surgery in the management of head and neck cancer
- Identify the recent data regarding the value of chemotherapy and radiation as postoperative adjuvant therapy
- Discuss the late toxicities and functional impact of current aggressive treatment approaches

Expert Opinion: Management of Thyroid Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M30A)
2:15 PM – 3:30 PM

Monday, June 2 (M30B)
9:30 AM – 10:45 AM

Richard J. Robbins, MD
Memorial Sloan-Kettering Cancer Center

Ashok R. Shaha, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Define high and low-risk patients
- Outline a postoperative surveillance program
- Interpret serum thyroglobulin levels
- Identify the optional imaging procedure to look for residual cancer

Head and Neck Cancer

CME credits: 3.5

Sunday, June 1
12:45 PM – 4:15 PM

Head and Neck Cancer

CME credits: 1.0

Tuesday, June 3
8:00 AM – 12:00 PM

Head and Neck Cancer

Saturday, May 31
2:00 PM – 5:30 PM

HEALTH SERVICES RESEARCH

Understanding Research Synthesis: Guide to Systematic Reviews/ Meta-Analyses with a Focus on Breast Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1
11:15 AM – 12:30 PM

Monday, June 2
11:15 AM – 12:30 PM

Benjamin Djulbegovic, MD, PhD—Chair
H. Lee Moffitt Cancer Center and Research Institute

Mike Clarke, DPhil
University of Oxford

Gary H. Lyman, MD, MPH, FRCP
James P. Wilmot Cancer Center

After this session, attendees should be able to

- Define the principles of systematic reviews and quantitative synthesis of data (meta-analysis)
- Interpret the results of meta-analyses
- List available knowledge resources as related to systematic reviews
- Discuss published systematic reviews/meta-analyses related to the management of breast cancer
- Identify the most important results from systematic reviews/meta-analyses focused on breast cancer that are of interest to practitioners
- Discuss the results of published meta-analyses of screening mammography studies
- Explain the results of research synthesis of sentinel node biopsy studies

Methods: Health-Related Quality of Life in Cancer Research, Patient Care, and Policymaking: Current State of the Science

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M32A)
4:00 PM – 5:15 PM

Monday, June 2 (M32B)
11:15 AM – 12:30 PM

Joseph Lipscomb, PhD
National Cancer Institute

After this session, attendees should be able to

- Identify key contributions of health-related quality-of-life endpoints in the determination of optimal cancer therapies and approval of pharmaceutical agents for cancer treatment
- Evaluate the strengths and weaknesses of different approaches to assessing health-related quality of life
- Utilize health-related quality-of-life assessment to improve physician-patient communication in clinical practice
- Discuss the application of health-related quality-of-life scores in the development of policies for the conduct of clinical trials, standards for patient care, and reimbursement for services

Research Seminar: Assessing Clinical Significance in Measuring Quality of Life for Patients with Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M31A)
2:15 PM – 3:30 PM

Monday, June 2 (M31B)
9:30 AM – 10:45 AM

Jeff A. Sloan, PhD
Mayo Clinic

After this session, attendees should be able to

- Apply the various methods of assessing clinical significance to a research project or clinical practice
- Select an appropriate quality-of-life measure for a research project or clinical application
- Evaluate published reports involving quality-of-life assessment in terms of the veracity and clinical relevance of the findings

Health Services Research

CME credits: 3.0

Sunday, June 1
2:45 PM – 5:45 PM

Health Services Research

CME credits: 1.0

Sunday, June 1
8:00 AM – 12:15 PM

Health Services Research

Saturday, May 31
2:00 PM – 5:30 PM

HEMATOLOGIC MALIGNANCIES

ASCO/American Society of Hematology Joint Symposium: Advances in Transfusion Medicine

CME credits and pharmacy contact hours: 1.5

Sunday, June 1
3:45 PM – 5:15 PM

Paul A. Bunn, Jr., MD—Co-Chair
University of Colorado Cancer Center

Ronald Hoffman, MD—Co-Chair
University of Illinois at Chicago

Mark E. Brecher, MD
University of North Carolina Hospitals

Lawrence Goodnough, MD
Washington University School of Medicine

Diane Krause, MD, PhD
Yale University School of Medcine

Scott Murphy, MD
American Red Cross Blood Services

After this session, attendees should be able to

- Identify current advances in minimizing transmission of infectious disease in blood products
- Discuss platelet transfusion therapy and its role in treatment
- Explain stem cell therapy from the perspective of the blood bank
- Interpret the critical analysis of alternate strategies to the use of blood products

Gene Expression Profiling in Leukemia and Lymphoma

CME credits: 1.5

Monday, June 2
4:00 PM – 5:30 PM

Richard M. Stone, MD—Chair
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Discuss the significance of genetic profiles in the biology, prognosis, and management of lymphoma and leukemia

Chronic Lymphocytic Leukemia: Emerging Role of Antibody Therapy and Molecular Biology

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1
12:15 PM – 1:30 PM

Monday, June 2
11:15 AM – 12:30 PM

Kanti R. Rai, MD—Chair
Long Island Jewish Medical Center and Albert Einstein College of Medicine

John Byrd, MD
The Ohio State University Medical Center

Terry Hamblin, MD, FRCP, FRCPath
Royal Bournemouth Hospital

After this session, attendees should be able to

- Define current treatment options for chronic lymphocytic leukemia, focusing on the role of immunotherapy and combination immunochemotherapy
- Identify molecular prognostics
- Explain molecular biology and prognostic variables
- Discuss controversies regarding chemotherapy/immunotherapy

Impact of Imatinib Mesylate on the Treatment of Chronic Myeloid Leukemia

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Monday, June 2 9:30 AM – 10:45 AM
Tuesday, June 3 9:30 AM – 10:45 AM

Brian J. Druker, MD—Chair
Howard Hughes Medical Institute

John M. Goldman, DM, FRCP
Imperial College School of Medicine at Hammersmith Hospital

Charles L. Sawyers, MD
University of California at Los Angeles School of Medicine

After this session, attendees should be able to

- Summarize the current data on the use of imatinib
- Explain the mechanisms of resistance to imatinib
- Discuss the integration of imatinib into current treatment algorithms for chronic myelogenous leukemia

Progress in Large Cell Lymphoma: Bedside and Bench

CME credits: 1.25

Sunday, June 1 2:00 PM – 3:15 PM
Monday, June 2 11:15 AM – 12:30 PM

Sandra J. Horning, MD—Chair
Stanford University

Bertrand Coiffier, MD, PhD
Centre Hospitalier Lyon

Thomas P. Miller, MD
Arizona Cancer Center

Margaret A. Shipp, MD
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Explain the evolving impact of molecular biology on diagnosis and prognosis
- Discuss results of large clinical trials for limited and advanced disease
- Identify major areas of uncertainty and clinical trials that address them

Stem Cell Plasticity and Multipotentiality

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2 9:30 AM – 10:45 AM
Tuesday, June 3 9:30 AM – 10:45 AM

Pamela S. Becker, MD, PhD—Chair
University of Massachusetts Medical School

Ronald M. Green, PhD
Dartmouth College

Neil Theise, MD
Beth Israel Medical Center

After this session, attendees should be able to

- Identify the different types of stem cells and their isolation
- Describe the multipotentiality of stem cells derived from adult bone marrow
- Appraise embryonic stem cells and their necessity for tissue regeneration
- Interpret the ethics of stem cells and therapeutic cloning

Controversies: Infections in Immunocompromised Patients

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M34A) 7:45 AM – 9:00 AM
Monday, June 2 (M34B) 7:45 AM – 9:00 AM

Estil Vance, MD
Baylor University Medical Center

After this session, attendees should be able to

- Describe the anti-infective approaches to immunocompromised patients, with an emphasis on new agents

Controversies: Management of Indolent Lymphomas

CME credits: 1.25

Sunday, June 1 (M41A) 4:30 PM – 5:45 PM
Tuesday, June 3 (M41B) 7:45 AM – 9:00 AM

James O. Armitage, MD
University of Nebraska Medical Center

After this session, attendees should be able to

- Identify the clinically relevant subtype of indolent lymphoma
- Explain the appropriate use of chemotherapy and antibody therapy

Controversies: Non-Hodgkin's Lymphoma—Pathology, Prognosis, and Therapy

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Monday, June 2 (M35A) 4:00 PM – 5:15 PM
Tuesday, June 3 (M35B) 7:45 AM – 9:00 AM

Randy Gascoyne, MD
British Columbia Cancer Agency

Michael E. Williams, MD
University of Virginia Health System

After this session, attendees should be able to

- Describe complex immunologic and molecular phenotyping studies and their clinical correlates
- Identify clinical case studies with implications for treatment
- Define clinical, phenotypic, and molecular correlates of prognosis

Emerging Concepts: Treatment Strategies for Myelodysplastic Syndromes

CME credits: 1.25

Saturday, May 31 (M39A) 2:15 PM – 3:30 PM
Monday, June 2 (M39B) 4:00 PM – 5:15 PM

H. Joachim Deeg, MD
Fred Hutchinson Cancer Research Center

After this session, attendees should be able to

- Identify prognostic risk factors
- Contrast transplant and nontransplant therapy
- Discuss the advantages and disadvantages of various treatment strategies
- Determine appropriate protocols for patients

Expert Opinion: Hematologic Consequences of Nuclear Terrorism

CME credits and pharmacy contact hours: 1.25

Monday, June 2 (M68A)
4:00 PM – 5:15 PM

Tuesday, June 3 (M68B)
7:45 AM – 9:00 AM

Jamie Waselenko, MD
Walter Reed Army Medical Center

After this session, attendees should be able to

- Define the nuclear terrorism threat and the principles of radiation injury
- Discuss casualty scenarios and statistics
- Describe acute radiation subsyndromes, the types and importance of dosimetry in triage, and the medical management of patients with this form of injury
- Discuss the medical management proposed by the National Pharmaceutical Stockpile working group, including the role of cytokines and other therapies and when to refer patients for allogeneic stem cell transplantation

Expert Opinion: Managing Thrombosis in Patients with Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2 (M36A)
4:00 PM – 5:15 PM

Tuesday, June 3 (M36B)
7:45 AM – 9:00 AM

Michael L. Linenberger, MD
Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center

After this session, attendees should be able to

- Discuss the unique management issues related to hypercoaguability in patients with cancer
- Describe the treatment of thromboembolic complications

Expert Opinion: Radiation Therapy for Hematologic Malignancies

CME credits: 1.25

Saturday, May 31 (M38A)
12:30 PM – 1:45 PM

Monday, June 2 (M38B)
7:45 AM – 9:00 AM

Joachim Yahalom, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Describe the standard indications for radiation therapy as primary treatment, consolidation, salvage, and palliation in Hodgkin's disease, non-Hodgkin's lymphoma, and plasma cell tumors
- Discuss controversial indications for radiation therapy
- Identify recent changes in reducing radiation therapy field and dose
- Explain new techniques for radiation planning and delivery that are relevant to the treatment of hematologic malignancies (three-dimensional conformal and intensity-modulated radiation therapy)

Expert Opinion: Waldenstrom's Macroglobulinemia: Update from the International Workshop

CME credits: 1.25

Saturday, May 31 (M33A)
7:45 AM – 9:00 AM

Monday, June 2 (M33B)
7:45 AM – 9:00 AM

Steven P. Treon, MD, PhD
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Distinguish the diagnosis of Waldenstrom's macroglobulinemia from other immunoglobulin M-related disorders
- Define the appropriate circumstances for treating patients with this disease
- Describe treatment options
- Apply the new response criteria for the disease

Research Seminar: Genes and Gene Expression in Cancer Research

CME credits: 1.25

Saturday, May 31 (M40A)
2:15 PM – 3:30 PM

Monday, June 2 (M40B)
4:00 PM – 5:15 PM

Jerald P. Radich, MD
Fred Hutchinson Cancer Research Center

After this session, attendees should be able to

- Discuss the technical and biologic foundation of gene expression studies
- Describe the potential and limitations of research design, laboratory issues, and data analyses in gene expression studies
- Summarize recent significant research, with an emphasis on how gene expression studies may potentially have an impact on the future care of patients with cancer

Research Seminar: Impact of Biology on the Treatment of Multiple Myeloma

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M37A)
12:30 PM – 1:45 PM

Monday, June 2 (M37B)
7:45 AM – 9:00 AM

Kenneth C. Anderson, MD
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Describe recent advances in the biology and pathogenesis of multiple myeloma
- Define the rationale for novel therapies that target not only the myeloma cell but also the myeloma-bone marrow interaction and bone marrow microenvironment
- Discuss the results of novel therapies and the role of such therapies in the management of multiple myeloma

Lymphoma/Myeloma (Adult)

CME credits: 4.0

Sunday, June 1
7:45 AM – 11:45 AM

HEMATOLOGIC MALIGNANCIES *(continued)*

Leukemia/Myelodysplasia (Adult)
CME credits: 3.0

Tuesday, June 3
7:45 AM – 10:45 AM

Leukemia/Myeloma (Adult)
CME credits: 1.0

Saturday, May 31
7:45 AM – 9:45 AM

Lymphoma (Adult)
CME credits: 1.0

Saturday, May 31
1:00 PM – 5:00 PM

Hematologic Malignancies

Sunday, June 1
2:00 PM – 5:30 PM

LUNG CANCER

Presidential Symposium: Multidisciplinary Approach to Treating Lung Cancer

CME credits and pharmacy contact hours: 1.5
Nursing contact hours: 1.8

Saturday, May 31
4:00 PM – 5:30 PM

Paul A. Bunn, Jr., MD—Chair
University of Colorado Cancer Center

Charles M. Balch, MD—Moderator
ASCO

Walter J. Curran, Jr., MD, FACR
Thomas Jefferson University

Wilbur A. Franklin, MD
University of Colorado Health Sciences Center

Giuseppe Giaccone, MD, PhD
Free University Hospital

Peter Goldstraw, FRCS
Royal Brompton Hospital

James R. Jett, MD
Mayo Clinic

After this session, attendees should be able to
- Compare lung cancer treatment options and apply the latest information regarding these options
- Evaluate patient and disease characteristics, including comorbidity
- Interpret current data on lung cancer management and relevant laboratory assessment of tumor biology
- Select optimal evidence-based therapies for lung cancer

Presidential Symposium: Tobacco Control and Global Issues

CME credits and pharmacy contact hours: 1.5
Nursing contact hours: 1.8

Saturday, May 31
2:00 PM – 3:30 PM

Paul A. Bunn, Jr., MD—Chair
University of Colorado Cancer Center

Dileep Bal, MD
California Department of Health Services

Nigel Gray, MD
European Institute of Oncology

Sir Richard Peto
Clinical Trials Service Unit, Oxford University

After this session, attendees should be able to
- Discuss the role of cigarette consumption as a causation of cancer
- Explain the global impact of cigarette consumption on cancer incidence
- Discuss ways to prevent cancer in smokers
- Determine the role of public policy in the regulation of tobacco consumption

Conundrums in the Management of Lung Cancer

CME credits and pharmacy contact hours: 1.25

Sunday, June 1
7:45 AM – 9:00 AM

Tuesday, June 3
9:30 AM – 10:45 AM

Karen Kelly, MD—Chair
University of Colorado Health Sciences Center

Mark A. Socinski, MD
University of North Carolina at Chapel Hill

David Sugarbaker, MD
Brigham and Women's Hospital

William D. Travis, MD
Armed Forces Institute of Pathology

Andrew T. Turrisi III, MD
Medical University of South Carolina

After this session, attendees should be able to
- Discuss the difficulties of making a definitive diagnosis of lung cancer
- Identify the increasing role for minimally invasive surgery
- Describe the complexity of radiotherapy issues
- Define guidelines for chemotherapy delivery for patients with advanced disease

Risk Assessment for Chemoprevention and Early Detection in Lung Cancer

CME credits: 1.25

Sunday, June 1
11:15 AM – 12:30 PM

Tuesday, June 3
7:45 AM – 9:00 AM

James R. Jett, MD—Chair
Mayo Clinic

Adi F. Gazdar, MD
University of Texas Southwestern

Fadlo Khuri, MD
Emory University School of Medicine

Thomas G. Sutedja, MD
Free University

After this session, attendees should be able to
- Describe the pathology of early bronchial lesions

- Discuss issues in clinical design for chemoprevention trials
- Define the current status of autofluorescence bronchoscopy

Second-Line Treatment and Beyond for Lung Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31 7:45 AM – 9:00 AM
Monday, June 2 4:00 PM – 5:15 PM

Frances A. Shepherd, MD—Chair
Princess Margaret Hospital

Roy S. Herbst, MD, PhD
M.D. Anderson Cancer Center

Nevin Murray, MD, FRCPC
British Columbia Cancer Agency

After this session, attendees should be able to

- Describe second-line chemotherapy approaches for non-small-cell lung cancer
- Explain the use of novel agents with or without second-line chemotherapy for non-small-cell lung cancer
- Discuss the role of second-line therapy for small-cell lung cancer

Use and Overuse of Positron Emission Tomography Scanning in Lung Cancer

CME credits: 1.25

Sunday, June 1 11:15 AM – 12:30 PM
Tuesday, June 3 7:45 AM – 9:00 AM

Eric Vallieres, MD—Chair
University of Washington Medical Center

Michael P. Macmanus, MD
Peter MacCallum Cancer Institute

Johan F. Vansteenkiste, MD, PhD
Catholic University, Luven, Belgium

Hubert Vesselle, MD, PhD
University of Washington School of Medicine

After this session, attendees should be able to

- Define the current recommendations for positron emission tomography (PET) for the staging of lung cancer
- Discuss the role of PET in prognosis and restaging
- Describe the technologic advances in PET

Controversies: Treatment of Lung Cancer in Special Populations

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M47A) 11:15 AM – 12:30 PM
Tuesday, June 3 (M47B) 9:30 AM – 10:45 AM

Rogerio C. Lilenbaum, MD
Mount Sinai Cancer Center

After this session, attendees should be able to

- Discuss the systemic treatment options for older patients with poor performance status and for poor-risk patients

Expert Opinion: Are We Making Progress in the Treatment of Mesothelioma?

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M42A) 12:30 PM – 1:45 PM
Monday, June 2 (M42B) 11:15 AM – 12:30 PM

Hedy L. Kindler, MD
University of Chicago

After this session, attendees should be able to

- Discuss the new, active chemotherapy drugs for mesothelioma
- Identify the most promising novel targeted agents being evaluated
- Describe how these drugs are being integrated into multimodality treatment strategies

Expert Opinion: Impact of Esophagitis in Locally Advanced Non-Small-Cell Lung Cancer

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M48A) 2:45 PM – 4:00 PM
Monday, June 2 (M48B) 4:00 PM – 5:15 PM

Benjamin Movsas, MD
Fox Chase Cancer Center

After this session, attendees should be able to

- Define the impact of esophagitis on completing curative therapy
- Identify factors that predict the degree of esophagitis
- Discuss interventions and strategies to manage and reduce esophagitis in patients receiving combined-modality treatement

Expert Opinion: Pulmonary Resection for High-Risk Patients

CME credits: 1.25

Saturday, May 31 (M44A) 12:30 PM – 1:45 PM
Monday, June 2 (M44B) 11:15 AM – 12:30 PM

Claude Deschamps, MD
Mayo Clinic

After this session, attendees should be able to

- Define a "borderline" patient
- Identify the surgical options
- Describe the other aspects of care
- Discuss the results of pulmonary resection

Expert Opinion: Small-Cell Lung Cancer: Current Therapy and Novel Agents

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M45A) 11:15 AM – 12:30 PM
Tuesday, June 3 (M45B) 9:30 AM – 10:45 AM

Nagahiro Saijo, MD, PhD
National Cancer Center Hospital, Tokyo

After this session, attendees should be able to

- Discuss current therapy for small-cell lung cancer
- Define the role of novel agents for the treatment of small-cell lung cancer

LUNG CANCER *(continued)*

Research Seminar: Biomarkers in Chemoprevention

CME credits: 1.25

Saturday, May 31 (M46A) 7:45 AM – 9:00 AM
Monday, June 2 (M46B) 11:15 AM – 12:30 PM

Wilbur A. Franklin, MD
University of Colorado Health Sciences Center

After this session, attendees should be able to

- Describe the multistep changes that precede invasive carcinoma of the lung
- Determine how premalignant changes differ from invasive carcinoma
- Identify promising biomarkers for both lung cancer and premalignancy
- Discuss the diverse role of biomarkers in the design of chemoprevention trials for lung cancer

Research Seminar: Use of Epidermal Growth Factor Receptor Inhibitors in Clinical Practice for Non-Small-Cell Lung Cancer

CME credits and pharmacy contact hours: 1.25

Sunday, June 1 (M43A) 2:45 PM – 4:00 PM
Monday, June 2 (M43B) 4:00 PM – 5:15 PM

Alan B. Sandler, MD
Vanderbilt University Medical Center

After this session, attendees should be able to

- Describe the biology of epidermal growth factor receptors
- Discuss the chemical data supporting the use of epidermal growth factor inhibitors

Challenges in Treating Patients with Lung Cancer and Brain Metastasis

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (CPO03A) 1:00 PM – 2:15 PM
Tuesday, June 3 (CPO03B) 11:15 AM – 12:30 PM

Laurie E. Gaspar, MD—Chair
Anschutz Cancer Pavilion

Kevin O. Lillihei, MD
University of Colorado Health Sciences Center

Roy Patchell, MD
University of Kentucky Medical Center

After this session, attendees should be able to

- Discuss the changing patterns of relapse in locally advanced non-small-cell lung cancer
- Explain the outcomes of randomized studies of radiosurgery, whole-brain radiation, and radiosensitizers
- Identify current controversies
- Interpret the rationale of ongoing studies, including prophylactic whole-brain radiation for non-small-cell lung cancer

Non-Small-Cell Lung Cancer

CME credits: 3.0

Sunday, June 1
7:45 AM – 10:45 AM

Small-Cell and Other Thoracic Malignancies

CME credits: 3.0

Monday, June 2
7:45 AM – 10:45 AM

Lung Cancer 1

CME credits: 1.0

Sunday, June 1
1:00 PM – 5:00 PM

Lung Cancer 2

CME credits: 1.0

Tuesday, June 3
8:00 AM – 12:00 PM

Lung Cancer

Saturday, May 31
9:00 AM – 1:00 PM

MELANOMA

Current Management Issues in Malignant Melanoma

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1 9:15 AM – 10:30 AM
Monday, June 2 9:30 AM – 10:45 AM

Lawrence E. Flaherty, MD—Co-Chair
Karmanos Cancer Institute, Wayne State University

Steven J. O'Day, MD—Co-Chair
John Wayne Cancer Institute

Alistair J. Cochran, MD
University of California at Los Angeles

R. Edward Coleman, MD
Duke University Medical College

Marc S. Ernstoff, MD
Dartmouth Hitchcock Medical Center

After this session, attendees should be able to

- Identify the sentinel node pathologic information necessary to correctly stage and manage malignant melanoma
- Discuss the use of positron emission tomography to provide information for the management of disease
- Describe the role of interferon and biochemotherapy in the management of disease

Expert Opinion: Management of Metastatic Melanoma

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M51A) 12:30 PM – 1:45 PM
Sunday, June 1 (M51B) 7:45 AM – 9:00 AM

Antonio Buzaid, MD
Hospital Sirio Libanes

After this session, attendees should be able to

- Describe the most active chemotherapy drugs and potential mechanisms to overcome drug resistance
- Discuss the results of immunotherapy, with an emphasis on interleukin-2-based programs

- Identify the results of biochemotherapy
- Define practical guidelines for the management of biochemotherapy-related toxicity

Expert Opinion: Surgical Management of Melanoma

CME credits: 1.25

Sunday, June 1 (M52A)
7:45 AM – 9:00 AM

Charles M. Balch, MD
ASCO

After this session, attendees should be able to

- Identify new staging criteria of the American Joint Commission on Cancer
- Discuss the results of melanoma surgical trials
- Describe indications and limitations of sentinel node technology
- Identify prognostic factors in planning multidisciplinary treatment

Expert Opinion: Vaccine Development and Treatment in Melanoma

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M53A)
2:15 PM – 3:30 PM

Sunday, June 1 (M53B)
1:00 PM – 2:15 PM

Donald L. Morton, MD
John Wayne Cancer Institute

After this session, attendees should be able to

- Discuss the conceptual basis for active specific immunotherapy for melanoma
- Identify the types of melanoma vaccines in clinical trials
- Define the types of patients most likely to benefit from melanoma vaccines

Melanoma

CME credits: 3.0

Saturday, May 31
7:45 AM – 10:45 AM

Melanoma

CME credits: 1.0

Sunday, June 1
1:00 PM – 5:30 PM

Melanoma

Saturday, May 31
2:00 PM – 5:30 PM

PATIENT CARE

Supportive Care and Symptom Control: Key Strategies for Providing the Best Patient Experience

CME credits and pharmacy contact hours: 4.0
Nursing contact hours: 4.8

Friday, May 30 (ES03)
12:00 PM – 4:00 PM

Jamie H. Von Roenn, MD—Chair
Northwestern University

See pages 51-52 for complete description.

American Cancer Society Award Lecture: Psychologic Care of Patients—Psycho-Oncology's Contribution

CME credits and pharmacy contact hours: 1.5
Nursing contact hours: 1.8

Monday, June 2
7:45 AM – 9:15 AM

Jimmie Holland, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to

- Discuss the attitudinal and cultural barriers that have slowed attention to psychologic care of patients
- Identify ways to help overcome the attitudinal barriers (similar to those with pain) that prevent patients' receiving optimal psychologic care
- Describe the standards of care and clinical practice guidelines that have been developed for management of distress (a term used to reduce stigma)

ASCO/Oncology Nursing Society Joint Symposium: Schwartz Center Rounds—The Value of Strengthening the Connections between Patients and Caregivers

CME credits: 1.25 Nursing contact hours: 1.5

Monday, June 2
9:30 AM – 10:45 AM

Mimi Bartholomay, RN—Co-Chair
Massachusetts General Hospital

Thomas J. Lynch, MD—Co-Chair
Massachusetts General Hospital

Jon Dubois, MD
Emerson Hospital

Joanne LaFrancesca, RN
Massachusetts General Hospital

Sally Mack, MSW
The Schwartz Center, Massachusetts General Hospital

Richard T. Penson, MD
Massachusetts General Hospital

Paula K. Rauch, MD
Massachusetts General Hospital

After this session, attendees should be able to

- Describe how connecting with patients enhances the quality of care and the career satisfaction of those who provide it
- Discuss how Schwartz Center Rounds allows the concerns and perspectives of nurses, physicians, social workers, and other members of the health-care team to be valued and how this process can improve care
- Apply this knowledge to the establishment of programs that enhance and support compassionate heath care at hospitals and cancer clinics
- Discuss the need for physicians and nurses to talk to each other about the stresses they share in caring for patients with advanced cancer

Best of Oncology

CME credits and pharmacy contact hours: 1.5

Monday, June 2
4:00 PM – 5:30 PM

Ronald H. Blum, MD—Co-Chair
Beth Israel Medical Center

Paul A. Bunn, Jr., MD—Co-Chair
University of Colorado Cancer Center

After this session, attendees should be able to

- Identify and discuss critical scientific advances in oncology, as originally presented at other oncology-related meetings
- Apply the concepts and outcomes presented to current research and/or practice

Patient Advocacy and Patient Care: A Session for Oncologists

CME credits: 1.5
Nursing contact hours: 1.8

Sunday, June 1
11:00 AM – 12:30 PM

Ellen Stovall—Chair
National Coalition for Cancer Survivorship

Diane Blum, MSW
Cancer Care, Inc.

Kathy Giusti
Multiple Myeloma Research Foundation

After this session, attendees should be able to

- Discuss with patients how they can better advocate for themselves, for patients with similar diagnoses, and for policy changes

Managing the Psychosocial Side Effects of Adjuvant Chemotherapy for Breast Cancer

CME credits: 1.5 Nursing contact hours: 1.8

Monday, June 2
4:00 PM – 5:30 PM

Eric P. Winer, MD—Chair
Dana-Farber Cancer Institute

After this session, attendees should be able to

- Identify psychosocial symptoms and provide advice to patients with these symptoms
- Select appropriate interventions for these symptoms

Pathogenesis-Based Treatment of Mucositis and Nausea and Vomiting

CME credits and pharmacy contact hours: 1.5
Nursing contact hours: 1.8

Saturday, May 31
12:45 PM – 2:15 PM

Paul J. Hesketh, MD—Chair
St. Elizabeth's Medical Center

Mark G. Kris, MD
Memorial Sloan-Kettering Cancer Center

Edward B. Rubenstein, MD
M.D. Anderson Cancer Center

After this session, attendees should be able to

- Define the current extent of unresolved issues in the management of mucositis and chemotherapy-induced emesis
- Discuss best standard care as supported by evidence-based guidelines
- Explain new insights into the pathophysiology and basic mechanisms of mucositis and chemotherapy-induced emesis
- Identify promising new treatment approaches in development

Bone Metastases: From the Bench to the Bedside

CME credits: 1.25 Nursing contact hours: 1.5

Sunday, June 1
9:30 AM – 10:45 AM

Tuesday, June 3
9:30 AM – 10:45 AM

Harold A. Harvey, MD—Chair
Milton S. Hershey Medical Center

Robert E. Coleman, MD
Cancer Research Center, Weston Park Hospital

Theresa Guise, MD
University of Virginia

Allan Lipton, BSc, MB, ChB, MD
Penn State College of Medicine

Alexander Paterson, BSc, MB, ChB, MD
Tom Baker Cancer Center

After this session, attendees should be able to

- Discuss the pathophysiology of bone metastases
- Describe the clinical significance, diagnosis, and evaluation of metastatic bone disease
- Evaluate clinical data on the use of bisphosphonates for the treatment and prevention of bone metastases
- Describe molecular mechanisms for novel approaches to treatment of bone metastases

Opioid Selection in the Treatment of Advanced Cancer Pain

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1
7:45 AM – 9:00 AM

Tuesday, June 3
7:45 AM – 9:00 AM

Kathleen M. Foley, MD—Chair
Memorial Sloan-Kettering Cancer Center

Eduardo Bruera, MD
M.D. Anderson Cancer Center

Steven D. Passik, PhD
University of Kentucky Markey Cancer Center

After this session, attendees should be able to
- Explain the importance of opioid pharmacokinetics, pharmacodynamics, and pharmacogenomics in selecting opioids
- Identify factors that influence opioid rotation and equianalgesic dosing
- Discuss side effects and risk of substance abuse

Expert Opinion: Spirituality, Disease, and Cancer

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31 (M54A) 7:45 AM – 9:00 AM
Monday, June 2 (M54B) 9:30 AM – 10:45 AM

Lodovico Balducci, MD
H. Lee Moffitt Cancer Center and Research Institute

After this session, attendees should be able to
- Interpret patient reaction to cancer in light of the religious tradition and beliefs of the patient
- Incorporate patients' beliefs and concerns in plans of care
- Discuss with patients the meaning of healing and alternative methods of care
- Establish meaningful relationships with patients in which there is recognition and respect for their beliefs

Methods: Using Poetry for Personal and Professional Communication

CME credits: 1.25

Saturday, May 31 (M65A) 12:30 PM – 1:45 PM
Monday, June 2 (M65B) 7:45 AM – 9:00 AM

Marc J. Straus, MD
Oxford Medical Group

After this session, attendees should be able to
- Discuss the value of poetry as a resource for communication
- Describe what the patient "hears"
- Discuss how oncologists can effectively use poetry to foster dialogue with patients
- Define ethical issues in oncology

Anger, Hope, and the Care of Patients with Cancer: Religious Thinkers Respond to Case Studies

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2 (CPO04A) 4:00 PM – 5:15 PM
Tuesday, June 3 (CPO04B) 9:30 AM – 10:45 AM

Alan B. Astrow, MD—Chair
St. Vincent's Comprehensive Cancer Center

Ingrid Mattson, PhD
Hartford Seminary

Rabbi James E. Ponet
The Joseph Slifka Center for Jewish Life

Daniel Sulmasy, OFM, MD, PhD
St. Vincent's Hospital

After this session, attendees should be able to
- Discuss concepts of the meaning of illness with patients and the sources of strength in their lives
- Define anger, hope, and suffering within the context of religious traditions
- Describe the impact of personal hopes and disappointments on patient care

Patient Care

CME credits: 4.0

Sunday, June 1
1:00 PM – 5:00 PM

Pain, Side Effects of Therapy, and Patient Wishes

CME credits: 1.0

Monday, June 2
8:00 AM – 12:00 PM

Communication, Fatigue, and Age

CME credits: 1.0

Sunday, June 1
8:00 AM – 12:00 PM

Palliative, Supportive, and Elderly Care

Saturday, May 31
2:00 PM – 5:30 PM

Pediatric Oncology Lectureship: Molecular Genetics and Natural History of Childhood Leukemia

CME credits: 1.25
Nursing contact hours: 1.5

Tuesday, June 3
7:45 AM – 9:00 AM

Melvyn Greaves, PhD
Institute of Cancer Research, London

After this session, attendees should be able to
- Discuss the current understanding of the biologic diversity of pediatric leukemia and the impact of this on both clinical outcome and pathogenesis
- Describe how chromosome translocations can be used as stable, sensitive, and specific markers for tracking the appearance of leukemic clones
- Discuss the evidence that most pediatric leukemias originate prenatally
- Explain how the distinctive natural histories of leukemia subtypes provide an important framework for molecular epidemiologic studies

Acute Leukemia: Preclinical Models and New Drug Development

CME credits and pharmacy contact hours: 1.25

Sunday, June 1
2:45 PM – 4:00 PM

A. Thomas Look, Jr., MD—Chair
Dana-Farber Cancer Institute

Gary Gilliland, MD, PhD
Harvard Institute of Human Genetics

Pier P. Pandolfi, MD
Memorial Sloan-Kettering Cancer Center

After this session, attendees should be able to
- Define five genetic types of human T-cell leukemia
- Identify the oncogenic types of acute promyelocytic leukemia that respond to all-trans-retinoic acid
- Define multistep mutational pathways of leukemogenesis

- Identify molecular genetic groups of T-cell leukemia with a favorable outcome
- Discuss what is the most frequently mutated tyrosine kinase receptor in acute myelogenous leukemia

Average-Risk Medulloblastoma: Potential for Biologic Redefinition and Advances in Therapy

CME credits and pharmacy contact hours: 1.25

Saturday, May 31
2:30 PM – 3:45 PM

Roger Packer, MD—Chair
Children's National Medical Center

Richard Gilbertson, MD, PhD
St. Jude Children's Research Hospital

Tobey J. MacDonald, MD
Children's National Medical Center

After this session, attendees should be able to

- Discuss new biology in relationship to risk
- Explain reduced field and dose options in average-risk medulloblastoma
- Describe multimodality therapy for average-risk medulloblastoma
- Determine sequelae of reduced or full-dose craniospinal irradiation

Etiology of Acute Leukemia

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Monday, June 2
4:00 PM – 5:15 PM

Melvyn Greaves, PhD—Chair
Institute of Cancer Research, London

Julie Ross, PhD
University of Minnesota

Christine F. Skibola, MD
University of California at Berkeley

After this session, attendees should be able to

- Discuss the importance of molecular subtypes of leukemia
- Describe the timing of molecular events in the pathogenesis of acute lymphocytic leukemia
- Define the importance of prenatal events in the development of pediatric leukemia
- Explain how maternal diet may influence the risk of pediatric leukemia

How to Optimize Staging of Cancer in Children and Adolescents by Inclusion of Biologic Studies

CME credits: 1.25

Sunday, June 1
12:45 PM – 2:00 PM

William L. Carroll, MD—Chair
Mount Sinai and New York University Schools of Medicine

Robert J. Arceci, MD, PhD
Johns Hopkins University School of Medicine

John M. Maris, MD
Children's Hospital of Philadelphia

After this session, attendees should be able to

- Describe methods of specimen collection that allow for the assessment of risk factors (known or potential)
- Apply this infomation to leukemias and solid tumors

Molecular Pathogenesis and New Approaches to Therapy in Pediatric Non-Hodgkin's Lymphoma

CME credits: 1.25

Sunday, June 1
2:30 PM – 3:45 PM

Howard J. Weinstein, MD—Chair
MassGeneral Hospital for Children

Elliott Kieff, MD, PhD
Brigham and Women's Hospital

John Sandlund, Jr., MD
St. Jude Children's Hospital

Thomas R. Spitzer, MD
Massachusetts General Hospital

After this session, attendees should be able to

- Discuss the molecular pathogenesis of Burkitt's lymphoma and lymphoproliferative disorders after transplantation
- Describe techniques for monitoring minimal residual disease
- Identify new approaches to therapy

New Approaches to Imaging in Pediatric Cancer

CME credits: 1.25

Saturday, May 31
12:45 PM – 2:00 PM

Helen Nadel, MD, FRCP—Chair
British Columbia's Children's Hospital

R. Paul Guillerman, MD, MA
Texas Children's Hospital

Sue Kaste, MD
St. Jude Children's Research Hospital

After this session, attendees should be able to

- Identify studies that provide the most information for planning, staging, and therapy for early detection of relapse
- Describe the advantage of new imaging modalities relative to standard imaging
- Discuss optimal timing and imaging strategies for surveillance and follow-up of potential long-term effects of cancer therapy for children

New Biologic and Therapeutic Developments in Acute Myeloid Leukemia

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31
12:45 PM – 2:00 PM

Franklin O. Smith, MD—Chair
University of Cincinnati College of Medicine

Gary Gilliland, MD, PhD
Harvard Institute of Human Genetics

Cheryl L. Willman, MD
University of New Mexico Cancer Research and Treatment Center

After this session, attendees should be able to
- Descibe new directions in the therapy of acute myeloid leukemia
- Determine the prognostic importance of molecular abnormalities in acute myeloid leukemia
- Explain the value of assessment of minimal residual disease in acute myeloid leukemia

Prior Therapeutic Failures and Future Therapeutic Hopes for Infants with Brain Tumors

CME credits: 1.25
Nursing contact hours: 1.5

Monday, June 2
9:30 AM – 10:45 AM

Jeffrey R. Geyer, MD—Chair
Children's Hospital, Seattle

Thomas E. Merchant, MD
St. Jude Children's Research Hospital

Raymond K. Mulhern, MD
St. Jude Children's Research Hospital

After this session, attendees should be able to
- Identify the current state of therapy for infants with brain tumors
- Describe the problems associated with using chemotherapy alone
- Predict the possibilities and difficulties of introducing radiotherapy for infants with brain tumors
- Discuss the neurocognitive problems related to radiotherapy field and dose

Selection of New Agents Using Preclinical Models and Molecular Targeting: Implications from Advances in Pediatric Oncology

CME credits and pharmacy contact hours: 1.25

Monday, June 2
7:45 AM – 9:00 AM

Gregory H. Reaman, MD—Chair
Children's Oncology Group

Peter C. Adamson, MD
Children's Hospital of Philadelphia

Steven Hirschfeld, MD
U.S. Food and Drug Administration

Peter J. Houghton, PhD
St. Jude Children's Research Hospital

After this session, attendees should be able to
- Define specific molecular targets relevant to pediatric cancer
- Discuss strategies for developing molecular targeted agents for pediatric cancers
- Describe the benefits of preclinical models for testing new agents to prioritize those for clinical evaluation in children

Use of a Multimodal Team to Optimize Local Control and Function in Bone and Soft Tissue Sarcomas: A Practical Approach

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Saturday, May 31
7:45 AM – 9:00 AM

Philip P. Breitfeld, MD—Chair
Duke University Medical Center

Kenneth L. B. Brown, MD, MSc, FRCSC
University of British Columbia

Robert B. Marcus, MD
Emory University

After this session, attendees should be able to
- Describe the limitations of surgery, radiation, and chemotherapy for primary lesions in sarcomas
- Discuss the unique challenges of local control in young patients
- Identify unfavorable anatomic factors that influence risk of poor local control and functional outcomes
- Describe methods to avert risks

Expert Opinion: Pediatric Brain Tumors

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M55A)
11:15 AM – 12:30 PM

Eric Bouffet, MD, MPH, FRCP
The Hospital for Sick Children

After this session, attendees should be able to
- Describe the most common brain tumors in children
- Explain the principle of management relative to children
- Define the late effects of treatments
- Discuss information available on the Internet about this topic

Expert Opinion: Pediatric Hodgkin's Disease

CME credits: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M56A)
4:30 PM – 5:45 PM

Melissa M. Hudson, MD
St. Jude Children's Research Hospital

After this session, attendees should be able to
- Explain the unique epidemiologic and biologic features of Hodgkin's disease in children
- Define factors influencing the evolution of staging and treatment
- Identify treatment sequelae
- Discuss new therapeutic approaches

PEDIATRIC CANCER *(continued)*

Expert Opinion: Pediatric Neuroblastoma

CME credits: 1.25

Monday, June 2 (M57A)
11:15 AM – 12:30 PM

Susan L. Cohn, MD
Northwestern University

After this session, attendees should be able to

- Define clinical and biologic factors that are predictive of outcome in neuroblastoma
- Identify patients as low, intermediate, or high risk and justify risk-adjusted therapy

Expert Opinion: Regulatory, Ethical, and Clinical Issues and Challenges in Pediatric Oncology Drug Development

CME credits and pharmacy contact hours: 1.25
Nursing contact hours: 1.5

Sunday, June 1 (M58A)
4:30 PM – 5:45 PM

Gregory H. Reaman, MD
Children's Oncology Group

After this session, attendees should be able to

- Describe the case statement for the need to develop new agents for childhood cancer
- Define regulatory challenges and pending legislation to facilitate drug development for pediatric cancer
- Discuss ethical considerations of early phase studies in pediatric oncology

Pediatric Leukemia/Lymphoma and Late Effects

CME credits: 3.0

Sunday, June 1
7:45 AM – 10:45 AM

Pediatric Solid Tumors and Supportive Care

CME credits: 3.0

Monday, June 2
7:45 AM – 10:45 AM

Pediatric Solid/CNS Tumors

Saturday, May 31
1:30 PM – 5:30 PM

Pediatric Leukemia and Developmental Therapeutics

Saturday, May 31
9:00 AM – 1:00 PM

PRACTICE MANAGEMENT AND PROFESSIONAL ISSUES

Forum on Reimbursement

CME credits and pharmacy contact hours: 1.5

Sunday, June 1
9:00 AM – 10:30 AM

Joseph S. Bailes, MD—Chair
US Oncology, Inc.

Terry Coleman
Ropes and Gray

After this session, attendees should be able to

- Describe the developments in reimbursement policy under Medicare and other programs
- Discuss government activities as they relate to oncology
- Apply changes in reimbursement to everyday practice

International Members: What Can ASCO Do for You?

Saturday, May 31
12:30 PM – 1:45 PM

Alexander M. Eggermont, MD, PhD—Chair
University Hospital Rotterdam

The goal of this session is to increase international members' awareness of ASCO programs and services and to explore ways ASCO can enhance the membership experience for international members. Participants will be encouraged to provide feedback on programs that have been implemented.

Report on the National Initiative on Cancer Care Quality (NICCQ)

CME credits and pharmacy contact hours: 1.5

Sunday, June 1
12:45 PM – 2:15 PM

Joseph S. Bailes, MD—Chair
US Oncology, Inc.

Ezekiel J. Emanuel, MD, PhD
Warren G. Magnuson Clinical Center

Arnold Epstein, MD
Harvard School of Public Health

Katherine Kahn, MD
RAND Corporation

Eric Schneider, MD, BSC
Harvard School of Public Health

After this session, attendees should be able to

- Describe the key objectives of the NICCQ, including project design, recruitment, and progress to date
- Apply key findings from the patient survey to better focus on communication and interaction with patients
- Identify the challenges associated with obtaining data about the continuity and coordination of care among providers
- Discuss the diverse group of participants and professional organizations necessary to implement a national quality monitoring system

Becoming a Political Advocate for Your Patients

CME credits and pharmacy contact hours: 1.25

Saturday, May 31
12:30 PM – 1:45 PM

Monday, June 2
4:00 PM – 5:15 PM

Joseph S. Bailes, MD—Co-Chair
US Oncology, Inc.

John E. Niederhuber, MD—Co-Chair
University of Wisconsin

Ellen Stovall
National Coalition for Cancer Survivorship

After this session, attendees should be able to

- Identify current health policy issues and the potential impact on cancer research, patient care, and the practice of oncology
- Describe the role of the federal government in supporting oncology research and access to cancer treatments
- Explain how ASCO volunteers and the Society formulate ASCO positions and work to influence decisions on health-care policy

Methods: Are You HIPAA Compliant?

CME credits and pharmacy contact hours: 1.25

Saturday, May 31 (M60A) 2:15 PM – 3:30 PM
Monday, June 2 (M60B) 9:30 AM – 10:45 AM

Daniel M. Bernick, JD, MBA
The Health Care Group

After this session, attendees should be able to

- Discuss the "ins and outs" of treatment payment and operations
- Explain the best way to handle friends and family
- Describe how to respond to a subpoena for patient records
- Determine whether a consent-to-release form prepared by a third party meets HIPAA requirements
- Define when to log a disclosure of patient information
- Describe how HIPAA intersects with state privacy rules
- Discuss status of HIPAA initiatives (e.g., Security Regulations)

Methods: Clinical Systems—Myth or Reality?

CME credits: 1.25

Saturday, May 31 (M61A) 4:00 PM – 5:15 PM
Monday, June 2 (M61B) 7:45 AM – 9:00 AM

Peter Dysert, MD
Baylor University Medical Center

After this session, attendees should be able to

- Define the key differences between financial and clinical computer systems
- Discuss the external forces driving the adoption of clinical computer systems
- Determine the need for such systems by evaluating current systems and competitive environment
- Apply the lessons learned by pioneering institutions to successfully integrate clinical computer systems into practice
- Discuss the state of the clinical systems marketplace (and the role of vendors) and the role of Internet technologies to develop strategies that maximize physician/institutional benefit

ASCO and Medical Oncology Recertification: Examination-Based Learning

CME credits: 1.25

Sunday, June 1 (CPO05A) 2:45 PM – 4:00 PM
Tuesday, June 3 (CPO05B) 7:45 AM – 9:00 AM

Anne Moore, MD—Co-Chair
New York Presbyterian Hospital-Weill Cornell Medical Center

Hyman B. Muss, MD—Co-Chair
University of Vermont

After this session, attendees should be able to

- Define and justify the rationale of recertification
- Describe examples of recertification questions
- Identify links that provide information helpful in answering questions
- Discuss how to study for the "secure examination"—clinical focus and the ABIM blueprint
- Describe ASCO-ABIM potential collaborations for recertifications and "lifelong learning"

New Approaches to Assessment, Classification, and Treatment of Soft Tissue Sarcomas

CME credits: 1.25 Nursing contact hours: 1.5

Saturday, May 31 4:15 PM – 5:30 PM
Sunday, June 1 4:30 PM – 5:45 PM

Jaap Verweij, MD, PhD—Chair
Erasmus University Medical Center

Jonathan A. Fletcher, MD
Brigham and Women's Hospital

Paul S. Meltzer, MD, PhD
National Human Genome Research Institute

After this session, attendees should be able to

- Describe the potentials and pitfalls of target discovery and how they may lead to the development of targeted treatment
- Identify the molecular biology of soft tissue sarcomas
- Discuss the pitfalls of trial methodology for targeted treatment of soft tissue sarcomas

Sarcoma

CME credits: 3.0

Sunday, June 1
12:45 PM – 3:45 PM

Sarcoma

CME credits: 1.0

Monday, June 2
8:00 AM – 12:15 PM

Sarcoma

Saturday, May 31
2:00 PM – 5:30 PM

SURGICAL ONCOLOGY AND MANAGEMENT

ASCO/Society of Surgical Oncology Joint Symposium: The How, When, and Why of Surgical Prophylaxis in High-Risk Patients

CME credits: 1.5

Sunday, June 1
11:00 AM – 12:30 PM

Jose G. Guillem, MD, MPH—Co-Chair
Memorial Sloan-Kettering Cancer Center

Kenneth Offit, MD, MPH—Co-Chair
Memorial Sloan-Kettering Cancer Center

Andrew Berchuck, MD
Duke University Medical Center

Jeffrey F. Moley, MD
Washington University School of Medicine

William C. Wood, MD
Emory University Hospital

After this session, attendees should be able to

- Discuss the role of surgical interventions for patients with hereditary cancers, including breast and ovarian cancers, MEN 2 syndrome, familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer
- Identify the subset of high-risk patients expected to benefit from prophylactic procedures
- Determine the optimal timing and mode of surgical intervention

Role of Sentinel Node in Staging and Therapy

CME credits: 1.25

Saturday, May 31
7:45 AM – 9:00 AM

Sunday, June 1
9:15 AM – 10:30 AM

Charles M. Balch, MD—Chair
ASCO

Anton J. Bilchik, MD, PhD, FACS
John Wayne Cancer Institute

Donald L. Morton, MD
John Wayne Cancer Institute

Umberto Veronesi, MD
European Institute of Oncology

After this session, attendees should be able to

- Describe the technical requirements and physical skills needed for using sentinel node technology
- Discuss the contribution of each specialty in the multidisciplinary coordination of the sentinel node procedure
- Interpret the results of sentinel node excision that affect prognosis and treatment management
- Identify clinical trials that validate this technology in cancer staging

TRANSPLANTATION

Frontiers in Stem Cell Transplantation

CME credits: 1.25
Nursing contact hours: 1.5

Saturday, May 31
12:45 PM – 2:00 PM

Sunday, June 1
12:30 PM – 1:45 PM

David G. Maloney, MD, PhD—Chair
Fred Hutchinson Cancer Research Center

Joseph H. Antin, MD
Dana-Farber Cancer Institute

Michael R. Bishop, MD
National Institutes of Health

After this session, attendees should be able to

- Discuss the current status of reduced-intensity or nonmyeloablative allogeneic stem cell transplantation for patients with hematologic malignancies
- Describe autologous stem cell transplant followed by nonmyeloablative transplant for lymphoma and myeloma
- Discuss the current status of allogeneic transplants for solid tumors

Advances in Stem Cell Transplantation

CME credits: 2.5

Sunday, June 1
8:00 AM – 10:30 AM

Transplantation

CME credits: 1.0

Monday, June 2
8:00 AM – 12:00 PM

Transplantation

Sunday, June 1
2:00 PM – 5:30 PM

TUMOR BIOLOGY/ HUMAN GENETICS

Principles of Molecular Oncology

CME credits and pharmacy contact hours: 4.0
Nursing contact hours: 4.8

Friday, May 30 (ES02)
12:00 PM – 4:00 PM

John Mendelsohn, MD—Chair
M.D. Anderson Cancer Center

See page 51 for complete description.

Best Science of Oncology

CME credits: 1.5

Sunday, June 1
1:00 PM – 2:30 PM

Larry Norton, MD—Co-Chair
Memorial Sloan-Kettering Cancer Center

Harold Varmus, MD—Co-Chair
Memorial Sloan-Kettering Cancer Center

Phillip Sharp, PhD
Massachusetts Institute of Technology

After this session, attendees should be able to

- Discuss the historical development and current status of key topics in the biology of cancer
- Describe basic science concepts relevant to the design of improved strategies in diagnosis, classification, and management

Critical Appraisal of Microarrays for Clinicians

CME credits: 1.25

Saturday, May 31
7:45 AM – 9:00 AM

Monday, June 2
7:45 AM – 9:00 AM

Gilbert Chu, MD, PhD—Chair
Stanford University

James R. Downing, MD
St. Jude Children's Research Hospital

Paul S. Meltzer, MD, PhD
National Human Genome Research Institute

After this session, attendees should be able to

- Describe the collection process for microarray data
- Discuss the methods for analyzing microarray data
- Define the application of microarrays to problems in cancer
- Critically evaluate the microarray literature

Regulating Apoptosis As a Therapeutic Target

CME credits and pharmacy contact hours: 1.25

Saturday, May 31
7:45 AM – 9:00 AM

Monday, June 2
4:00 PM – 5:15 PM

Scott W. Lowe, PhD—Chair
Cold Spring Harbor Laboratory

John Reed, PhD
Burnham Institute

Craig Thompson, PhD
University of Pennsylvania

After this session, attendees should be able to

- Describe the basic and clinical aspects of apoptosis
- Discuss the rationale for targeting apoptosis in cancer therapy
- Identify the pharmacologic agents that regulate apoptosis

Research Seminar: Transforming Growth Factor-beta and Carcinogenesis

CME credits: 1.25

Monday, June 2 (M62A)
11:30 AM – 12:45 PM

Tuesday, June 3 (M62B)
7:45 AM – 9:00 AM

Harold L. Moses, MD
Vanderbilt-Ingram Cancer Center

After this session, attendees should be able to

- Discuss the role of tranforming growth factor-beta signaling and the pathways involved in tumor suppression and tumor progression
- Identify potential targets for therapeutic intervention

Predicting Risk and Outcome in Solid Tumors

CME credits: 3.0

Sunday, June 1
7:45 AM – 10:45 AM

Tumor Biology/Human Genetics 1

CME credits: 1.0

Saturday, May 31
1:30 PM – 5:30 PM

Tumor Biology/Human Genetics 2

CME credits: 1.0

Sunday, June 1
1:00 PM – 5:00 PM

Tumor Biology/Human Genetics

Monday, June 2
9:00 AM – 1:00 PM

PHARMACOLOGY AND DRUG DEVELOPMENT

This new symposium is designed to provide education in an area not often included in oncologists' formal training.

At the conclusion of this symposium, attendees should be able to

- Discuss studies that precede clinical development (Investigational New Drug [IND] stage), pharmacokinetics, pharmacodynamics, correlative studies, and regulatory affairs

Who Should Attend

This symposium is designed for academic and clinical oncologists who currently have a limited exposure to the topics outlined here. Others who may benefit include trainees, pharmaceutical scientists, program directors, oncology nurses, and additional health-care professionals who treat patients with cancer.

Credit Designation

The American Society of Clinical Oncology designates this educational activity for a maximum of 4.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Professional Education Services Group is accredited by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Universal program number: 829-000-03-008-L01. This program provides 4.0 contact hours (0.40 CEUs) of continuing education credit. Continuing Education Statements of Credit will be distributed by mail four weeks after successful completion of a CE workbook and a separate program evaluation form.

This activity for 4.8 contact hours is provided by Professional Education Services Group, which is accredited by the American Nurses Credentialing Center's Commission on Accreditation as a provider of continuing education in nursing. Activity number: 829-03-001-L.

PROGRAM

11:30 AM **Box lunch available**

Preclinical Studies to Support a Decision to Initiate Clinical Development
Marie-Christine Bissery, PhD
Aventis Pharmaceuticals

12:00 PM **Questions and Answers**

12:10 PM **Pharmacokinetics**
Jerry M. Collins, PhD
U.S. Food and Drug Administration

12:40 PM **Questions and Answers**

12:50 PM **Pharmacokinetic-Pharmacodynamic Relationships**
Merrill J. Egorin, MD
University of Pittsburgh Cancer Institute

1:20 PM **Questions and Answers**

1:30 PM **Break**

2:00 PM **Use and Misuse of Tumor Specimens for Pharmacodynamic Studies in Association with Early Clinical Trials**
Lee M. Ellis, MD
M.D. Anderson Cancer Center

2:30 PM **Questions and Answers**

2:40 PM **Pharmacogenomics**
Mark Ratain, MD
University of Chicago

3:10 PM **Questions and Answers**

3:20 PM **Clinical Trial Designs that Highlight Rather than Obscure Evidence of Efficacy**
Richard Pazdur, MD
U.S. Food and Drug Administration

3:50 PM **Questions and Answers**

PRINCIPLES OF MOLECULAR ONCOLOGY

The continuing evolution of molecular oncology affects cancer research as well as patient care. Because this area is relatively new and rapidly developing, it is imperative that both clinical and academic oncologists become and remain familiar with the principles of molecular oncology to maintain the highest quality of care for patients with cancer. The symposium can provide background for many educational and scientific sessions at the Meeting.

At the conclusion of this symposium, attendees should be able to

- Provide a brief scientific overview and explanation of new technologies and molecular assays relevant to clinical research
- Facilitate appropriate use of molecular diagnostic tests and their interpretation
- Incorporate new targeted treatments and experimental therapies into clinical practice based on an understanding of the molecular biology

Who Should Attend

This symposium is designed for academic and clinical oncologists who currently have a limited exposure to molecular oncology in either research or practice and/or would like to become more familiar with the principles outlined here. Others who may benefit from this symposium include fellows, program directors, oncology nurses, and additional health-care professionals who treat patients with cancer.

Credit Designation

The American Society of Clinical Oncology designates this educational activity for a maximum of 4.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Professional Education Services Group is accredited by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Universal program number: 829-000-03-010-L01. This program provides 4.0 contact hours (0.40 CEUs) of continuing education credit. Continuing Education Statements of Credit will be distributed by mail four weeks after successful completion of a CE workbook and a separate program evaluation form.

This activity for 4.8 contact hours is provided by Professional Education Services Group, which is accredited by the American Nurses Credentialing Center's Commission on Accreditation as a provider of continuing education in nursing. Activity number: 829-03-003-L.

PROGRAM

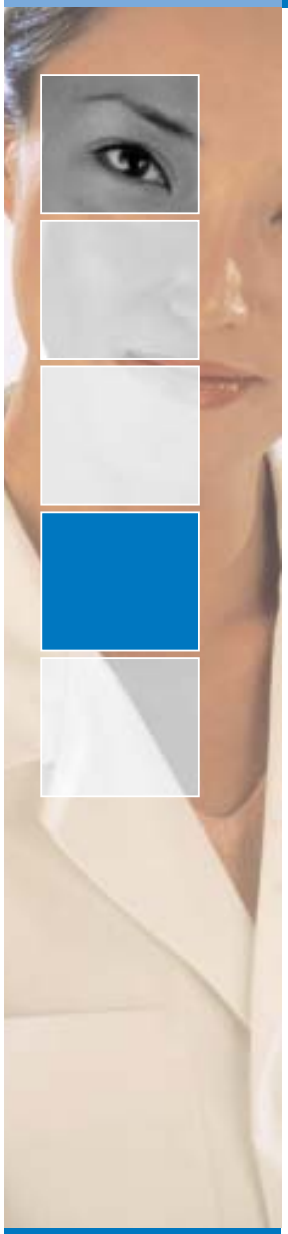
11:45 AM	**Box lunch available**
12:00 PM	**Opening Remarks** John Mendelsohn, MD, Chair *M.D. Anderson Cancer Center*
12:10 PM	**Genes** Stanley R. Hamilton, MD *M.D. Anderson Cancer Center*
1:05 PM	**Signaling Pathways** Edward A. Sausville, MD, PhD *National Cancer Institute*
2:00 PM	**Angiogenesis** Isaiah J. Fidler, DVM, PhD *M.D. Anderson Cancer Center*
2:55 PM	**Apoptosis** Craig Thompson, PhD *University of Pennsylvania*
3:50 PM	**Questions and Answers**

SUPPORTIVE CARE AND SYMPTOM CONTROL: KEY STRATEGIES FOR PROVIDING THE BEST PATIENT EXPERIENCE

This symposium is part of ASCO's continuing effort to highlight the importance of integrating effective symptom control from the point of diagnosis throughout the trajectory of care. Much of the content is based on ASCO's successful symposium held last February, as well as on the *ASCO Curriculum: Optimizing Cancer Care—The Importance of Symptom Management.*

Who Should Attend

This symposium is designed for clinical oncologists. Others who may benefit include oncology nurses, medical social workers, and additional health-care professionals involved in the clinical care of patients with cancer.



At the conclusion of this symposium, attendees should be able to

- Identify effective tools for the management and treatment of nausea and vomiting, fatigue, insomnia, and pain
- Describe the importance of communication in several aspects of the doctor-patient relationship
- Describe strategies for dealing with our losses
- Identify key strategies for symptom control and supportive care of patients with cancer

Credit Designation

The American Society of Clinical Oncology designates this educational activity for a maximum of 4.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Professional Education Services Group is accredited by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Universal program number: 829-000-03-009-L01. This program provides 4.0 contact hours (0.40 CEUs) of continuing education credit. Continuing Education Statements of Credit will be distributed by mail four weeks after successful completion of a CE workbook and a separate program evaluation form.

This activity for 4.8 contact hours is provided by Professional Education Services Group, which is accredited by the American Nurses Credentialing Center's Commission on Accreditation as a provider of continuing education in nursing. Activity number: 829-03-002-L.

PROGRAM

11:45 AM **Box lunch available**
Opening Remarks
Jamie H. Von Roenn, MD, Chair
Northwestern University

12:00 PM **Treatment of Nausea and Vomiting**
Paul Hesketh, MD
St. Elizabeth's Medical Center

12:20 PM **Questions and Answers**

12:30 PM **Care without Chemotherapy**
Janet Abrahm, MD
Dana-Farber Cancer Institute

12:50 PM **Questions and Answers**

1:00 PM **Insomnia**
John Shuster, MD
University of Alabama, Birmingham

1:15 PM **Questions and Answers**

1:20 PM **Fatigue**
Declan Walsh, MD
Cleveland Clinic Foundation

1:35 PM **Questions and Answers**

1:40 PM **Break**

2:00 PM **Parents with Cancer: How to Tell the Children**
Paula Rauch, MD
Massachusetts General Hospital

2:20 PM **Questions and Answers**

2:30 PM **Strategies for Supporting Family and Caregivers**
Lidia Schapira, MD
Massachusetts General Hospital

2:50 PM **Questions and Answers**

3:00 PM **Complex Pain Management Issues**
Kathleen Foley, MD
Memorial Sloan-Kettering Cancer Center

3:20 PM **Questions and Answers**

3:30 PM **Dealing with Our Losses**
Laurie Lyckholm, MD
Medical College of Virginia

3:50 PM **Questions and Answers**

TREATMENT OF BREAST, PROSTATE, AND COLORECTAL CANCERS: HISTORICAL PERSPECTIVES, CURRENT STATE OF THE ART, AND NEW TARGETS

Through didactic lectures from leading experts in breast, prostate, and colorectal cancers, fellows, young oncology academicians, and beginning oncology practitioners will learn how today's standards of care have evolved as well as how molecular targeted therapies will influence future treatments. The breakout sessions help attendees gain a better understanding of their area of specific interest.

Who Should Attend

This symposium is designed for trainees, junior faculty, and beginning practitioners in all subspecialties of oncology.

Registration for this symposium is free.

At the conclusion of this symposium, attendees should be able to

- Identify landmark clinical trials in the evolution of the treatment of breast, prostate and colorectal cancers
- Discuss the evolving molecular biology of these cancers
- Explain the current standards of care for the treatment of these malignancies
- Describe the designs of the representative clinical trials
- Discuss future trends in the therapy of breast, prostate, and colorectal cancers

Credit Designation

The American Society of Clinical Oncology designates this educational activity for a maximum of 4.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

PROGRAM

12:00 PM **Opening Remarks**
Marvin J. Stone, MD, Chair
Baylor University Medical Center

12:10 PM **Molecular Therapeutics in Human Neoplasia**
Carlos L. Arteaga, MD
Vanderbilt University

12:45 PM **Systemic Treatment of Breast Cancer: Key Messages from the Past...and for the Future**
Martine J. Piccart-Gebhart, MD, PhD
Jules Bordet Institute

1:20 PM **Colorectal Cancer**
Robert J. Mayer, MD
Dana-Farber Cancer Institute

1:55 PM **History and Current Studies of Drug Therapy for Prostate Cancer**
A. Oliver Sartor, MD
Stanley S. Scott Cancer Center

2:30 PM **Break**

2:45 PM **Breakout Sessions (concurrent)**

Clinical Case Studies in Breast Cancer
Martine J. Piccart-Gebhart, MD, PhD
Alaa Adassi, MD
University of Minnesota
Antoinette R. Tan, MD
Cancer Institute of New Jersey

Clinical Case Studies in Colorectal Cancer
Robert J. Mayer, MD
Visa Haran Sivasubramaniam, MD
Medical College of Georgia
Rohini Sharma, MBBS
Royal Prince Alfred Hospital

Clinical Case Studies in Prostate Cancer
A. Oliver Sartor, MD
Maria Q. Baggstrom, MD
University of North Carolina at Chapel Hill
Andreea A. Nanci, MD
University of California, Irvine Medical Center

AIR TRAVEL

To make your travel arrangements, please contact ASCO's official travel agency:

TravelStore, Inc.
11601 Wilshire Boulevard
Los Angeles, CA 90025
Travel Agent: Elsa Atayan
Telephone: 800-343-9779 or 310-752-9197
Fax: 310-575-5541
E-mail: elsa.a@travel-store.com
Hours: Monday through Friday, 8:00 AM-5:30 PM (Pacific Time)

Discounted rates have been negotiated with several airlines for attendees of the 2003 ASCO Annual Meeting. Please refer to the following discount codes when making your airline reservation to obtain the lowest fares. Some restrictions may apply.

Airline	Discount Code
American	A4953AC
Continental	U20ME4/ZUVF
Delta	190308A
United	513EW
US Airways	56652507

To take advantage of the special fares, you must purchase your ticket within 24 hours after making your reservation. Therefore, only credit card payment is accepted. Other restrictions may apply.

GROUND TRANSPORTATION

McCormick Place is located approximately 20 miles from O'Hare International Airport and 11 miles from Midway Airport. The cab fare for O'Hare Airport to the downtown area is approximately $30-$35, and the fare for Midway Airport to the downtown area is approximately $15-$20. An airport shuttle service is also available for transportation from both airports to all official ASCO Hotels. Tickets for the shuttle can be purchased at the ground transportation area in each airport. The one-way fee ranges from $18-$20 per person from O'Hare and $13 per person from Midway.

McCormick Place is approximately four miles from the downtown area. During the Meeting, ASCO will provide complimentary shuttle transportation between McCormick Place and all of the official ASCO Hotels except the Hyatt Regency McCormick Place, which is adjacent to the Meeting venue.

If you wish to rent a car during your stay for the Meeting, please refer to the following discount codes when arranging for the rental. Discounted rates have been negotiated with these agencies.

Rental Agency	Discount Code
Avis	A892299
Hertz	CV022R0645

To make your travel arrangements, visit the Meetings and Education section of ASCO.org.

ONSITE DETAILS

ASCO Annual Business Meeting and Highlights

ASCO members are encouraged to participate in the ASCO Annual Business Meeting and Highlights, to be held on Monday, June 2, 2003, at 11:00 AM in Room E350 at McCormick Place. The agenda includes a report on the financial state of the Society, presentation of membership and Meeting statistics and *Journal of Clinical Oncology* subscriber growth, introduction of newly elected ASCO officers, and the passing of the Presidential gavel. Time will be set aside for ASCO members to discuss other Society matters of particular interest to them.

ASCO Booth

The newly enhanced ASCO Booth is designed to better highlight ASCO's programs and services. Attendees will have the opportunity to learn about

- People Living With Cancer, the ASCO website dedicated to helping patients and their families find accurate, reliable, and oncologist-approved information about cancer
- ASCO MD, a free service for ASCO members that allows them to create a practice-related website and a customized portal page
- The ASCO Foundation's mission to support ASCO's education and research worldwide
- Current Clinical Practice Guidelines and Patient Guides
- Policy issues that have an impact on cancer care as well as issues of interest to clinicians in private practice, including reimbursement and coverage of services, coding/billing, and government-mandated regulatory initiatives
- Benefits of ASCO membership

Attendee Services

The following services will be available during the Annual Meeting in the Grand Concourse Lobby of McCormick Place: air travel advice for those who made their arrangements through the TravelStore, Inc., housing assistance, international assistance, as well as information about Chicago tours, attractions, and restaurants. Also, attendees may purchase audiotapes of the Annual Meeting and ASCO publications. Member Services staff will be available to accept applications for membership, process dues payments, make address changes, and answer questions.

Exhibit Hall

The ASCO Exhibit Hall will feature commercial displays with representatives from the health-care industry, pharmaceutical companies, scientific publishing, and advocacy groups. The Exhibit Hall will be located in Hall A1 at McCormick Place, and the tentative open hours are

Saturday, May 31	9:00 AM – 5:30 PM
Sunday, June 1	9:00 AM – 5:30 PM
Monday, June 2	9:00 AM – 5:30 PM

POLICIES

Age Requirement for Attendees. Because of the detailed nature of the programs and forums, no one under the age of 17 will be admitted into any official ASCO function. This includes, but is not limited to, Education and Scientific Sessions, as well as the Exhibit Hall. ASCO appreciates your understanding and cooperation.

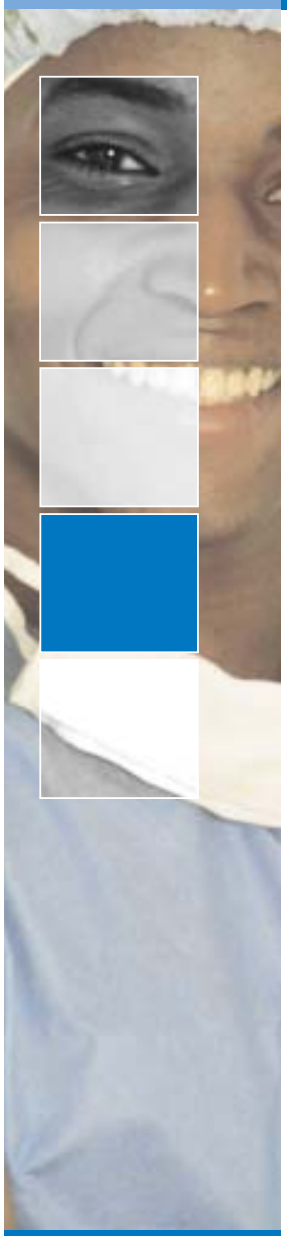
Videotaping/Photography. Any taping, filming, or other reproduction of any of the programs presented at the 2003 ASCO Annual Meeting without the express written permission of the American Society of Clinical Oncology is strictly prohibited. This policy will be enforced.

Smoking. Smoking is prohibited in all meeting facilities and the Exhibit Hall.

Attendee Conduct. Attendees of the ASCO Annual Meeting may not engage in any demonstrations or other behavior that ASCO deems in its sole discretion to be potentially disruptive to the conduct of the Annual Meeting. Violation of this rule is grounds for immediate dismissal from the current ASCO Annual Meeting and/or ineligibility for attendance at future ASCO Annual Meetings within the sole discretion of ASCO. Any attendee who is dismissed from the Meeting by ASCO may request that ASCO review the matter, provided, however, that such dismissal will be effective immediately and will continue unless and until ASCO issues a contrary decision.

SPECIAL EVENT

In celebration of National Cancer Survivors Day on Sunday, June 1, 2003, ASCO is working with Chicago's Robert H. Lurie Comprehensive Cancer Center of Northwestern University to support its 10th Annual Cancer Survivors Celebration and Walk. The five-mile leisurely walk, with more than 3,500 participants, will begin at 9:00 AM at Grant Park, proceed south along the lakefront to McCormick Place, and then return to Grant Park. This annual community event honors survivors, families and friends, and all whose lives have been touched by cancer. Details about individual



participation are available on the cancer center's website at www.cancer.northwestern.edu or by phone at 312-695-1304.

ANNUAL MEETING ON ASCO.ORG

A wide variety of online tools are available on ASCO.org to help prospective attendees plan for the Annual Meeting. As stated elsewhere in this Program Announcement, registration and housing reservations can be carried out online, and other information related to the Meeting and the Chicago area can also be accessed by clicking on Annual Meeting. At the Meeting, several sessions will be captured for the ASCO Virtual Meeting, and these audio-slide presentations will be available on ASCO.org after the Meeting. Also after the Meeting, ASCO.org will include a link to purchase audiocassettes of most Meeting sessions.

INDUSTRY-SPONSORED SATELLITE SYMPOSIA

Several industry-sponsored satellite symposia will be offered on Friday, May 30, 2003, before the official start of the Annual Meeting, and on Tuesday, June 3, 2003. These events are not part of the official ASCO Annual Meeting program. ASCO reviews the industry-sponsored satellite symposia and approves them only after determining that they are balanced and scientifically rigorous and include up-to-date information that is complementary to the official ASCO Annual Meeting program and consistent with ASCO's educational mission. The content of the industry-sponsored satellite symposia and the views expressed therein are those of the industry supporter and not of ASCO. Each industry supporter will independently manage registration and the provision of continuing medical education (CME) credit for its symposium; ASCO is not the CME provider for these events.

Ways to Register for the Meeting and Reserve Housing

You can register for the Annual Meeting and reserve your housing by using one of three methods. Please use only one of these methods. Submission of multiple forms will result in duplicate registrations or housing reservations and duplicate billing.

1. *ASCO.org*

The quickest and easiest way to reserve housing or register for the Meeting is to log onto ASCO.org (www.asco.org). With the online method, you can see a current inventory of available sessions and hotel rooms. Your registration or housing request is processed immediately and confirmed by e-mail. Please print this e-mail confirmation and save it for your records; it is the only confirmation you will receive. If you do not provide an e-mail address, the confirmation will be faxed or mailed to you.
You must pay with a credit card when using this method. The online system is designed to ensure the security of your credit card information. If you do not have access to a secure website, you can complete the forms online, print them out, and send them by fax or mail, as described next.

2. Fax

You can fax the Individual Registration Form (page 67) and/or Housing Request Form (page 71), along with your credit card information, to the ASCO Housing and Registration Center. You will receive confirmation of your registration or housing reservation by e-mail, fax, or mail within five business days after your form has been received.

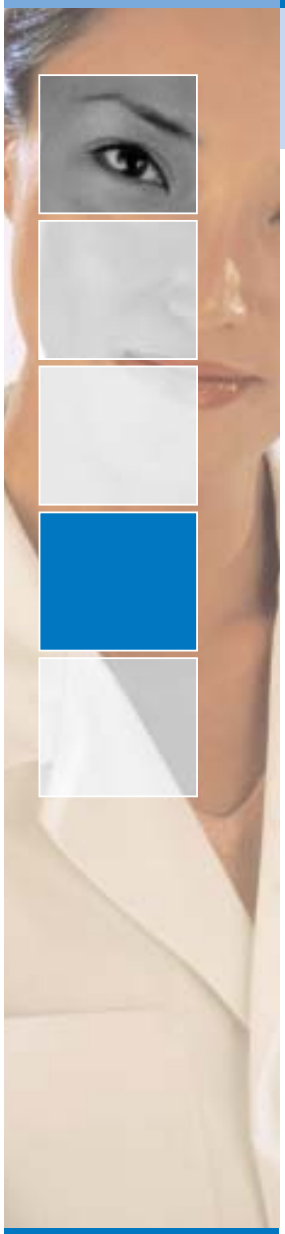
3. Mail

You can mail the Individual Registration Form (page 67) and/or Housing Request Form (page 71), along with your credit card information, check, or wire transfer, to the ASCO Housing and Registration Center. You will receive confirmation of your registration or housing reservation by e-mail, fax, or mail within five business days after your form has been received.

ASCO Housing and Registration Center
11212 Waples Mill Road, Suite 104
Fairfax, VA 22030

Telephone:	888-788-1522 (within United States)
	703-449-6418 (outside United States)
Fax:	703-818-6425
E-mail:	ascoregistration@jspargo.com (individual registration)
	ascogroupreg@jspargo.com (group registration)
	ascohousing@jspargo.com (individual housing)
	ascogroups@jspargo.com (group housing)

Hours of operation: Monday through Friday, 8:30 AM – 5:00 PM (Eastern Standard Time)
The Center is closed on weekends and U.S. holidays.



Meeting Registration

Individual and Group Registration is available for prospective attendees of the Annual Meeting.

INDIVIDUAL REGISTRATION

Registrants who submit their Individual Registration Forms by April 30, 2003, pay a reduced registration fee and receive their Meeting materials before the Meeting. *(See Special Note at bottom of page.)*

Registrants who submit their Individual Registration Forms after April 30, 2003, will pay a higher registration fee and obtain their Meeting materials onsite at the Individual Advance Registration counters at McCormick Place (See page 66 for registration fees.)

GROUP REGISTRATION

Group registration also must be completed by April 30, 2003, to avoid higher registration fees and to obtain Meeting materials in advance. *(See Special Note at bottom of page.)* Groups who choose to pick up registration materials onsite will be contacted to schedule an appointment for pick up.

To register a group online, please go to the Meetings & Education section of ASCO.org, and click on Group Registration under Annual Meeting. You will receive an immediate e-mail confirmation and will have access to online status reports of your group registration.

If you have 15 or fewer members in your group, you may mail or fax the completed Group Contact Information Form (page 69), as well as an Individual Registration Form (page 67) for each member in the group.

REGISTRATION CHANGE/CANCELLATION POLICY

All registration changes and cancellations must be received in writing by April 30, 2003, to qualify for a refund. Refunds will be issued 30 days after the Meeting. No refunds will be processed for requests for changes or cancellations that are received after April 30, 2003.

ASCO REGISTRATION FEE

The ASCO registration fee includes access to all special sessions, education sessions, and scientific sessions (Oral Abstract Presentation Sessions, Poster Discussion Sessions, and General Poster Sessions); entrance to the Exhibit Hall; use of shuttle service between McCormick Place and Official ASCO hotels; and the following publications: *Educational Book*, ASCO Meeting Program, ASCO *Meeting Proceedings*, and Pocket Program. Additional registration is necessary for Meet the Professor Sessions, Clinical Problems in Oncology Sessions, Fellows and Junior Faculty Meet the Professor Sessions, and ASCO Educational Symposia (held on the Friday before the official start of the Annual Meeting). The registration fees and codes for ticketed sessions and the Educational Symposia are on page 66.

Special Note: ASCO *Meeting Proceedings* will not be mailed in advance of the Meeting. Attendees will recieve this publication onsite.

ONSITE REGISTRATION

Meeting Registration Center. ASCO encourages all prospective attendees to register as soon as possible for the Annual Meeting to take advantage of reduced registration fees and to avoid waiting in long lines onsite. If you are unable to register in advance, the Registration Center will be open at McCormick Place as follows:

Friday, May 30	7:00 AM – 6:00 PM
Saturday, May 31	7:00 AM – 6:00 PM
Sunday, June 1	7:00 AM – 6:00 PM
Monday, June 2	7:00 AM – 6:00 PM
Tuesday, June 3	7:00 AM – Noon

For your convenience, self-registration counters will be available in the Registration Center in McCormick Place during the hours listed here.

Educational Symposia. Onsite registration for the ASCO Educational Symposia will be available at the Hilton Chicago ("Supportive Care and Symptom Control" and the Fellows Symposium) and the Sheraton Chicago Hotel & Towers ("Principles of Molecular Oncology" and "Pharmacology and Drug Development"), where the symposia will be held.

Online Registration. You can register online from the convenience of your home, office, or hotel room until 9:00 AM on Tuesday, June 3, 2003. Log on to www.asco.org, and then stop by the Registration Center during registration hours to pick up your badge and Meeting materials.

MEDIA REGISTRATION

Media registration materials are available at www.asco.org/mediacenter. A fully equipped newsroom will be available to registered reporters. Media representatives who are unable to attend the Meeting may request press materials and arrange for telephone interviews by contacting the ASCO Communications and Patient Information Department at 703-299-1014.

Housing Accommodations

INDIVIDUAL HOUSING REQUESTS

Housing Request Forms received after April 30, 2003, will be processed on a space-available basis and may be subject to higher rates. Hotel accommodations are assigned on a first-come, first-served basis. If your preferences are sold out, ASCO will secure a room reservation at a hotel with a daily rate similar to those of your preferences. Early submission of your Housing Request Form is strongly recommended.

Each individual who needs accommodations MUST complete a Housing Request Form. Forms requesting housing for more than one person will be returned. The Housing Request Form may be photocopied.

A hotel reservation will be made for each Housing Request Form submitted. Submission of multiple forms will result in duplicate reservations and duplicate charges to your credit card. A confirmation of the hotel reservation will be sent by fax or e-mail within five business days after your form has been received. If your fax number or e-mail address has not been provided, the confirmation will be mailed to the address on the Housing Request Form. Please call the ASCO Housing Center if you do not receive a confirmation; do not assume that a reservation was made.

You will receive a confirmation from your assigned hotel three weeks before your arrival date.

GROUP HOUSING REQUESTS

Group housing should be arranged through the ASCO Group Housing Manager at 888-788-1522 or 703-449-6418, or by e-mail at ascogroups@jspargo.com.

IMPORTANT NOTE: If a group chooses not to make housing reservations through the ASCO Housing Center, each individual in the group will be charged the onsite (higher) registration fee. These fees must be paid in full for the entire group before the group's registration can be processed. The registration materials for the entire group will not be released to either the Group Contact or the individual attendees until all registration fees have been paid in full. If you have any questions about this policy, please contact the Group Housing Manager.

HOUSING CHANGE/CANCELLATION POLICY

Before May 15, 2003, if you need to change or cancel your reservation, you must submit a written request to the ASCO Housing Center. Your request will be acknowledged by a confirmation sent to you within five business days. If you do not receive this confirmation, please call the ASCO Housing Center to verify that your request has been received.

On or after May 15, 2003, if you need to change or cancel your reservation, you must call your hotel directly. A cancellation must be made at least 72 hours before your scheduled arrival date, or you will be assessed a cancellation fee equivalent to 100% of your entire scheduled stay, which will be charged to your credit card.

The cancellation policy will be strictly enforced. Please retain the cancellation confirmation from the ASCO Housing Center or the cancellation number provided to you by the hotel, as this proof of cancellation will be required to resolve any credit card disputes.

SPECIAL ASSISTANCE

All of the Official ASCO Hotels, as well as McCormick Place, comply with the Americans with Disabilities Act. If you require special assistance, please contact the ASCO Housing Center at 888-788-1522 or 703-449-6418.

The ASCO Foundation 2003 Benefit Concert

SIR ELTON JOHN
Saturday, May 31, 2003
Arie Crown Theater
McCormick Place

The ASCO Foundation is anticipating an evening of unforgettable entertainment when Sir Elton John performs at the 2003 Benefit Concert, held on the opening night of the ASCO Annual Meeting on Saturday, May 31. A giant in the music world for more than three decades, Sir Elton John is an electrifying songwriter, singer, and pianist. His live performances are legendary.

Sir Elton's seemingly limitless reserve of creative energy extends to his philanthropic endeavors. He has generously given of his time, energy, and talent to The ASCO Foundation to make this concert a reality.

The ASCO Foundation thanks all of the Annual Meeting attendees who have shown their support for The Foundation by purchasing tickets for this exceptional musical experience.

3rd Annual Oncology Career Event

Over 100 companies and institutions have participated in the past two events.

May 31 – June 2, 2003
Chicago, Illinois
McCormick Place
Exhibit Hall

Hours

Saturday, May 31	**9:00 AM – 5:30 PM**
Sunday, June 1	**9:00 AM – 5:30 PM**
Monday, June 2	**9:00 AM – 5:30 PM**

ASCO is proud to announce the 3rd Annual Oncology Career Event, a three-day recruiting event to be held in conjunction with the 39th ASCO Annual Meeting. The Oncology Career Event offers a convenient way for Meeting attendees to

- Learn about employment possibilities, from entry level to senior positions, in all areas of the rapidly developing oncology profession
- Meet face-to-face with recruiters from a variety of settings, including academic, private practice, and industry
- Submit their curriculum vitae online so that companies can review qualifications for job matching
- Schedule interviews for positions featured at the Annual Meeting

Look for more information at careers.jco.org

Companies interested in securing a booth at the Oncology Career Event should call Rachael Bruette at 443-512-8899, ext. 108 or send an e-mail to rachael.bruette@wt-group.com.

Welcome to Chicago

Chicago is world renowned for its magnificent and innovative architecture and its many fine cultural and educational institutions. This exciting metropolitan city is a melting pot of cultural diversity with world-class entertainment, shopping, attractions, city-view parks, and dining.

There are numerous attractions you may wish to visit while you are in Chicago. Please stop by the Chicago Attractions and Restaurant Reservations Desk located in the Grand Concourse Lobby of McCormick Place for more information. Details about Chicago's tourist attractions are also available on the Annual Meeting page at ASCO.org. Go to General Information and click on Chicago Information.

HERE ARE A FEW OF THE EXCITING ATTRACTIONS TO SEE WHILE VISITING CHICAGO:

Michigan Avenue

Featuring a spectacular row of historic buildings, this is one of Chicago's grandest streets. It's an excellent place to window shop or dine while admiring the varied architectural styles for which the city is famous.

Navy Pier

Located on Lake Michigan, just east of Chicago's downtown area, Navy Pier has been a Chicago landmark since it first opened in 1916. Here, you can immerse yourself in a day of fun, marveling at Chicago's skyline from the 25-story Ferris wheel or from one of the breathtaking boat cruises. The Navy Pier is surrounded by more than 50 acres of parks, gardens, shops, restaurants, and attractions of every kind.

Art Institute of Chicago

Founded by civic leaders and art collectors in 1879, the Art Institute of Chicago houses an extensive collection that represents nearly 5,000 years of human creativity through paintings, sculptures, textiles, photographs, cultural objects, and decorative artifacts from around the world.

OTHER CHICAGO ATTRACTIONS TO VISIT INCLUDE

The Chicago Botanic Garden, the Adler Planetarium and Astronomy Museum, the Chicago Architecture Center, the Chicago Children's Museum, the Frank Lloyd Wright Home and Studio, the Sears Tower Skydeck, and the Hancock Observatory.

No.*	Hotel	Daily Rate+	Distance to McCormick Place	Restaurant	Pool‡	Room Service	Mobil Rating#	AAA Rating†
1	Comfort Inn & Suites Downtown 15 E. Ohio Street	$235 1 Bdrm Suite	3 Miles	No	No	No	Not Rated	Not Rated
2	Holiday Inn Chicago Mart Plaza 350 N. Orleans Street	$230	3 Miles	Yes	Yes	Yes	**	▲▲▲
3	Hotel 71 71 E. Wacker Avenue	$243	3 Miles	Yes	No	Yes	Not Rated	Not Rated
4	The Palmer House Hilton 17 E. Monroe Street	$260 (Sgl/Dbl), $289 (Concierge Sgl) $299 (Concierge, Dbl)	2.5 Miles	Yes	Yes	Yes	***	▲▲▲▲
5	The Talbott Hotel 20 E. Delaware Place	$219 (Sgl), $239 (Dbl) $319/$339 (Suite)	3.5 Miles	Yes	No	Yes	***	Not Rated
6	Whitehall Hotel 105 E. Delaware Place	$249	2.5 Miles	Yes	No	Yes	***	▲▲▲▲
7	Wyndham Chicago 633 N. St. Clair Street	$265	4 Miles	Yes	Yes	Yes	***	▲▲▲▲

* The numbers correspond to the numbers on the map on page 65.

+ For each hotel, the rates for single and double (one bed, two people) are the same, except as noted.

‡ Health club facilities are available at all hotels.

The Mobil Rating System is based on detailed inspection reports by experienced field representatives and/or written evaluations by senior staff members who stay and dine anonymously. Also factored into the rating is an extensive review of comments from readers of the *Mobil Guide.*
** = Comfortable establishment with expanded services.
*** = Well appointed establishment, with full services and amenities.
**** = Outstanding establishment with exceptional service and expanded amenities.

† For the AAA Rating System, the hotels are evaluated annually during unannounced visits by full-time inspectors. Hotels must satisfy a set of minimum requirements that reflect the basic lodging needs that have been identified by members of the American Automobile Association (AAA).

▲▲ = Hotel maintains the attributes offered at the ▲ level, while showing noticeable enhancements in room decor and quality of furniture.
▲▲▲ = Hotel shows a marked upgrade in physical attributes, services, and comfort. Additional amenities, services, and facilities may be offered.
▲▲▲▲ = Hotel reflects an exceptional degree of hospitality, service, and attention to detail, while offering upscale facilities and a variety of amenities.


CHICAGO Downtown Hotels
1 Comfort Inn & Suites Downtown
15 E. Ohio Street
2 Holiday Inn Chicago Mart Plaza
350 N. Orleans Street
3 Hotel 71
71 E. Wacker Avenue
4 The Palmer House Hilton
17 E. Monroe Street
5 The Talbott Hotel
20 E. Delaware Place
6 Whitehall Hotel
106 E. Delaware Street
7 Wyndham Chicago
633 N. St. Clair Street
O'Hare International Airport
Midway Airport
Eisenhower Expy.
Dan Ryan Expy.
Kennedy Expy.
Congress Parkway
Stevenson Expy.
CHICAGO RIVER
Michigan Ave.
State St.
Lake Shore Drive
Grant Park
Monroe Harbor
Burnham Harbor
Lake Michigan
Navy Pier
Museum of Contemporary Art
Art Institute
Buckingham Fountain
Shedd Aquarium
Field Museum
Soldier Field
Adler Planetarium
McCormick Place North
McCormick Place South
Hyatt Regency McCormick Place Conference Center
Lakeside Center
Museum of Science and Industry
All locations are approximate.
ILLINOIS

Registration Fees

Please refer to the following charts when indicating your registration codes and fees on the Individual Registration Form.
All registration fees are payable in U.S. dollars.

ANNUAL MEETING

		By April 30		After April 30
Registration	**Code**	**Fee**	**Code**	**Fee**
ASCO Active Member	A	$350	1	$500
ASCO Active-Jr. Member	B	$175	2	$250
ASCO Associate Member	C	$ 50	3	$ 75
ASCO Affiliate Member	D	$150	4	$225
ASCO Emeritus Member	E	$150	5	$225
Nonmember	F	$500	6	$650
Nonmember in Training	G	$150	7	$225
Member of State Oncology Society but not of ASCO	H	$350	8	$500
Nurse, Physician's Asst., Social Worker, Genetic Counselor	I	$250	9	$325

(Note: Please submit ONS Member Number or a copy of current professional license or certification with registration form.)

Ticketed Sessions

Meet the Professor Sessions (Limit Two)				
ASCO Member	A	$ 50	1	$ 65
Nonmember	B	$ 75	2	$ 90

Fellows and Junior Faculty Meet the Professor Sessions (No Limit)				
ASCO Member	A	$ 25	1	$ 40
Nonmember	B	$ 35	2	$ 50

Clinical Problems in Oncology (Limit One)				
ASCO Member	A	$ 50	1	$ 65
Nonmember	B	$ 75	2	$ 90

ASCO EDUCATIONAL SYMPOSIA

ES01 Pharmacology and Drug Development
ES02 Principles of Molecular Oncology
ES03 Supportive Care and Symptom Control: Key Strategies for Providing the Best Patient Experience

Registration	**Code**	**Fee**	**Code**	**Fee**
ASCO Active Member	A	$100	1	$175
ASCO Active-Jr. Member	B	$ 50	2	$100
ASCO Associate Member	C	$ 50	3	$ 50
ASCO Affiliate Member	D	$ 75	4	$100
ASCO Emeritus Member	E	$ 75	5	$100
Nonmember	F	$150	6	$225
Nonmember in Training	G	$100	7	$125
Member of State Oncology Society but not of ASCO	H	$100	8	$175
Nurse, Physician's Asst., Social Worker, Genetic Counselor	I	$100	9	$125

(Note: Please submit ONS Member Number or a copy of current professional license or certification with registration form.)

ES04 Treatment of Breast, Prostate, and Colorectal Cancers: Historical Perspectives, Current State of the Art, and New Targets

(Available only to fellows, junior faculty, and beginning practitioners)

	Code	**Fee**	**Code**	**Fee**
ASCO Active-Jr. Member	A	No Fee	1	No Fee
ASCO Associate Member	B	No Fee	2	No Fee
Nonmember in Training	C	No Fee	3	No Fee

INDIVIDUAL REGISTRATION FORM: 2003 ANNUAL MEETING

Deadline to receive materials in advance: April 30, 2003
For fastest registration, log on to www.asco.org

INDIVIDUAL REGISTRATION

Please type, print, or affix label.

ASCO Member ID # (*if applicable*)_____

Last Name _____

First Name_____ MI _____

Degree ❑ MD ❑ DO ❑ RN ❑ PharmD ❑ PhD ❑ Other _____

Are you an Oncology Training Program Director? Yes____ No____

PREFERRED MAILING ADDRESS (for Meeting materials)

Organization (if applicable) _____

Address_____

_____

City _____

State/Province_____ ZIP/Postal Code _____

Country _____

Phone _____

Fax (required) _____

E-mail (required) _____

Are you part of a group?_____ No _____ Yes *(Please list name below)*

Group Contact Name _____

Which Meeting schedule would you prefer?

❑ Friday mid-day to Monday evening
❑ Saturday morning to Tuesday afternoon

If the Meeting were held from Friday mid-day to Monday evening, would you be interested in attending an ASCO Educational Symposium on Tuesday?

❑ Yes ❑ No

Industry-sponsored satellite symposium on Tuesday?

❑ Yes ❑ No

TICKETED SESSION PREFERENCES

Please enter the codes (found in the Daily Schedule or the Program by Track) for your top choices for each ticketed session.

REGISTRATION FOR TICKETED SESSIONS

Please enter the codes (found in the Daily Schedule) for your preferred ticketed session: seats are assigned on a first-come, first-served-basis.

Clinical Problems in Oncology Sessions (Limit One)

1 _____ 2 _____ 3 _____

Meet the Professor Sessions (Limit Two)

1 _____ 2 _____ 3 _____ 4 _____

Fellows and Jr. Faculty Meet the Professor Sessions (No Limit)

For fellows and junior faculty only.

Codes_____/_____/_____/_____/_____

_____/_____/_____/_____/_____

SPOUSE/GUEST BADGE $35 (Limit One)

Attendance for Exhibit Hall only. Please enter complete name (up to 40 characters).

Spouse/Guest Name: _____

ASCO SAMPLER for NONMEMBERS $25

❑ Check here to receive the ASCO Sampler, a preview of ASCO member-benefit publications. You will receive one issue of the *Journal of Clinical Oncology,* a recent issue of *ASCO News,* and the 2003 Wrap-Up issue of *ASCO Daily News.* (The ASCO Sampler will be mailed after the Annual Meeting.)

REGISTRATION CODES AND FEES

Please see adjoining page for all codes and fees for the Annual Meeting, ASCO Educational Symposia, and Ticketed Sessions.

	Qty	Code	Fee
Annual Meeting			
AM01 Registration		_____	$_____
Educational Symposia			
ES01 Pharm. and Drug Development		_____	$_____
ES02 Principles of Molecular Oncology		_____	$_____
ES03 Supportive Care and Symptom Control		_____	$_____
ES04 Treatment of Breast, Prostate, and Colorectal Cancers		_____	$ NC
Ticketed Sessions			
Clinical Problems in Oncology		_____	$_____
Meet the Professor	_____	_____	$_____
Fellows and Jr. Faculty Meet the Professor	_____	_____	$_____
Other			
SG01 Spouse/Guest Badge ($35)		_____	$_____
AS01 ASCO Sampler ($25)		_____	$_____
Wire Transfer Processing Fee ($15 per transfer)			$_____
TOTAL AMOUNT DUE			**$**_____

In the event that ASCO must cancel a ticketed session, registrants of that session may request a refund at Registration onsite. Refunds will be processed after the Meeting.

PAYMENT INFORMATION

Payment must be included in order to process your registration.

❑ Payment made by Group Contact
❑ Enclosed Check or Money Order
(Please make payable to the American Society of Clinical Oncology)
❑ Wire Transfer
(Please add $15 processing fee per transfer)
You must include your name and telephone number or that of the Group Contact in the reference section. A copy of the wire transfer confirmation must be enclosed in order to process your registration. SunTrust Bank, Richmond, VA
ATTN: Greater Washington Region ABA Routing Number: 061000104
Account Number: 202992829

❑ American Express ❑ Discover ❑ MasterCard ❑ VISA

Credit Card Number _____

Expiration Date _____

Cardholder Name _____

Cardholder Signature _____

CHANGE/CANCELLATION POLICY

All changes and cancellations must be submitted in writing by April 30, 2003, to qualify for a refund. Refunds will be issued 30 days after the Meeting. No refunds will be processed for cancellations made after April 30.

SUBMIT INDIVIDUAL REGISTRATION FORM TO

ASCO Registration Center
11212 Waples Mill Road, Suite 104
Fairfax, VA 22030
Fax: 703-818-6425

QUESTIONS

Phone: 888-788-1522 or 703-449-6418
E-mail: ascoregistration@jspargo.com

FOR OFFICE USE ONLY

PAYT_____ CK/WT# _____ AMT _____

Attachment 3a: Program for the 2003 ASCO Annual Meeting

GROUP CONTACT INFORMATION FORM: 2003 ANNUAL MEETING

Deadline to receive materials in advance: April 30, 2003

GROUP REGISTRATION INFORMATION

Please indicate the size of your group.

Number of Individuals in Group:_____

Please select one of the following methods of registration.

❑ **www.asco.org**

To register your group online, go to Group Registration in the ANNUAL MEETING section of ASCO.org. You will recieve a login code and password that you can use to register online and access status reports.

❑ **Fax/Mail (ONLY FOR GROUPS OF 15 OR FEWER)**

Complete this form and an Individual Registration Form for each individual in your group. Send the forms, along with payment, to the attention of the Group Registration Manager at the ASCO Housing and Registration Center.

GROUP CONTACT INFORMATION *Please type or print or affix label*

Group Contacts who wish to attend the Meeting must register as an attendee. For an Exhibit Hall Pass only, please register as a Spouse/Guest of a group attendee. Otherwise, you may only pick up Meeting materials for your group.

Group Contact Name _____

Group Name _____

Preferred Mailing Address *(for Meeting materials and future mailings)*

_____

_____

City _____

State/Province_____ZIP/Postal Code _____

Country_____

Phone_____

*Fax *(required)* _____

*E-mail *(required)* _____

INDIVIDUALS IN THE GROUP *(only for fax/mail option)*

Please list the names of the individuals in your group here. You must enclose an Individual Registration Form (page 67) for each person on this list. On each Individual Registration Form, use the address of the individual who will attend the Meeting (not the address of the Group Contact).

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____
13. _____
14. _____
15. _____

To make arrangements for group housing, contact the ASCO Group Housing Manager at 888-788-1522 or 703-449-6418 or by e-mail at *ascogroups@jspargo.com.*

Important Note: If a group chooses not to make housing reservations through the ASCO Housing Center, each individual in the group will be charged the onsite (higher) registration fee. These fees must be paid in full for the entire group before the group registration can be processed. The registration materials for the entire group will not be released to either the Group Contact or the individual attendees until all registration fees have been paid in full. If you have any questions about this policy, please contact the ASCO Group Housing Manager at ascogroups@jspargo.com.

Group housing has been reserved through the ASCO Housing Center.

❑ Yes ❑ No

Hotel Name(s) _____

REGISTRATION MATERIALS DELIVERY/PICK UP OPTION

(Please select only one)

❑ Advance Delivery to Group Contact

❑ Advance Delivery to Each Individual

❑ Onsite Pick Up by Group Contact (appointment will be scheduled)

❑ Onsite Pick Up by Each Individual at Advance Registration

GROUP PAYMENT INFORMATION

Online: Payment type must be selected in order to receive a password.

Fax/Mail: Payment must be included in order to process the group registration. On each Individual Registration Form, either indicate that payment is being made by the Group Contact or complete the individual payment information for each person in the group on each form.

❑ Enclosed Check or Money Order *(Please make payable to the American Society of Clinical Oncology)*

❑ Wire Transfer *(Please add $15 processing fee per transfer)*

You must include the Group Contact name and phone number in the reference section. A copy of the wire transfer confirmation must be enclosed with the registration form in order to process the registration.

SunTrust Bank, Richmond, VA ATTN: Greater Washington Region ABA Routing Number: 061000104 Account Number: 202992829

❑ American Express ❑ Discover ❑ MasterCard ❑ VISA

Credit Card Number _____

Expiration Date_____

Cardholder Name _____

Cardholder Signature_____

Credit Card Billing Address _____

_____

CHANGE/CANCELLATION POLICY

All changes and cancellations must be submitted in writing by April 30, 2003, to qualify for a refund. Refunds will be issued 30 days after the Meeting. No refunds will be granted for requests for changes or cancellations received after April 30, 2003.

SUBMIT GROUP CONTACT INFORMATION FORM TO

ASCO Registration Center
ATTN: GROUP REGISTRATION MANAGER
11212 Waples Mill Road, Suite 104
Fairfax, VA 22030
Fax: 703-818-6425

QUESTIONS

Phone: 888-788-1522 or 703-449-6418; please ask for the Group Registration Manager
E-mail: ascogroupreg@jspargo.com

FOR OFFICE USE ONLY

PAYT_____ CK/WT# _____ AMT DUE _____

Attachment 3a: Program for the 2003 ASCO Annual Meeting

Housing Request Form: 2003 ASCO Annual Meeting

ASCO Housing Center
11212 Waples Mill Road, Suite 104
Fairfax, VA 22030
Fax: 703-818-6425

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Questions: Phone: 888-788-1522 or 703-449-6418; E-mail: *ascohousing@jspargo.com*

All Housing Request Forms must be received by April 30, 2003. We strongly encourage you to submit your form early. Forms received after April 30 will be processed on a space-available basis and may be subject to a higher rate. Please submit only one form per person. Multiple forms will result in duplicate reservations and duplicate billing.

Please type or print or affix label.

ASCO Member ID # (if applicable) _____

Last Name _____ First Name _____ MI _____ Title _____

Organization _____

Address _____

City _____ State _____ ZIP/Postal Code _____ Country _____

Phone _____ Fax _____ E-mail _____

HOUSING PAYMENT

A first night's deposit is required to guarantee your reservation and will be charged to your credit card. The credit card must have an expiration date of at least June 2003. **Forms submitted without information from a valid credit card will be returned.**

❑ American Express ❑ Discover ❑ MasterCard ❑ Visa ❑ Diners Club

Credit Card Number _____ Expiration Date _____

Cardholder Name _____ Signature _____

A hotel reservation will be made for each Housing Request Form submitted. You will receive a confirmation of your hotel reservation by fax, mail, or e-mail within five business days after your form has been received. If you do not receive this confirmation, please call the ASCO Housing and Registration Center to verify that your Request Form was received. Do not assume that a reservation was made. Multiple submissions of Housing Request Forms will result in duplicate reservations and duplicate charges to your credit card.

To arrange group housing, contact the Group Housing Manager at 888-788-1522 or 703-449-6918 or by e-mail at *ascogroups@jspargo.com.*

CANCELLATION/CHANGE POLICY

Prior to May 15, 2003, you must submit your change or cancellation in writing to the ASCO Housing and Registration Center. You will receive confirmation of your request within five business days. If you do not receive this confirmation, please call the ASCO Housing and Registration Center to verify that your cancellation or change has been received.

On or after May 15, 2003, you must call your hotel directly to change or cancel your reservation. A cancellation must be made at least 72 hours before your scheduled arrival date or your credit card will be charged a cancellation fee equivalent to 100% of your scheduled stay. This cancellation policy will be strictly enforced.

Please retain the cancellation confirmation from the ASCO Housing Center or the cancellation number provided to you by the hotel. This proof of cancellation will be required to resolve any credit card disputes.

ACCOMMODATIONS

Arrival Date _____ Departure Date _____

Sharing Room with _____ Special Requirements/Needs _____

❑ Sgl. (1 bed, 1 person) ❑ Dbl. (1 bed, 2 people) ❑ Dbl./Dbl. (2 beds, 2 people)
❑ Smoking ❑ Nonsmoking ❑ Handicap Facilities Required

HOTEL PREFERENCES

Review the list of hotels on page TK and enter your top five choices here (with 1 being your first choice). Please note that selections cannot be guaranteed. If your preferences are sold out, ASCO will secure a room reservation at a hotel with a daily rate that is similar to those of your preferences.

Rank **Hotel**

1. _____
2. _____
3. _____
4. _____
5. _____

FOR OFFICE USE ONLY

Htl Code _____ Rate Code _____ Blk Code _____

Attachment 3a: Program for the 2003 ASCO Annual Meeting

VOLUME 22

MEETING PROCEEDINGS

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Thirty-Ninth Annual Meeting

May 31–June 3, 2003
Chicago, Illinois

The *American Society of Clinical Oncology Meeting Proceedings* (ISBN 1-932312-02-1) is published by the American Society of Clinical Oncology.

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Singe issues, both current and back, exist in limited quantities and are offered for sale subject to availability. For further information, call 888-273-3508.

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Contents

800 **Poster Discussion, Tue, 8:00 AM - 12:00 PM**

A phase II study of E7070 in patients with metastatic, recurrent, or refractory head and neck squamous cell carcinoma (HNSCC): Clinical activity and post-treatment modulation of Rb phosphorylation. *R. I. Haddad, G. I. Shapiro, L. Weinstein, T. Wieczorek, N. Bhattarcharya, M. Loda, J. L. Faucher, H. Raftopoulos, M. Oster, M. Posner; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Columbia University, New York, NY*

E7070 is a synthetic sulfonamide that targets the G1 phase of the cell cycle. It causes depletion of cyclin E, upregulation of p53 and p21Waf1/Cip1, as well as inhibition of cdk2 phosphorylation. All of these events contribute to hypophosphorylation of the retinoblastoma (Rb) protein and cause a blockade in the G1/S transition. We conducted a phase II study of E7070 in patients with noncurable HNSCC. Patients received 700 mg/m2 over one hour every 3 weeks. Fifteen patients were treated with a median age of 59 years. A total of 39 cycles of E7070 were delivered, median 2.6 per patient. Six patients had progressive disease (PD) after 2 cycles and 3 patients had PD after one cycle. Five patients showed stable disease (SD) after 2 cycles and went on to receive 1 (2 patients), 2 (2 patients) and 3 additional cycles (1 patients), respectively, before showing PD. One patient remains on study and has received 5 cycles with SD. A fine needle aspirate (FNA) was obtained from 5 patients prior to treatment and within 24 hrs after the completion of the first 3-hr infusion to determine whether the phosphorylation of Rb was modulated in tumor cells following drug exposure. Aspirates were subjected to immunohistochemistry with phospho-specific anti-Rb antibodies directed at the T821, S795 and S807/811 cdk2- and cdk4-specific phosphorylation sites.Among the 3 patients with informative samples, results were as follows: E7070 demonstrated very limited activity against SCCHN.However,our data suggest that cdk activity can be inhibited in tumor cells, resulting in a post-treatment modulation of Rb phosphorylation. In the absence of cytotoxic activity, more frequent administration of E7070 may be required to sustain Rb hypophosphorylation and cytostatic growth arrest.

patient	antibody	% (2+,3+) pre-treatment	% (2+,3+) post-treatment	Clinical Outcome
1	Anti-Rb [pT821]	32	5	PD after 2 cycles
	Anti-Rb [pS795]	86	21	
2	Anti-Rb [pT821]	13	0	SD after 2cycles PD after 4
	Anti-Rb [pS795]	41	0	
3	Anti-Rb [pS807/811]	80	0	SD after 4 cycles. Still on study
	Anti-Rb [pS795]	80	5	
	Anti-Rb [Total]	70	50	

801 **Poster Discussion, Tue, 8:00 AM - 12:00 PM**

Phase I study of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with refractory hematologic malignancies. *R. Z. Orlowski, P. M. Voorhees, R. Garcia, M. Hall, J. Adams, D. Esseltine, C. Dees; Univ of North Carolina at Chapel Hill, Chapel Hill, NC; Millennium Pharmaceuticals, Inc., Cambridge, MA*

The proteasome is involved in intracellular protein degradation, and is a novel target for therapy of hematologic malignancies. Proteasome inhibitors also block activation of several survival pathways, including NF-KB and p44/42-MAPK, that may limit the effectiveness of anthracyclines, suggesting such combinations might have enhanced anti-tumor efficacy. We sought to evaluate the maximum tolerated dose(MTD), dose limiting toxicity(DLT), pharmacokinetics, and pharmacodynamics of the proteasome inhibitor bortezomib(B;Velcade) and pegylated, liposomal doxorubicin(D;Doxil) in patients(pts) with hematologic malignancies. B was given as an intravenous bolus at 0.90–1.30-mg/m^2 on days-1, -4, -8, and -11 of a 3-week cycle, and D on day-4 at 30-mg/m^2. The MTD was defined based on cycle-1, while responses were evaluated every 2 cycles. 19 pts have been treated, and have included 14 multiple myeloma(MM) pts. A mean of 4.4 cycles (range 1–10) has been administered, with 15 pts evaluable for toxicity. At 0.90-mg/m^2 a pt with Crohns disease had grade(g)-3 diarrhea, hypotension, confusion and syncope, but no other DLTs were noted at this or other levels, and the MTD has yet to be defined. All other non-hematologic drug-related toxicities during cycle-1 have been g-1/2 in intensity. G-3/4 toxicities in later cycles included fatigue, palmar plantar erythrodysesthesia, cytopenias, and neuropathy. Of 10 evaluable MM pts complete responses(CR) have been observed in 3, near-CR in 1, partial responses(PR) in 3, 1 pt each had a minor response or stable disease, while one progressed. Five of these pts, including two of the CRs, had disease that previously progressed, or did not respond to anthracycline-based therapy, and five are continuing treatment. Also, one pt with relapsed acute myeloid leukemia had a PR. Early results from this study suggest that BD may be well-tolerated and active in patients with multiple myeloma, and possibly other hematologic malignancies. Accrual is continuing to define the MTD and DLT.

802 **Poster Discussion, Tue, 8:00 AM - 12:00 PM**

A phase I trial of an oral histone deacetylase inhibitor, MS-275, in advanced solid tumor and lymphoma patients. *Q. C. Ryan, D. Headlee, A. Sparreboom, W. Figg, S. Zhai, J. Trepel, A. Murgo, Y. Elsayed, J. Karp, E. Sausville; National Cancer Institue, Bethesda, MD; Cancer Institute of New Jessy, New Brunswick, NJ; The Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD*

We are conducting a Phase I trial using MS-275, an orally administered, synthetic histone deacetylase inhibitor, in advanced solid tumor and lymphoma patients. The trial initially used a daily x 28, repeated every six weeks, dosing schedule with an accelerated titration design, beginning at 2 mg/m2 (i.e., 1/10 of rat maximal tolerated dose {MTD}). However, in humans the MTD was exceeded at the 1st dose level, with grade 3 AST, hyposphosphatemia, hypoalbuminemia, pleural effusion and epigastric pain. Preliminary evidence of a substantially longer half-life of MS-275 in humans as compared to preclinical species likely accounts for this finding. A once q14 day schedule was then implemented, also starting at 2 mg/m2 but escalating with 2 mg/m2 increments. To date, 20 patients have been treated on this schedule. Although escalated to level 5 (10 mg/m2 q 2 wk), the MTD has not yet been reached. Frequent grade 1–2 toxicities include fatigue (50%); nausea (50%); hypoalbuminemia (35%), headache (35%), anxiety (30 %), dyspepsia (30%), vomiting (30%); dysgeusia (20%), anemia (20%), fever (20%), and hyponatremia (20%). Besides the first course toxicities, hypoalbuminemia and progressive fatigue as a continuing effect of MS-275 occurred, especially at higher dose levels, and are of concern for long term dosing. Peak plasma concentrations were observed at 6 - 24 h after dosing, suggesting slow absorption, and in the range of 10 - 50 ng/ml. This concentration is within the range that might affect proliferation of certain cell types preclinically. Dose dependence of exposure to MS-275 occurred, but no further increase in area under the curve at doses above 6 mg/m2 was evident. This phenomenon likely involves nonlinear, apparent saturable absorption processess. Increased histone H3 acetylation in peripheral blood mononuclear cells was apparent at all dose levels, by immunofluorescent analysis. Based on these data, a new oral schedule, weekly x4, repeated every six weeks, as well as an intravenous formulation are being developed.

803 **Poster Discussion, Tue, 8:00 AM - 12:00 PM**

A phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours. *A. O'Donnell, S. Faivre, I. Judson, C. Delbado, C. Brock, H. Lane, N. Shand, K. Hazell, J.-P. Armand, E. Raymond; Royal Marsden Hospital, Sutton, UK; Institute Gustave Roussy, Villejuif, France; Novartis Pharma AG, Basel, Switzerland*

RAD001, a novel derivative of rapamycin, interacts with the mTOR protein kinase to inhibit downstream signalling proteins crucial to cell cycle progression. Pre-clinical *in vitro* and *in vivo* studies have shown dose dependent inhibition of tumour growth and reduced tumour vascularity, as well as the ability to potentiate the activity of a number of cytotoxics including paclitaxel and gemcitabine. Methods: This phase I dose escalation study was performed to identify the optimal biologically effective dose based on toxicity, PK and PD assessments using the biomarker p70 S6 kinase 1 (S6K1) activity in peripheral blood mononuclear cells (PBMCs). Indication of activity was also sought using conventional and PET imaging. Treatment with RAD001 was given orally, once weekly. Results: Cohorts of 4 patients were treated at each of 4 dose levels: 5, 10, 20 and 30mg. (7M:9F; Median age 60y, Range 32–75 y) RAD001 was well tolerated with only mild degrees (Gr 1/2) of anorexia, fatigue, rash, mucositis, headache, hyperlipidemia and gastrointestinal disturbance. PK results are consistent with prior experience (renal transplant and healthy subject studies): AUC increasing in proportion to dose, a plateau in Cmax occurring at doses ≥20mg and a terminal $t_{1/2}$ of 26—38 hours. 4 patients (hepatocellular 10mg; fibrosarcoma 10mg; NSCLC x 2, 30mg) have stable disease >16 weeks. A responding patient with NSCLC showed a reduction in ^{18}FDG uptake on PET scanning after week 3. S6K1 activity in PBMCs was inhibited for 3—5 days at 5 and 10 mg dose levels. At doses ≥20mg 7/8 patients exhibited inhibition for at least 7 days. Conclusions: Weekly administration of 20mg RAD001 in patients, gives plasma concentrations and sustained S6K1 inhibition equivalent to the PK levels and PD changes that correlate with anti-tumour effects in rodents treated with this schedule. Doses above 20mg result in only marginally increased inhibition. Combination studies have been initiated and we continue to explore the PD impact of mTOR inhibition in human tumours.

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110 2 |aAmerican Society of Clinical Oncology.|bMeeting.
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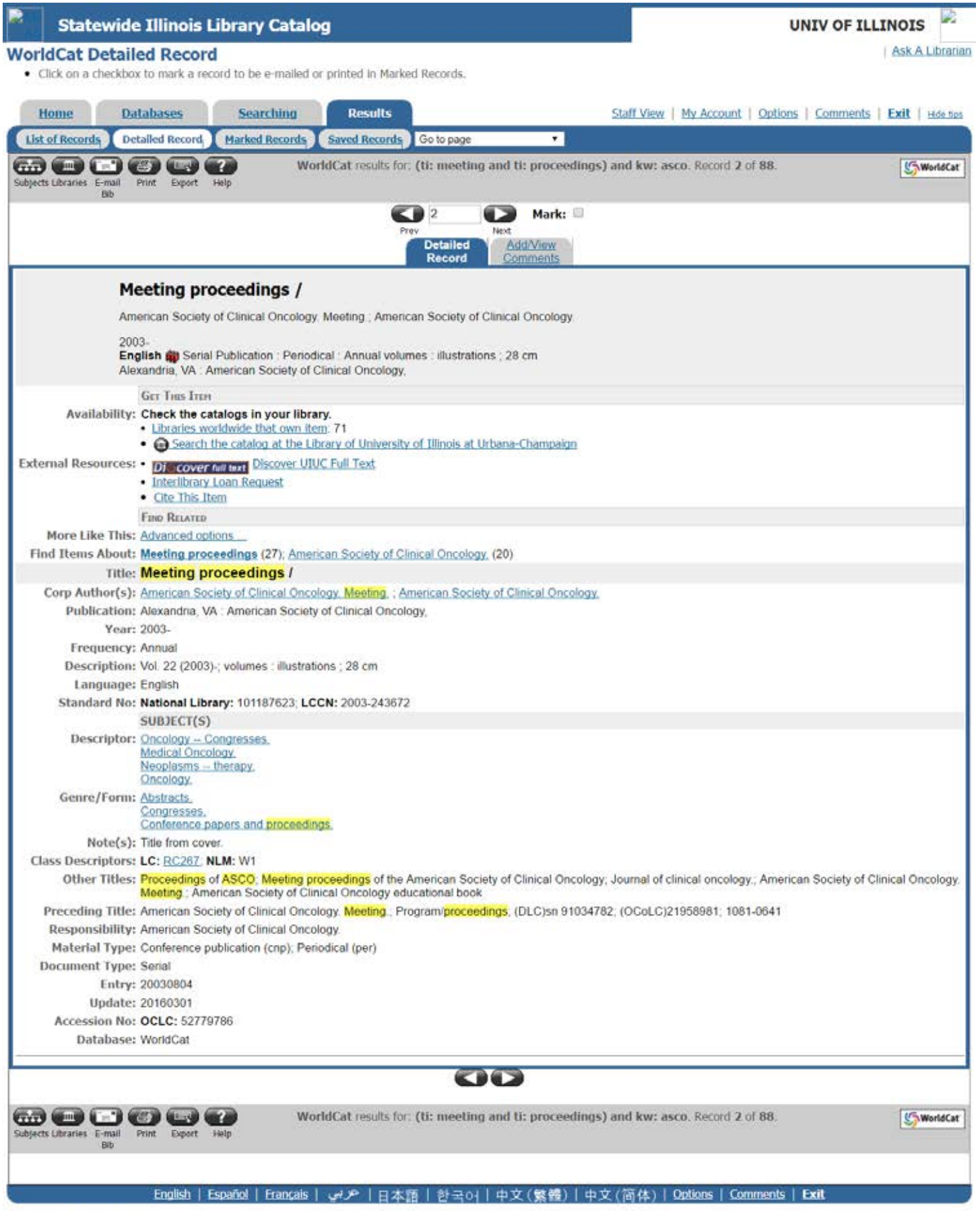

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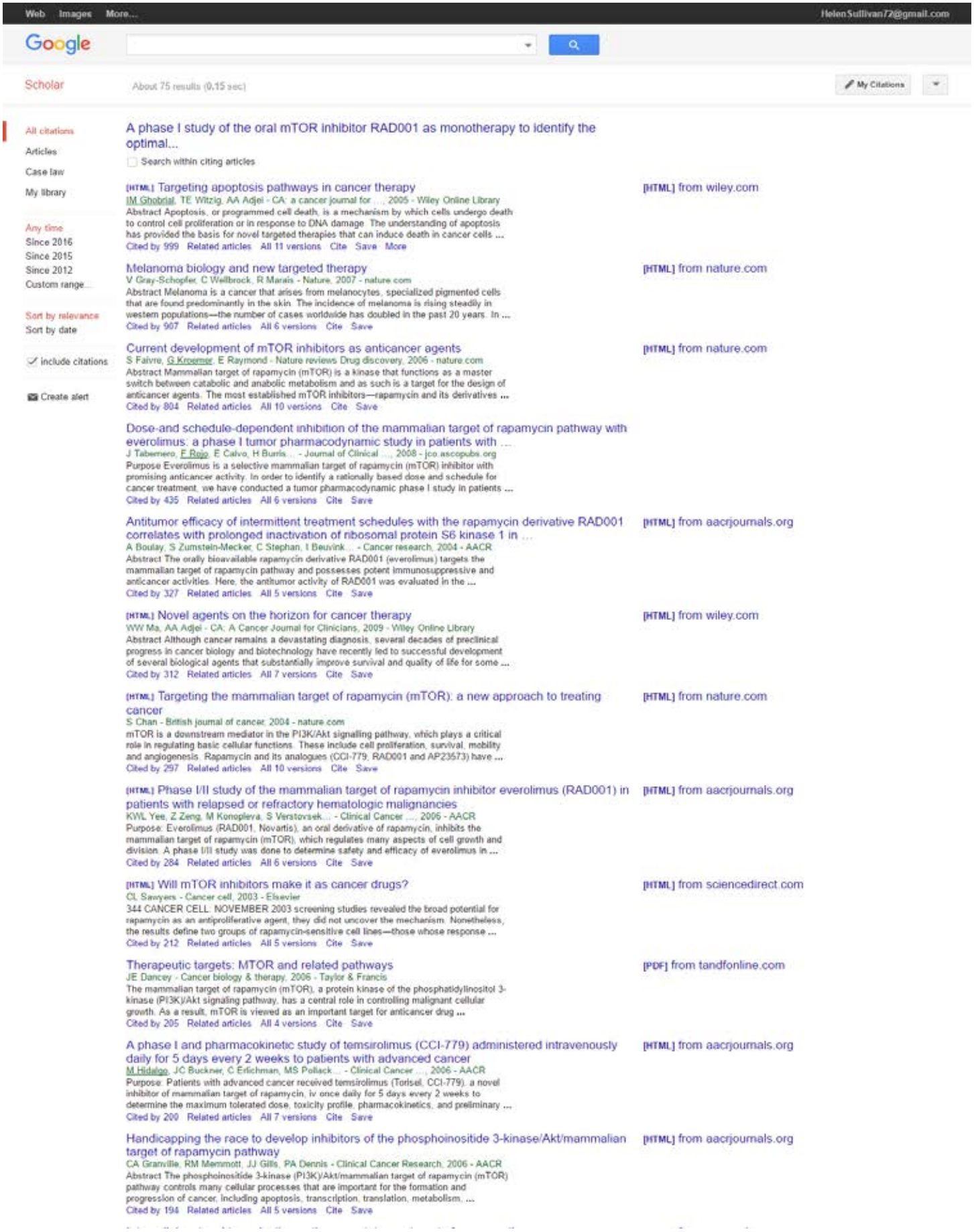

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V Gray-Schopfer, C Wellbrock, R Marais - Nature, 2007 - nature.com
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Current development of mTOR inhibitors as anticancer agents [HTML] from nature.com
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J Tabernero, F Rojo, E Calvo, H Burris ... - Journal of Clinical ..., 2008 - jco.ascopubs.org
Purpose Everolimus is a selective mammalian target of rapamycin (mTOR) inhibitor with promising anticancer activity. In order to identify a rationally based dose and schedule for cancer treatment, we have conducted a tumor pharmacodynamic phase I study in patients ...
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Antitumor efficacy of intermittent treatment schedules with the rapamycin derivative RAD001 correlates with prolonged inactivation of ribosomal protein S6 kinase 1 in ... [HTML] from aacrjournals.org
A Boulay, S Zumstein-Mecker, C Stephan, I Beuvink ... - Cancer research, 2004 - AACR
Abstract The orally bioavailable rapamycin derivative RAD001 (everolimus) targets the mammalian target of rapamycin pathway and possesses potent immunosuppressive and anticancer activities. Here, the antitumor activity of RAD001 was evaluated in the ...
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[HTML] Novel agents on the horizon for cancer therapy [HTML] from wiley.com
WW Ma, AA Adjei - CA: A Cancer Journal for Clinicians, 2009 - Wiley Online Library
Abstract Although cancer remains a devastating diagnosis, several decades of preclinical progress in cancer biology and biotechnology have recently led to successful development of several biological agents that substantially improve survival and quality of life for some ...
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[HTML] Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer [HTML] from nature.com
S Chan - British journal of cancer, 2004 - nature.com
mTOR is a downstream mediator in the PI3K/Akt signalling pathway, which plays a critical role in regulating basic cellular functions. These include cell proliferation, survival, mobility and angiogenesis. Rapamycin and its analogues (CCI-779, RAD001 and AP23573) have ...
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[HTML] Phase I/II study of the mammalian target of rapamycin inhibitor everolimus (RAD001) in patients with relapsed or refractory hematologic malignancies [HTML] from aacrjournals.org
KWL Yee, Z Zeng, M Konopleva, S Verstovsek ... - Clinical Cancer ..., 2006 - AACR
Purpose: Everolimus (RAD001, Novartis), an oral derivative of rapamycin, inhibits the mammalian target of rapamycin (mTOR), which regulates many aspects of cell growth and division. A phase I/II study was done to determine safety and efficacy of everolimus in ...
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[HTML] Will mTOR inhibitors make it as cancer drugs? [HTML] from sciencedirect.com
CL Sawyers - Cancer cell, 2003 - Elsevier
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Therapeutic targets: MTOR and related pathways [PDF] from tandfonline.com
JE Dancey - Cancer biology & therapy, 2006 - Taylor & Francis
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A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously daily for 5 days every 2 weeks to patients with advanced cancer [HTML] from aacrjournals.org
M Hidalgo, JC Buckner, C Erlichman, MS Pollack ... - Clinical Cancer ..., 2006 - AACR
Purpose: Patients with advanced cancer received temsirolimus (Torisel, CCI-779), a novel inhibitor of mammalian target of rapamycin, iv once daily for 5 days every 2 weeks to determine the maximum tolerated dose, toxicity profile, pharmacokinetics, and preliminary ...
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Handicapping the race to develop inhibitors of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway [HTML] from aacrjournals.org
CA Granville, RM Memmott, JJ Gills, PA Dennis - Clinical Cancer Research, 2006 - AACR
Abstract The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway controls many cellular processes that are important for the formation and progression of cancer, including apoptosis, transcription, translation, metabolism, ...
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Intracellular signal transduction pathway proteins as targets for cancer therapy [HTML] from ascopubs.org
AA Adjei, M Hidalgo - Journal of clinical oncology, 2005 - jco.ascopubs.org
Abstract Circulating cytokines, hormones, and growth factors control all aspects of cell proliferation, differentiation, angiogenesis, apoptosis, and senescence. These chemical signals are propagated from the cell surface to intracellular processes via sequential ...
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Targeting the molecular target of rapamycin (mTOR)
EK Rowinsky - Current opinion in oncology, 2004 - journals.lww.com
Abstract Purpose of review: The molecular target of rapamycin, which is a member of the phosphoinositide 3-kinase related kinase family and a central modulator of cell growth, is a unique and prime strategic target for anticancer therapeutic development.
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The biology behind mTOR inhibition in sarcoma [HTML] from alphamedpress.org
X Wan, LJ Helman - The Oncologist, 2007 - AlphaMed Press
Abstract Dysregulation of the mammalian target of rapamycin (mTOR) pathway has been found in many human tumors and implicated in the promotion of cancer cell growth and survival. Hence, the mTOR pathway is considered an important target for anticancer drug ...
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Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors [HTML] from oxfordjournals.org
JC Soria, FA Shepherd, JY Douillard... - Annals of ..., 2009 - Eur Soc Med Oncology
Background: Treatment options are scarce in pretreated advanced non-small-cell lung cancer (NSCLC) patients. RAD001, an oral inhibitor of the mammalian target of rapamycin (mTOR), has shown phase I efficacy in NSCLC. Methods: Stage IIIb or IV NSCLC patients, ...
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Pharmacodynamic biomarkers for molecular cancer therapeutics
D Sarker, P Workman - Advances in cancer research, 2006 - Elsevier
VII. Biomarker Methodology A. Minimally Invasive Imaging B. Invasive Molecular Endpoints C. Immunohistochemistry D. Gene Expression Microarrays and Proteomics VIII. Examples of PD Biomarkers for Specific New Drug Classes A. Imatinib Mesylate as a Paradigm for the ...
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Therapeutic options for gastrointestinal carcinoids [PDF] from researchgate.net
IM Modlin, I Latich, M Kidd, M Zikusoka... - Clinical Gastroenterology ..., 2006 - Elsevier
Although wide surgical resection is the optimal curative therapy for carcinoid tumors, in most patients the presence of metastatic disease at diagnosis usually renders excision a palliative procedure. This nevertheless decreases tumor burden, facilitates symptom control, and ...
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Mammalian target of rapamycin inhibition [HTML] from aacrjournals.org
JP Dutcher - Clinical Cancer Research, 2004 - AACR
Abstract The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that has been increasingly recognized as key to the regulation of cell growth and proliferation. mTOR either directly or indirectly regulates translation initiation, actin organization, tRNA ...
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Recent developments in targeting the mammalian target of rapamycin (mTOR) kinase pathway
P Smolewski - Anti-cancer drugs, 2006 - journals.lww.com
Abstract The mammalian target of rapamycin (mTOR) is a threonine kinase involved in intracellular pro-survival signaling. Its activation leads to progression from the G 1 to S phase of the cell cycle. Constitutive activation of the mTOR-related messengers, including ...
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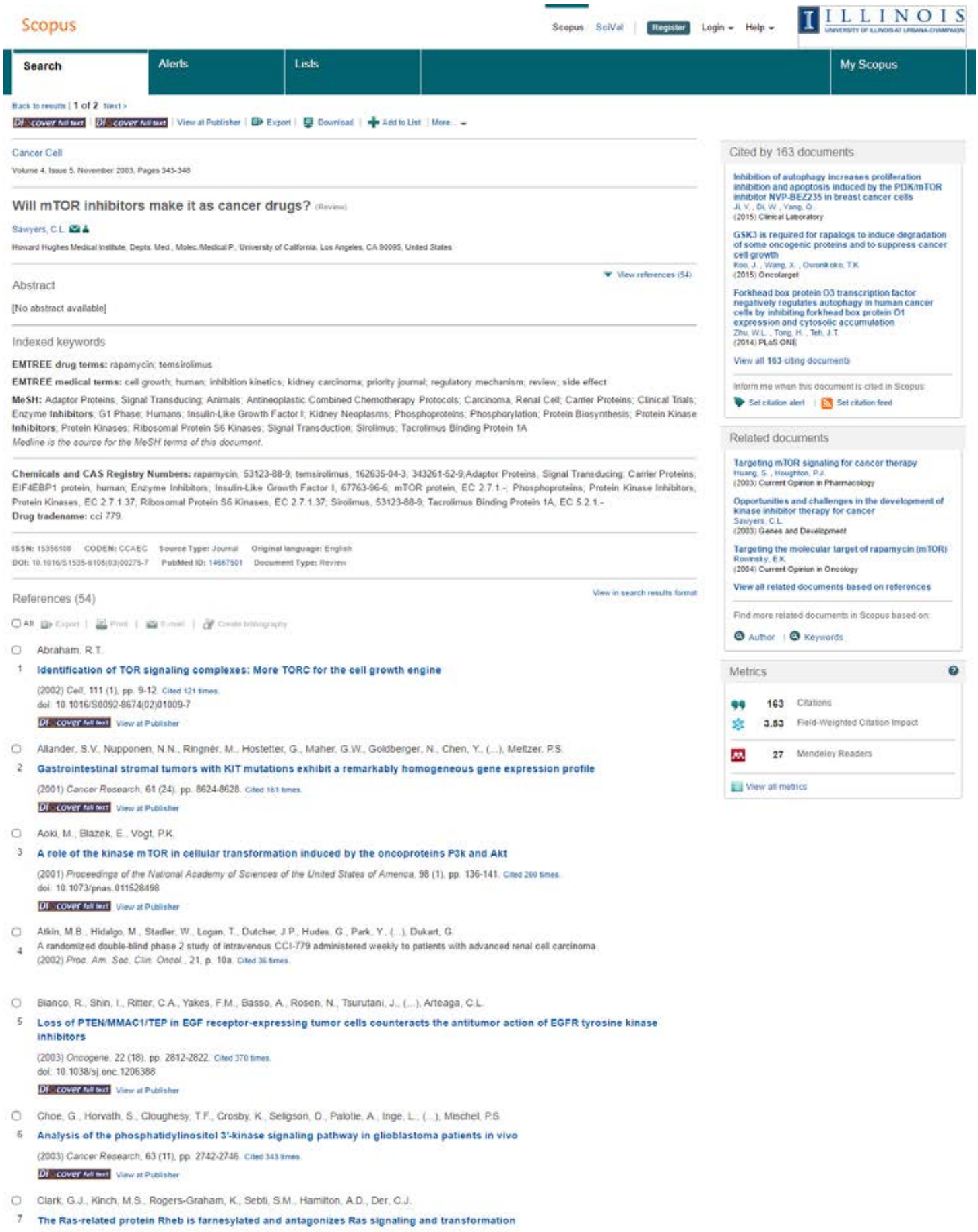

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Cancer Cell

Volume 4, Issue 5, November 2003, Pages 343-348

Will mTOR inhibitors make it as cancer drugs? (Review)

Sawyers, C.L.

Howard Hughes Medical Institute, Depts. Med., Molec./Medical P., University of California, Los Angeles, CA 90095, United States

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Abstract

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EMTREE drug terms: rapamycin; temsirolimus

EMTREE medical terms: cell growth; human; inhibition kinetics; kidney carcinoma; priority journal; regulatory mechanism; review; side effect

MeSH: Adaptor Proteins, Signal Transducing; Animals; Antineoplastic Combined Chemotherapy Protocols; Carcinoma, Renal Cell; Carrier Proteins; Clinical Trials; Enzyme Inhibitors; G1 Phase; Humans; Insulin-Like Growth Factor I; Kidney Neoplasms; Phosphoproteins; Phosphorylation; Protein Biosynthesis; Protein Kinase Inhibitors; Protein Kinases; Ribosomal Protein S6 Kinases; Signal Transduction; Sirolimus; Tacrolimus Binding Protein 1A

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Chemicals and CAS Registry Numbers: rapamycin, 53123-88-9; temsirolimus, 162635-04-3, 343261-52-9;Adaptor Proteins, Signal Transducing; Carrier Proteins; EIF4EBP1 protein, human; Enzyme Inhibitors; Insulin-Like Growth Factor I, 67763-96-6; mTOR protein, EC 2.7.1.-; Phosphoproteins; Protein Kinase Inhibitors, Protein Kinases, EC 2.7.1.37; Ribosomal Protein S6 Kinases, EC 2.7.1.37; Sirolimus, 53123-88-9; Tacrolimus Binding Protein 1A, EC 5.2.1.-

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References (54)

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1 Abraham, R.T.
Identification of TOR signaling complexes: More TORC for the cell growth engine
(2002) Cell, 111 (1), pp. 9-12. Cited 121 times.
doi: 10.1016/S0092-8674(02)01009-7
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2 Allander, S.V., Nupponen, N.N., Ringnér, M., Hostetter, G., Maher, G.W., Goldberger, N., Chen, Y., (...), Meltzer, P.S.
Gastrointestinal stromal tumors with KIT mutations exhibit a remarkably homogeneous gene expression profile
(2001) Cancer Research, 61 (24), pp. 8624-8628. Cited 161 times.
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3 Aoki, M., Blazek, E., Vogt, P.K.
A role of the kinase mTOR in cellular transformation induced by the oncoproteins P3k and Akt
(2001) Proceedings of the National Academy of Sciences of the United States of America, 98 (1), pp. 136-141. Cited 200 times.
doi: 10.1073/pnas.011528498
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4 Atkin, M.B., Hidalgo, M., Stadler, W., Logan, T., Dutcher, J.P., Hudes, G., Park, Y., (...), Dukart, G.
A randomized double-blind phase 2 study of intravenous CCI-779 administered weekly to patients with advanced renal cell carcinoma
(2002) Proc. Am. Soc. Clin. Oncol., 21, p. 10a. Cited 36 times.

5 Bianco, R., Shin, I., Ritter, C.A., Yakes, F.M., Basso, A., Rosen, N., Tsurutani, J., (...), Arteaga, C.L.
Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors
(2003) Oncogene, 22 (18), pp. 2812-2822. Cited 370 times.
doi: 10.1038/sj.onc.1206388
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6 Choe, G., Horvath, S., Cloughesy, T.F., Crosby, K., Seligson, D., Palotie, A., Inge, L., (...), Mischel, P.S.
Analysis of the phosphatidylinositol 3'-kinase signaling pathway in glioblastoma patients in vivo
(2003) Cancer Research, 63 (11), pp. 2742-2746. Cited 343 times.
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7 Clark, G.J., Kinch, M.S., Rogers-Graham, K., Sebti, S.M., Hamilton, A.D., Der, C.J.
The Ras-related protein Rheb is farnesylated and antagonizes Ras signaling and transformation

Cited by 163 documents

Inhibition of autophagy increases proliferation inhibition and apoptosis induced by the PI3K/mTOR inhibitor NVP-BEZ235 in breast cancer cells
Ji, Y., Di, W., Yang, Q.
(2015) Clinical Laboratory

GSK3 is required for rapalogs to induce degradation of some oncogenic proteins and to suppress cancer cell growth
Kao, J., Wang, X., Ouerfelli, O., T.K.
(2015) Oncotarget

Forkhead box protein O3 transcription factor negatively regulates autophagy in human cancer cells by inhibiting forkhead box protein O1 expression and cytosolic accumulation
Zhu, W.L., Tong, H., Teh, J.T.
(2014) PLoS ONE

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Huang, S., Houghton, P.J.
(2003) Current Opinion in Pharmacology

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(2003) Genes and Development

Targeting the molecular target of rapamycin (mTOR)
Rowinsky, E.K.
(2004) Current Opinion in Oncology

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(1997) *Journal of Biological Chemistry*, 272 (16), pp. 10608-10615. Cited 126 times.
doi: 10.1074/jbc.272.16.10608
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○ Dancey, J.E.

8 **Clinical development of mammalian target of rapamycin inhibitors**

(2002) *Hematology/Oncology Clinics of North America*, 16 (5), pp. 1101-1114. Cited 68 times.
doi: 10.1016/S0889-8588(02)00051-5
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○ Dancey, J.E., Freidlin, B.

9 **Targeting epidermal growth factor receptor - Are we missing the mark?**

(2003) *Lancet*, 362 (9377), pp. 62-64. Cited 174 times.
doi: 10.1016/S0140-6736(03)13810-X
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○ Douros, J., Suffness, M.

10 **New antitumor substances of natural origin**

(1981) *Cancer Treatment Reviews*, 8 (1), pp. 63-87. Cited 124 times.
doi: 10.1016/S0305-7372(81)80006-0
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○ Garami, A., Zwartkruis, F.J.T., Nobukuni, T., Joaquin, M., Roccio, M., Stocker, H., Kozma, S.C., (...), Thomas, G.

11 **Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2**

(2003) *Molecular Cell*, 11 (6), pp. 1457-1466. Cited 624 times.
doi: 10.1016/S1097-2765(03)00220-X
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○ Gera, J.F., Mellinghoff, I.K., Shi, Y., Rettig, M.B., Tran, C., Hsu, J.H., Sawyers, C.L., (...), Lichtenstein, A.K.

12 AKT activity determines sensitivity to mTOR inhibitors by regulating cyclin D1 and c-myc expression
(2003) *J. Biol. Chem.*. Cited 2 times.
in press. Published online October 23, 2003
10.1074/jbc.M309999200

○ Grunwald, V., DeGraffenried, L., Russel, D., Friedrichs, W.E., Ray, R.B., Hidalgo, M.

13 **Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells**

(2002) *Cancer Research*, 62 (21), pp. 6141-6145. Cited 225 times.
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○ Guba, M., Von Breitenbuch, P., Steinbauer, M., Koehl, G., Flegel, S., Hornung, M., Bruns, C.J., (...), Geissler, E.K.

14 **Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor**

(2002) *Nature Medicine*, 8 (2), pp. 128-135. Cited 1266 times.
doi: 10.1038/nm0202-128
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○ Hara, K., Maruki, Y., Long, X., Yoshino, K.-I., Oshiro, N., Hidayat, S., Tokunaga, C., (...), Yonezawa, K.

15 **Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action**

(2002) *Cell*, 110 (2), pp. 177-189. Cited 980 times.
doi: 10.1016/S0092-8674(02)00833-4
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○ Hietman, J., Movva, N.R., Hall, M.N.

16 **Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast**

(1991) *Science*, 253 (5022), pp. 905-909. Cited 998 times.
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○ Hidalgo, M., Rowinsky, E., Erlichman, C., Drengler, R., Marshall, B.

17 CCI-779, a rapamycin analog and multifaceted inhibitor of signal transduction: A phase I study
(2000) *Proc. Am. Soc. Clin. Oncol.*, 19, p. 10a. Cited 45 times.

○ Hosoi, H., Dilling, M.B., Liu, L.N., Danks, M.K., Shikata, T., Sekulic, A., Abraham, R.T., (...), Houghton, P.J.

18 **Studies on the mechanism of resistance to rapamycin in human cancer cells**

(1998) *Molecular Pharmacology*, 54 (5), pp. 815-824. Cited 155 times.
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○ Hudson, C.C., Liu, M., Chiang, G.G., Otterness, D.M., Loomis, D.C., Kaper, F., Giaccia, A.J., (...), Abraham, R.T.

19 **Regulation of hypoxia-inducible factor 1α expression and function by the mammalian target of rapamycin**

(2002) *Molecular and Cellular Biology*, 22 (20), pp. 7004-7014. Cited 780 times.
doi: 10.1128/MCB.22.20.7004-7014.2002
Discover full text View at Publisher

○ Im, E., Von Lintig, F.C., Chen, J., Zhuang, S., Qui, W., Chowdhury, S., Worley, P.F., (...), Pilz, R.B.

20 **Rheb is in a high activation state and inhibits B-Raf kinase in mammalian cells**

(2002) *Oncogene*, 21 (41), pp. 6356-6365. Cited 98 times.

Attachment 3f: Index record for a documenting citing O'Donnell

doi: 10.1038/sj.onc.1205732

Discover full text View at Publisher

Inoki, K., Li, Y., Zhu, T., Wu, J., Guan, K.-L.

21 **TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling**

(2002) *Nature Cell Biology*, 4 (9), pp. 648-657. Cited 1580 times.
doi: 10.1038/ncb839

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Kaelin Jr., W.G.

22 **Molecular basis of the VHL hereditary cancer syndrome**

(2002) *Nature Reviews Cancer*, 2 (9), pp. 673-682. Cited 518 times.
doi: 10.1038/nrc885

Discover full text View at Publisher

Kenerson, H.L., Aicher, L.D., True, L.D., Yeung, R.S.

23 **Activated mammalian target of rapamycin pathway in the pathogenesis of tuberous sclerosis complex renal tumors**

(2002) *Cancer Research*, 62 (20), pp. 5645-5650. Cited 219 times.

Discover full text View at Publisher

Kim, D.-H., Sarbassov, D.D., Ali, S.M., King, J.E., Latek, R.R., Erdjument-Bromage, H., Tempst, P., (...), Sabatini, D.M.

24 **mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery**

(2002) *Cell*, 110 (2), pp. 163-175. Cited 1533 times.
doi: 10.1016/S0092-8674(02)00808-5

Discover full text View at Publisher

Kwon, C.-H., Zhu, X., Zhang, J., Baker, S.J.

25 **mTor is required for hypertrophy of Pten-deficient neuronal soma in vivo**

(2003) *Proceedings of the National Academy of Sciences of the United States of America*, 100 (22), pp. 12923-12928. Cited 151 times.
doi: 10.1073/pnas.2132711100

Discover full text View at Publisher

Long, X., Spycher, C., Han, Z.Stanley, Rose, A.M., Müller, F., Avruch, J.

26 **TOR deficiency in C. elegans causes developmental arrest and intestinal atrophy by inhibition of mRNA translation**

(2002) *Current Biology*, 12 (17), pp. 1448-1461. Cited 159 times.
doi: 10.1016/S0960-9822(02)01091-6

Discover full text View at Publisher

Manning, B.D., Tee, A.R., Logsdon, M.Nicole, Blenis, J., Cantley, L.C.

27 **Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/Akt pathway**

(2002) *Molecular Cell*, 10 (1), pp. 151-162. Cited 929 times.
doi: 10.1016/S1097-2765(02)00568-3

Discover full text View at Publisher

Morice, M.-C., Serruys, P.W., Eduardo Sousa, J., Fajadet, J., Hayashi, E.B., Perin, M., Colombo, A., (...), Falotico, R.

28 **A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization**

(2002) *New England Journal of Medicine*, 346 (23), pp. 1773-1780. Cited 3313 times.
doi: 10.1056/NEJMoa012843

Discover full text View at Publisher

Muise-Helmericks, R.C., Grimes, H.L., Bellacosa, A., Malstrom, S.E., Tsichlis, P.N., Rosen, N.

29 **Cyclin D expression is controlled post-transcriptionally via a phosphatidylinositol 3-kinase/Akt-dependent pathway**

(1998) *Journal of Biological Chemistry*, 273 (45), pp. 29864-29872. Cited 465 times.
doi: 10.1074/jbc.273.45.29864

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Neshat, M.S., Mellinghoff, I.K., Tran, C., Stiles, B., Thomas, G., Petersen, R., Frost, P., (...), Sawyers, C.L.

30 **Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR**

(2001) *Proceedings of the National Academy of Sciences of the United States of America*, 98 (18), pp. 10314-10319. Cited 808 times.
doi: 10.1073/pnas.171076798

Discover full text View at Publisher

O'Donnell, A., Faivre, S., Judson, I., Delbado, C., Brock, C., Lane, H., Shand, N., (...), Raymond, E.

31 A phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours
(2003) *Proc. Am. Soc. Clin. Oncol.*, 22, p. 200. Cited 60 times.
abstract 803

Oldham, S., Montagne, J., Radimerski, T., Thomas, G., Hafen, E.

32 **Genetic and biochemical characterization of dTOR, the Drosophila homolog of the target of rapamycin**

(2000) *Genes and Development*, 14 (21), pp. 2689-2694. Cited 295 times.
doi: 10.1101/gad.845700

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Peng, T., Golub, T.R., Sabatini, D.M.

Attachment 3f: Index record for a documenting citing O'Donnell

33 **The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation**

(2002) *Molecular and Cellular Biology*, 22 (15), pp. 5575-5584. Cited 248 times.
doi: 10.1128/MCB.22.15.5575-5584.2002
Discover full text View at Publisher

○ Podsypanina, K., Lee, R.T., Politis, C., Hennessy, I., Crane, A., Puc, J., Neshat, M., (...), Parsons, R.

34 **An inhibitor of mTOR reduces neoplasia and normalizes p70/s6 kinase activity in Pten+/- mice**

(2001) *Proceedings of the National Academy of Sciences of the United States of America*, 98 (18), pp. 10320-10325. Cited 505 times.
doi: 10.1073/pnas.171060098
Discover full text View at Publisher

○ Potter, C.J., Pedraza, L.G., Xu, T.

35 **Akt regulates growth by directly phosphorylating Tsc2**

(2002) *Nature Cell Biology*, 4 (9), pp. 658-665. Cited 592 times.
doi: 10.1038/ncb840
Discover full text View at Publisher

○ Radimerski, T., Montagne, J., Rintelen, F., Stocker, H., van der Kaay, J., Downes, C.P., Hafen, E., (...), Thomas, G.

36 **dS6K-regulated cell growth is dPKB/dPI(3)K-independent, but requires dPDK1**

(2002) *Nature Cell Biology*, 4 (3), pp. 251-255. Cited 132 times.
doi: 10.1038/ncb763
Discover full text View at Publisher

○ Rajasekhar, V.K., Viale, A., Socci, N.D., Wiedmann, M., Hu, X., Holland, E.C.

37 **Oncogenic Ras and Akt signaling contribute to glioblastoma formation by differential recruitment of existing mRNAs to polysomes**

(2003) *Molecular Cell*, 12 (4), pp. 889-901. Cited 296 times.
doi: 10.1016/S1097-2765(03)00395-2
Discover full text View at Publisher

○ Raymond, E., Alexandre, J., Depenbrock, H., Mekhaldi, S., Angevin, E., Hanauske, A., Baudin, E., (...), Armand, J.P.

38 CCI-779, a rapamycin analog with antitumor activity: A phase I study utilizing a weekly schedule
(2000) *Proc. Am. Soc. Clin. Oncol.*, 19. Cited 46 times.
abstract 728

○ Sawyers, C.L.

39 **Opportunities and challenges in the development of kinase inhibitor therapy for cancer**

(2003) *Genes and Development*, 17 (24), pp. 2998-3010. Cited 135 times.
doi: 10.1101/gad.1152403
Discover full text View at Publisher

○ Saucedo, L.J., Gao, X., Chiarelli, D.A., Li, L., Pan, D., Edgar, B.A.

40 **Rheb promotes cell growth as a component of the insulin/TOR signalling network**

(2003) *Nature Cell Biology*, 5 (6), pp. 566-571. Cited 399 times.
doi: 10.1038/ncb996
Discover full text View at Publisher

○ Schmelzle, T., Hall, M.N.

41 **TOR, a central controller of cell growth**

(2000) *Cell*, 103 (2), pp. 253-262. Cited 1337 times.
Discover full text View at Publisher

○ Shai, R., Shi, T., Kremen, T.J., Horvath, S., Liau, L.M., Cloughesy, T.F., Mischel, P.S., (...), Nelson, S.F.

42 **Gene expression profiling identifies molecular subtypes of gliomas**

(2003) *Oncogene*, 22 (31), pp. 4918-4923. Cited 176 times.
doi: 10.1038/sj.onc.1206753
Discover full text View at Publisher

○ Shamji, A.F., Kuruvilla, F.G., Schreiber, S.L.

43 **Partitioning the transcriptional program induced by rapamycin among the effectors of the Tor proteins**

(2000) *Current Biology*, 10 (24), pp. 1574-1581. Cited 161 times.
doi: 10.1016/S0960-9822(00)00866-6
Discover full text View at Publisher

○ Shamji, A.F., Nghiem, P., Schreiber, S.L.

44 **Integration of growth factor and nutrient signaling: Implications for cancer biology**

(2003) *Molecular Cell*, 12 (2), pp. 271-280. Cited 150 times.
doi: 10.1016/j.molcel.2003.08.016
Discover full text View at Publisher

○ She, Q.-B., Solit, D., Basso, A., Moasser, M.M.

45 **Resistance to gefitinib in PTEN-Null HER-overexpressing tumor cells can be overcome through restoration of PTEN function or pharmacologic modulation of constitutive phosphatidylinositol 3'-kinase/Akt pathway signaling**

(2003) *Clinical Cancer Research*, 9 (12), pp. 4340-4346. Cited 245 times.
Discover full text View at Publisher

Attachment 3f: Index record for a documenting citing O'Donnell

Shi, Y., Gera, J., Hu, L., Hsu, J.-H., Bookstein, R., Li, W., Lichtenstein, A.

46 **Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779**

(2002) *Cancer Research*, 62 (17), pp. 5027-5034. Cited 222 times.

Discover full text View at Publisher

Stocker, H., Radimerski, T., Schindelholz, B., Wittwer, F., Belawat, P., Daram, P., Breuer, S., (...), Hafen, E.

47 **Rheb is an essential regulator of S6K in controlling cell growth in Drosophila**

(2003) *Nature Cell Biology*, 5 (6), pp. 559-565. Cited 327 times.
doi: 10.1038/ncb995

Discover full text View at Publisher

Takuwa, N., Fukui, Y., Takuwa, Y.

48 **Cyclin D1 expression mediated by phosphatidylinositol 3-kinase through mTOR-p70(S6K)-independent signaling in growth factor-stimulated NIH 3T3 fibroblasts**

(1999) *Molecular and Cellular Biology*, 19 (2), pp. 1346-1358. Cited 138 times.

Discover full text View at Publisher

Vivanco, I., Sawyers, C.L.

49 **The phosphatidylinositol 3-kinase-AKT pathway in human cancer**

(2002) *Nature Reviews Cancer*, 2 (7), pp. 489-501. Cited 3650 times.

Discover full text View at Publisher

Yang, J.C., Haworth, L., Sherry, R.M., Hwu, P., Schwartzentruber, D.J., Topalian, S.L., Steinberg, S.M., (...), Rosenberg, S.A.

50 **A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer**

(2003) *New England Journal of Medicine*, 349 (5), pp. 427-434. Cited 2172 times.
doi: 10.1056/NEJMoa021491

Discover full text View at Publisher

Yu, Y., Sato, J.D.

51 **MAP kinases, phosphatidylinositol 3-kinase, and p70 S6 kinase mediate the mitogenic response of human endothelial cells to vascular endothelial growth factor**

(1999) *Journal of Cellular Physiology*, 178 (2), pp. 235-246. Cited 184 times.
doi: 10.1002/(SICI)1097-4652(199902)178:2<235::AID-JCP13>3.0.CO;2-S

Discover full text View at Publisher

Zhang, H., Stallock, J.P., Ng, J.C., Reinhard, C., Neufeld, T.P.

52 **Regulation of cellular growth by the Drosophila target of rapamycin dTOR**

(2000) *Genes and Development*, 14 (21), pp. 2712-2724. Cited 390 times.
doi: 10.1101/gad.835000

Discover full text View at Publisher

Zhang, Y., Gao, X., Saucedo, L.J., Ru, B., Edgar, B.A., Pan, D.

53 **Rheb is a direct target of the tuberous sclerosis tumour suppressor proteins**

(2003) *Nature Cell Biology*, 5 (6), pp. 578-581. Cited 523 times.
doi: 10.1038/ncb999

Discover full text View at Publisher

Zhong, H., Chiles, K., Feldser, D., Laughner, E., Hanrahan, C., Georgescu, M.-M., Simons, J.W., (...), Semenza, G.L.

54 **Modulation of hypoxia-inducible factor 1α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics**

(2000) *Cancer Research*, 60 (6), pp. 1541-1545. Cited 1067 times.

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2005 ASCO Annual Meeting Proceedings

41st Annual Meeting
May 13-17, 2005
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2005 Annual Meeting Proceedings Part I

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American Society of Clinical Oncology
41st Annual Meeting

2005 Abstracts

Abstract Session Descriptions for Scheduled Presentations

Oral Abstract Presentation Sessions

Oral Abstract Presentation Sessions include didactic presentations of the abstracts determined by the Scientific Program Committee to be of the highest scientific merit. Experts in the field serve as Discussants to place the findings into perspective. The Plenary Sessions include the abstracts selected by the Scientific Program Committee as having significant findings.

Integrated Education Sessions

Integrated Education Sessions provide a forum for science in oncology, combining the presentation of selected abstracts on a specific topic with didactic lectures. Experts in the field place the studies in the appropriate context based on the strength of the evidence and critically discuss the conclusions in terms of their applicability to clinical practice.

Poster Discussion Sessions

Poster Discussion Sessions highlight selected abstracts of clinical research in poster format. The posters are grouped by topic or by the questions posed as a result of the research findings. The posters are on display for a specified time, followed by a discussion session in which experts provide commentary on the research findings.

General Poster Sessions

General Poster Sessions include selected abstracts of clinical research in poster format. The posters are grouped by topic and are on display for a specified time.

Publication Abstracts

Publish only abstracts were selected to be published in conjunction with the Annual Meeting, but not to be presented at the Meeting.

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2005 Annual Meeting and for publication. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Pocket Program or ASCO.org.

Dates and times are subject to change.
All modifications will be posted on *ASCO.org* (www.asco.org).

Letter from the Editor

The *2005 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) contains more than 2,000 abstracts selected by the ASCO Scientific Program Committee for presentation at the 41st Annual Meeting of the American Society of Clinical Oncology, held May 13-17, 2005, in Orlando, Florida, and more than 1,400 abstracts selected for publication. The abstracts are categorized by scientific track and ordered numerically within each track by presentation type: Plenary; Integrated Education Session; Oral Presentation; Poster Discussion; General Poster; and Publication. The scientific program uses a 500-series classification system (e.g., Plenary abstracts are numbered 1-12; Breast Cancer, 500-999; Cancer Prevention 1,000-1,500). The Table of Contents lists the abstract number ranges for abstracts scheduled for presentation.

This year, ASCO has once again accepted late-breaking abstract submissions for the Meeting. These abstracts feature the results of major phase III trials for which final data were not available at the time of ASCO's regular abstract submission deadline. In order to facilitate Annual Meeting planning, the late-breaking abstract "placeholders"—without the final results and conclusions—are included in this supplement. The final late-breaking abstracts will be included in the *2005 ASCO Annual Meeting Proceedings Part II* (a supplement to the *Journal of Clinical Oncology*), which will be available onsite at the Annual Meeting on Saturday, May 14, 2005, and will be mailed to JCO subscribers with the June 1, 2005, issue of JCO.

The *2005 ASCO Annual Meeting Proceedings* serves as the publication of record for citation of abstracts. The following is a sample citation:

T. Fama, M. Wood, H. Muss: Patient preferences for adjuvant treatment of early-stage breast cancer. J Clin Oncol 23:61s, 2005 (suppl, abstr 733)

An additional advantage of publishing the *Annual Meeting Proceedings I* and *II* as supplements to JCO is that the abstracts are housed as part of www.jco.org. Readers can search online by keyword, author, etc, not only within the abstracts themselves but also in conjunction with other JCO content. The abstracts are housed additionally on www.asco.org and can be accessed through the Virtual Meeting.

We encourage you, as always, to provide us with any feedback that will augment the quality of information contained in our publications. Should you have any questions or comments about the usefulness, format, and indexes pertaining to the abstracts, please feel free to contact us at abstracts@asco.org.

Steven M. Grunberg, MD
Proceedings Editor

ASCO ABSTRACTS POLICY

ASCO has formalized the following confidentiality policy governing the use of information contained in abstracts of the ASCO *2005 Annual Meeting Proceedings Part I* (a Supplement to the *Journal of Clinical Oncology*), which contains all abstracts to be presented at the 2005 Annual Meeting, all publish-only abstracts, and late-breaking abstract "placeholders" (without final results and conclusions). Abstracts are short, preliminary summaries of research that are used by ASCO to determine whether or not a study is accepted into its Annual Meeting program. These 300 word or less summaries typically include preliminary data that, subsequent to their submission to ASCO, are analyzed in the months leading up to the Annual Meeting. Therefore, these abstracts do not necessarily contain the final results or conclusions that are reported at the Meeting.

In an effort to ensure that premature research data are not publicly reported prior to the scientific review at the Annual Meeting, ASCO has instituted the following confidentiality policy governing the use of the information contained in this publication. The Society's official Embargo Policy, designed to ensure the integrity of the information that is communicated from the ASCO Annual Meeting, is also published below. Both the Confidentiality Policy and the Embargo Policy are in effect until they are lifted, on an abstract-by-abstract basis, as stated in each of the respective policies below.

CONFIDENTIALITY AGREEMENT

The information contained in the ASCO *2005 Annual Meeting Proceedings Part I* (individually, the Abstracts, and collectively, the Proceedings) is confidential information until its public release. Distribution of this information in advance of public release is solely for the purpose of preparing for and planning Annual Meeting activities.

Until the public release of this information, this information must be kept confidential. Specifically, and without limiting the generality of your agreement to maintain the confidentiality of the Abstracts, you agree that:

- You will not publish the information contained in an Abstract, or provide the information to others for publication, prior to the time the Abstract is made public at the Annual Meeting or on www.asco.org; and
- You will not use the information contained in any Abstract for any purpose other than the purpose set forth above, including but not limited to trading in the securities of any issuer or providing the information to others who may use it for securities trading purposes, until after the opening of trading on the second trading day following the date the Abstract is made public at the Annual Meeting or on www.asco.org.

A violation of your agreement not to use Abstract information for securities trading purposes or to provide it to others who may use it for securities trading purposes may constitute a violation of federal or state securities laws and may subject you to civil or criminal liability.

For purposes of this Confidentiality Agreement, Abstracts are considered to have been made public at the time when the embargo on them has been lifted under the official Embargo Policy below.

ASCO EMBARGO POLICY

All abstracts presented at the Annual Meeting are embargoed until the beginning of the Scientific Session containing the research, with the following exceptions:

- Abstracts in ASCO's Official Press Program: Embargoes lift at the beginning of the News Briefing, or the beginning of the Scientific Session containing the research, whichever comes first.
- Publish-Only Abstracts: For abstracts published in the *2005 ASCO Annual Meeting Proceedings* but not scheduled for presentation, embargoes lift at the official start of the meeting at 1:00 PM (EST) on Friday, May 13, 2005.
- Late-Breaking Abstracts (LBAs): Embargoes on all ASCO-designated LBAs lift at 7:45 AM (EST) on Saturday, May 14, 2005.

3000 **Integrated Education Session, Mon, 11:15 AM - 12:30 PM**

A phase I trial of the combination of erlotinib and tipifarnib in patients with advanced solid tumors. *C. X. Ma, G. Croghan, J. Reid, L. Hanson, S. Mandrekar, R. Marks, A. Adjei, A. Furth; Mayo Clinic Coll of Medicine, Rochester, MN*

Background: Preclinical data indicates that the EGFR tyrosine kinase inhibitor erlotinib demonstrates greater than additive cytotoxic effects in combination with the farnesyl transferase inhibitor (FTI), tipifarnib (R115777, Zarnestra), and blocks the PI3-K/Akt pathway which has been implicated in tumor resistance to tipifarnib. The goal of this phase I study was to determine the maximum tolerated dose (MTD), pharmacokinetics (PK), and pharmacodynamics of erlotinib in combination with tipifarnib. **Methods:** Patients with advanced solid tumors received escalating doses of erlotinib (once daily orally) and tipifarnib (bid orally on days 1–21) on a 28-day cycle. The dose-limiting toxicity (DLT) was defined as cycle 1 grade 4 ANC > 5 days, grade 4 thrombocytompenia, serum cr. > 2x baseline, grade 3+ vomiting, diarrhea, skin rash despite maximal support or other non-heme toxicities. **Results:** To date, 12 patients (9F/3M, median age 49) have been treated through 4 dose levels as shown below. Nine patients, treated at dose levels 1 to 3, have received 20 cycles of treatment and are evaluable for toxicities. Three patients have just began treatment at dose level 4, the reported MTD for single agents, and are not yet evaluable for toxicity. No DLTs have been observed. Grade 2+ treatment related toxicities in all cycles of treatment include rash (15% grade 2), diarrhea (5% grade 2, 5% grade 3), fatigue (10% grade 2), and abnormal LFTs(10% grade 2). No objective response has been observed. Four patients have stable disease for at least 2 months. Additional patients will be enrolled at the recommended phase II dose, which is anticipated to be dose level 4, for further evaluation of dose and adverse events relationship, PK and markers of FT and EGFR inhibition, results of which will be presented. **Conclusions:** The combination of erlotinib and tipifarnib is well tolerated. The expected phase II doses to be recommended are erlotinib at 150mg once daily and tipifarnib at 300mg bid.

Dose Level	n	OSI-774 (mg, QD)	R115777 (mg, BID)
1	3	75	200
2	3	100	200
3	3	100	300
4	3	150	300

3001 **Integrated Education Session, Mon, 11:15 AM - 12:30 PM**

A phase I, open-label study of the safety, tolerability and pharmacokinetics of lapatinib (GW572016) in combination with letrozole in cancer patients. *Q. Chu, L. Goldstein, N. Murray, E. Rowinsky, M. Cianfrocca, M. Gale, P. Ho, E. Paul, J. Loftiss, L. Pandite; Cancer Therapy Research Ctr, San Antonio, TX; Fox Chase Cancer Ctr, Philadelphia, PA; Univ of Southampton Cancer Ctr, Southampton, United Kingdom; GlaxoSmithKline, Durham, NC*

Background: Lapatinib is a selective and highly potent dual, competitive inhibitor of ErbB1 and ErbB2 tyrosine kinases leading to cell growth arrest and/or apoptosis in ErbB1 and ErbB2 dependent tumor cell lines and xenografts. Co-expression of ErbB2 and ER is associated with a reduced response rate to hormone therapy in breast cancer. A rational approach to treatment may be to block simultaneously both ER and ErbB2 pathways. **Methods:** Patients (pts) with advanced breast cancer, ER or PR +, or other tumors (e.g., ovarian, endometrial) that would be likely to respond to the combination therapy were enrolled. Escalating doses of lapatinib (1250–1500 mg/d) were administered in combination with letrozole (2.5 mg/d). Three pts were treated at each dose level, with expansion to 6 in the event of dose-limiting toxicity (DLT). Once the optimally tolerated regimen (OTR) was determined, an additional 8 - 16 pts were to be enrolled to establish the pharmacokinetic profiles of lapatinib and letrozole when administered alone and in combination. **Results:** Thirty-six pts (35 F, 1 M, median age 55 yrs, median Karnofsky PS 90%) were enrolled at the 2 dose levels (1250 mg 4 pts, 1500 mg 32 pts). One hundred and twenty-three treatment periods (4 weeks = 1 treatment period) were completed: median 2. One DLT (Gr 3 diarrhea) was reported at the 1500 mg/d dose level. The optimally tolerated regimen was determined to be letrozole 2.5 mg + lapatinib 1500 mg/d. Gr 1–2 diarrhea, nausea, rash and fatigue were the common non-hematologic toxicities. Out of 36 evaluable pts, 4 pts experienced SD for > 5 mo. (breast 2 pts, ovarian 2 pts). One endometrial pt experienced a PR at treatment period 8. **Conclusions:** Lapatinib may be administered safely in combination with letrozole at known effective single agent doses for each. The pharmacokinetic portion of the study is enrolling pts.

3002 **Integrated Education Session, Sun, 11:15 AM - 12:30 PM**

Phase I clinical evaluation of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, in patients with advanced tumors. *J. Drevs, M. Medinger, K. Mross, U. Zirrgiebel, R. Strecker, C. Unger, T. A. Puchalski, N. Fernandes, J. Roberston, P. Siegert; Albert Ludwigs Univ, Freiburg, Germany; ProQinase GmbH, Freiburg, Germany; AstraZeneca, Wilmington, DE; AstraZeneca, Macclesfield, United Kingdom*

Background: AZD2171 is a highly potent and orally available inhibitor of VEGF receptor tyrosine kinase activity, and has shown antitumor activity in a wide range of tumor xenograft models. This Phase I trial was designed to assess the safety, tolerability and pharmacokinetics (PK) of ascending doses of AZD2171 in patients with advanced tumors with liver metastases. **Methods:** Eligibility criteria included solid tumors refractory to standard therapies and a WHO performance status of 0–2. Patients received a single oral dose of AZD2171 (0.5–60 mg) followed by a 7-day washout period, before continuing daily oral therapy at the same initial dose for 28 days. Further 28-day cycles were administered until a withdrawal criterion was met. **Results:** As of Sep 10, 2004, 36 patients (19–75 years) have received treatment with AZD2171 (0.5, 1, 2.5, 5, 10, 20, 30, 45 or 60 mg; n = 3, 3, 3, 3, 4, 3, 5, 4 and 8, respectively). AZD2171 was generally well tolerated at doses ≤45 mg/day. Overall, the most common adverse events were fatigue (n = 13), nausea (n = 13), diarrhea (n = 10) and vomiting (n = 10). Three patients in the 60 mg cohort each experienced one serious adverse event possibly related to AZD2171: grade 4 cerebral hemorrhage, grade 4 hypoglycemia and grade 3 hypertension. Following a single dose, the terminal phase half-life ranged from 12.5–35.4 hours. Steady-state plasma concentrations predicted by single-dose PK did not support time-dependent changes in PK. Across the entire dosing range, plasma concentrations increased linearly following single and multiple doses. Biomarker observations included acute increases in VEGF that were not dose dependent, and dose- and time-dependent reductions in soluble VEGFR-2 levels. Early clinical response data are encouraging, with two unconfirmed partial responses in the ongoing 60 mg cohort and three minor responses at lower doses. Moreover, DCE-MRI assessment showed decreases of >40% in iAUC at consecutive visits in 2/3 patients receiving 20 mg and in 3/4 patients receiving 45 mg, indicating reduced tumor blood flow and permeability. **Conclusions:** In this ongoing Phase I study, continuous once-daily treatment with AZD2171 is generally well tolerated at doses ≤45 mg.

3003 **Integrated Education Session, Sun, 11:15 AM - 12:30 PM**

Surrogate markers of activity of AG-013736, a multi-target tyrosine kinase receptor inhibitor, in metastatic renal cell cancer (RCC). *O. Rixe, J.-B. Meric, J. Bloch, A. Gentile, R. Mouawad, V. Adam, D. Buthiau, D. Khayat; Salpetriere Hosp, Paris, France; Pfizer, Sandwich, United Kingdom; G. E. M. S., Buc, France; Scanner Alesia, Paris, France*

Background: Significant activity of AG-013736, an oral small molecule with potent inhibitory effects against the VEGF receptors 1 (VEGFR-1) and 2 (VEGFR-2) and PDGF receptor, is reported in a phase 2 study in metastatic RCC (*Rini D. et al*, ASCO 2005). Over the 52 enrolled patients (pts), best response assessed by RECIST criteria is 40% (21 partial responses). However, the frequency of stable disease and clinical improvement lead to define new parameters of therapeutic evaluation. The question was addressed in 13 patients treated in Salpêtrière Hospital, included in this phase 2 study. Ancillary studies were conducted to monitor (i) vascular tumour flow using qualitative and quantitative CT perfusion for visceral and non-visceral metastases (ii) biological effect of the anti-angiogenic therapy including soluble proteins involved in the angiogenic pathway. **Methods:** To calculate various tumours perfusion parameters, regional blood flow and volume, mean transit time, hepatic arterial fraction were determined with General Electric's CT Perfusion Program. Serum were collected pre- and 1, 2, 4, 6-months post AG-013736 treatment initiation and analysed by ELISA tests for VEGFs, VEGFR-1, VEGFR-2. **Results:** Decreased tumour perfusion (TP) was observed in patients responding to therapy, including liver metastases. Furthermore, in 4 out of 6 patients with stable or progressive disease by RECIST, decreased TP was strongly correlated with clinical improvement. No relation was observed in this cohort between responders (RECIST criteria, n=7 pts), non-responders (n=6) and biological parameters (VEGFs, VEGFR-1, VEGFR-2). **Conclusion:** Conventional RECIST criteria were designed as a tool for evaluating cytoxic agents. New tools, such as the quantification of tumor blood flow, may yield additional information in the evaluation of anti-angiogenic therapy for solid tumours. Although this observation is based on the data from a small number of patients, this preliminary finding leads us to believe that TP is a useful parameter in evaluating disease status.

3004 **Integrated Education Session, Sat, 11:15 AM - 12:30 PM**

Determining relevant biomarkers from tissue and serum that may predict response to single agent lapatinib in trastuzumab refractory metastatic breast cancer. *K. L. Blackwell, H. Burstein, M. Pegram, A. M. Storniolo, V. M. Salazar, J. E. Maleski, X. Lin, N. Spector, S. H. Stein, M. S. Berger; Duke Univ Medcl Ctr, Durham, NC; Dana-Farber Cancer Inst, Boston, MA; Univ of CA, Los Angeles, Los Angeles, CA; Indiana Univ Cancer Ctr, Indianapolis, IN; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Research Triangle Park, NC*

Background: Lapatinib is an oral tyrosine kinase inhibitor that potently inhibits both ErbB1 and ErbB2 tyrosine kinase activity. Results of two Phase II trials in metastatic breast cancer (MBC) suggest activity of lapatinib in trastuzumab (T) pretreated patients. The main objective of this report was a combined biomarker analysis from these two large studies to evaluate correlations between clinical parameters, tissue/serum biomarker expression and response to lapatinib. **Methods:** Eligible patients had MBC with disease progression following T-containing regimens in the 1st phase II study and were anthracycline, taxane, capecitabine and T exposed in the 2nd phase II study. Tumor tissues were obtained on each patient from the time of most recent biopsy. Using standard IHC techniques, tumors were stained for: ErbB1–4, IGF1R, truncated ErbB2 (p95), heregulin and p-Erk 1/2. Sequential quanitation of extra-cellular domain (ECD) for both ErbB1 and ErbB2 were obtained. **Results:** Investigator reported efficacy data on the first 81 patients from the combined trials demonstrates a total of 19 patients progression-free at 16 weeks of which 7 achieved an objective response (CR or PR). The mean T exposure in the 1st study was 46 weeks and in the 2nd study 84 weeks. As of Dec 2004, both studies have completed accrual with a total of 215 patients. For the initial 37 tumors analyzed, IHC data indicate only 6/37 patients overexpressed both ErbB1 and ErbB2. To date, over 100 tumor tissues have been collected and tested for ErbB1–4, IGF1R, p95, heregulin, and p-Erk 1/2. Initial data suggest that expression levels of ER, PR and ErbB1 may be related to lapatinib response in T pre-treated patients. Declines of ErbB2 ECD at both week 4 and week 8 appear to predict response to lapatinib. A multivariate analysis for response predictors, including all collected tumors, sequential ECD levels and clinical parameters will be performed. **Conclusions:** Inhibition of both ErbB1 and ErbB2 with lapatinib represents a promising approach in the treatment of MBC. This analysis of potential predictive molecular phenotypes for response to lapatinib in T-resistant tumors will be the most extensive to date.

3005 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

Pharmacodynamic study of BAY 43–9006 in patients with metastatic renal cell carcinoma. *P. J. O'Dwyer, M. Rosen, M. Gallagher, B. Schwartz, K. T. Flaherty; Univ of Pennsylvania, Philadelphia, PA; Bayer Pharmaceuticals Corp, West Haven, CT*

Background: BAY 43–9006 (BAY) is a novel signal transduction inhibitor that prevents tumor cell proliferation and angiogenesis through blockade of the Raf/MEK/ERK pathway at the level of Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR-β. In preclinical models BAY administration is associated with decreased microvessel density and area in colon and breast cancer xenografts. We investigated alterations in tumor perfusion and vascular permeability associated with BAY using dynamic contrast-enhanced MRI (DCE-MRI). **Methods:** BAY was given from day 1 to 28 of a 28 day cycle at 400 mg bid. DCE-MRI was performed at baseline and after a median of 6.1 weeks (range 2.7–10.9 weeks). The rate constant for gadolinium transfer from the vasculature to the interstitium (Ktrans) and volume fraction of the tissue extracellular and extravascular space (Ve) were calculated for an index lesion for each patient and were normalized for the arterial input function. Response was assessed with CT scans after 12 weeks, then every 8 weeks for four months, then every 12 weeks using WHO criteria. **Results:** 17 renal cell carcinoma patients (pts) (median age 59, PS 0–1) have been enrolled on this pharmacodynamic study and 16 underwent baseline and follow-up MRIs. Data are available from both scans for 12 patients. 65% of patients had clear cell histology and had a median of 1 prior therapy (range 0–6). As in previous studies, BAY was well-tolerated at this dose and schedule. Responses using WHO criteria included 7 partial responses (ORR 41%), 7 minor responses (25–50% reduction), 2 stable disease and 1 progression prior to 12 weeks. Median time to progression has not been reached, but is at least 10.8 months. Among the 12 patients with data from both DCE-MRIs, Ktrans declined by 60.9% on average (95% CI 45.5–76.4%), and Ve declined by 23.4% (95% CI 4.8–41.9%). Both high Ktrans at baseline, and percent decline in Ktrans, correlated with time to progression. **Conclusions:** BAY 43–9006 is well-tolerated as a single-agent and is associated with significant alterations in measures of vascular permeability and tumor perfusion in patients with renal cell carcinoma. Preliminary evidence is adduced that therapeutic efficacy is a consequence of angiogenesis inhibition.

3006 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

Pharmacodynamic analysis of target receptor tyrosine kinase activity and apoptosis in GIST tumors responding to therapy with SU11248. *D. W. Davis, D. J. McConkey, J. V. Heymach, J. Desai, S. George, J. Jackson, C. L. Bello, C. Baum, D. R. Shalinsky, G. D. Demetri; Univ of Texas MD Anderson Cancer Ctr, Houston, TX; Dana-Farber Cancer Inst, Boston, MA; Pfizer Global Research and Development, La Jolla, San Diego, CA*

Background: Most GIST lesions contain activating mutations in the receptor tyrosine kinases, KIT and/or PDGFR. SU11248 is an oral, multitargeted tyrosine kinase inhibitor of KIT, PDGFR, and VEGFR-1, -2 and -3 active against imatinib-resistant GIST. We report here effects of SU11248 on endothelial and tumor compartments in GIST. **Methods:** Paired tumor biopsies were obtained from 19 GIST patients (pts) undergoing phase 1/2 therapy with SU11248 (Proc. ASCO 22:A3001, 2004). Biopsies were collected at baseline before and after at least 14d of treatment with SU11248 in the first cycle of treatment. Biopsies were examined using immunofluorescence coupled with laser scanning cytometry to quantify endothelial and tumor cell apoptosis, microvessel density (MVD), and the phosphorylation of PDGR-β and other RTKs. **Results:** Eight of 19 pairs of tumor samples came from patients who had clinical benefit (CB), defined as either partial response (PR) by RECIST criteria or stable disease (SD) for >6 months and 11 from pts with progressive disease (PD). Compared with baseline, tumors from pts with CB had a significant decrease of 15.0±0.03 % (SD; p=0.016, t-test) in phosphorylated PDGFR-β activity in the tumor cell compartment whereas tumors in non-responders had an increase in PDGFR-β activity of 11.0±0.17%. Two pts had PR and six had SD, corresponding to a 23 and 11% decrease in phosphorylated PDGFR-β activity, respectively (p<0.05). Overall, tumors in pts with CB displayed a 3.6- and 6-fold (p<0.05) increase in endothelial and tumor cell apoptosis, respectively. In contrast, tumors in pts with PD had little or no change in endothelial and tumor cell apoptosis from baseline. **Conclusions:** PDGFR-β phosphorylation was significantly decreased in tumor biopsies from GIST pts treated with SU11248 who had CB but not in those who had PD. Activities of other target RTKs are under investigation and will be presented. These data demonstrate that SU11248 inhibits PDGFR-β activity in addition to other RTKs in GIST. We hypothesize that SU11248 exerts direct antitumor and indirect antiangiogenic effects in GIST as the basis for its anticancer efficacy.

3007 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors. *J. Tabernero, F. Rojo, H. Burris, E. Casado, T. Macarulla, S. Jones, S. Dimitrijevic, K. Hazell, N. Shand, J. Baselga, for the study group; Vall d'Hebron Univ Hosp, Barcelona, Spain; Sarah Cannon Cancer Ctr, Nashville, TN; Novartis Oncology, Basel, Switzerland*

Background: Everolimus (E), an oral derivative of rapamycin, inhibits mTOR, a protein kinase downstream of PI3K and Akt, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of E is associated with reduction of mTOR downstream phosphorylated(p)-S6 (p-S6) and p-4E-BP1, and occasionally with increase in upstream p-Akt. This study explores safety, PK and MPD changes in tumor at different doses and schedules of E to define the recommended dose for further development. **Methods:** Pts with advanced solid tumors were treated in successive cohorts of E: weekly 20, 50 and 70 mg or daily 5 and 10 mg. Dose escalation depended on dose limiting toxicity (DLT) rate during the first 4-week period. Pre- and on-treatment steady-state (24hr post-dose and, for the weekly schedule, 5 days post-dose) tumor biopsies were obtained from each pt. Tumor tissue was evaluated by immunohistochemistry (IHC) for p-S6, p-4E-BP1 and p-Akt expression by a pathologist blinded for the biopsy sequence. **Results:** 33 pts have been treated with 6–8 pts in each cohort. Grade 3 DLT occurred in 5 pts comprising stomatitis (1 pt at 10 mg daily, 2 at 70 mg weekly), neutropenia and hyperglycemia (1 pt each at 70 mg weekly). There were one partial response (colon cancer) and 2 stabilizations of >4 months (renal cell and breast cancer). MPD studies (see table) demonstrated an almost complete inhibition of p-S6 at all doses and schedules (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥50 mg weekly. **Conclusions:** This phase I study shows that E, at the doses and schedules studied, results in intratumoral inhibition of mTOR signaling. Based on the toxicity profile and the MPD findings, a dosage of 10 mg daily can be recommended for further phase II-III development with E as a single agent.

Schedule/Dose	Mean p-S6 inhibition (%)	Mean p-4E-BP1 inhibition (%)	Mean p-Akt activation (%)
Daily 5 mg (n=3)	100	48	22.2
Daily 10 mg (n=6)	92.5	58.2	45.5
Weekly 20 mg (n=5)	96.7	5.9	32.7
Weekly ≥50 mg (n=6)	100	63.8	63.1

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Letter from the Editor

The *2005 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) contains more than 2,000 abstracts selected by the ASCO Scientific Program Committee for presentation at the 41st Annual Meeting of the American Society of Clinical Oncology, held May 13-17, 2005, in Orlando, Florida, and more than 1,400 abstracts selected for publication. The abstracts are categorized by scientific track and ordered numerically within each track by presentation type: Plenary; Integrated Education Session; Oral Presentation; Poster Discussion; General Poster; and Publication. The scientific program uses a 500-series classification system (e.g., Plenary abstracts are numbered 1-12; Breast Cancer, 500-999; Cancer Prevention 1,000-1,500). The Table of Contents lists the abstract number ranges for abstracts scheduled for presentation.

This year, ASCO has once again accepted late-breaking abstract submissions for the Meeting. These abstracts feature the results of major phase III trials for which final data were not available at the time of ASCO's regular abstract submission deadline. In order to facilitate Annual Meeting planning, the late-breaking abstract "placeholders"—without the final results and conclusions—are included in this supplement. The final late-breaking abstracts will be included in the *2005 ASCO Annual Meeting Proceedings Part II* (a supplement to the *Journal of Clinical Oncology*), which will be available onsite at the Annual Meeting on Saturday, May 14, 2005, and will be mailed to JCO subscribers with the June 1, 2005, issue of JCO.

The *2005 ASCO Annual Meeting Proceedings* serves as the publication of record for citation of abstracts. The following is a sample citation:

T. Fama, M. Wood, H. Muss: Patient preferences for adjuvant treatment of early-stage breast cancer. J Clin Oncol 23:61s, 2005 (suppl, abstr 733)

An additional advantage of publishing the *Annual Meeting Proceedings I* and *II* as supplements to JCO is that the abstracts are housed as part of www.jco.org. Readers can search online by keyword, author, etc, not only within the abstracts themselves but also in conjunction with other JCO content. The abstracts are housed additionally on www.asco.org and can be accessed through the Virtual Meeting.

We encourage you, as always, to provide us with any feedback that will augment the quality of information contained in our publications. Should you have any questions or comments about the usefulness, format, and indexes pertaining to the abstracts, please feel free to contact us at abstracts@asco.org.

Steven M. Grunberg, MD
Proceedings Editor

ASCO ABSTRACTS POLICY

ASCO has formalized the following confidentiality policy governing the use of information contained in abstracts of the ASCO *2005 Annual Meeting Proceedings Part I* (a Supplement to the *Journal of Clinical Oncology*), which contains all abstracts to be presented at the 2005 Annual Meeting, all publish-only abstracts, and late-breaking abstract "placeholders" (without final results and conclusions). Abstracts are short, preliminary summaries of research that are used by ASCO to determine whether or not a study is accepted into its Annual Meeting program. These 300 word or less summaries typically include preliminary data that, subsequent to their submission to ASCO, are analyzed in the months leading up to the Annual Meeting. Therefore, these abstracts do not necessarily contain the final results or conclusions that are reported at the Meeting.

In an effort to ensure that premature research data are not publicly reported prior to the scientific review at the Annual Meeting, ASCO has instituted the following confidentiality policy governing the use of the information contained in this publication. The Society's official Embargo Policy, designed to ensure the integrity of the information that is communicated from the ASCO Annual Meeting, is also published below. Both the Confidentiality Policy and the Embargo Policy are in effect until they are lifted, on an abstract-by-abstract basis, as stated in each of the respective policies below.

CONFIDENTIALITY AGREEMENT

The information contained in the ASCO *2005 Annual Meeting Proceedings Part I* (individually, the Abstracts, and collectively, the Proceedings) is confidential information until its public release. Distribution of this information in advance of public release is solely for the purpose of preparing for and planning Annual Meeting activities.

Until the public release of this information, this information must be kept confidential. Specifically, and without limiting the generality of your agreement to maintain the confidentiality of the Abstracts, you agree that:

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A violation of your agreement not to use Abstract information for securities trading purposes or to provide it to others who may use it for securities trading purposes may constitute a violation of federal or state securities laws and may subject you to civil or criminal liability.

For purposes of this Confidentiality Agreement, Abstracts are considered to have been made public at the time when the embargo on them has been lifted under the official Embargo Policy below.

ASCO EMBARGO POLICY

All abstracts presented at the Annual Meeting are embargoed until the beginning of the Scientific Session containing the research, with the following exceptions:

- Abstracts in ASCO's Official Press Program: Embargoes lift at the beginning of the News Briefing, or the beginning of the Scientific Session containing the research, whichever comes first.
- Publish-Only Abstracts: For abstracts published in the *2005 ASCO Annual Meeting Proceedings* but not scheduled for presentation, embargoes lift at the official start of the meeting at 1:00 PM (EST) on Friday, May 13, 2005.
- Late-Breaking Abstracts (LBAs): Embargoes on all ASCO-designated LBAs lift at 7:45 AM (EST) on Saturday, May 14, 2005.

3004 **Integrated Education Session, Sat, 11:15 AM - 12:30 PM**

Determining relevant biomarkers from tissue and serum that may predict response to single agent lapatinib in trastuzumab refractory metastatic breast cancer. *K. L. Blackwell, H. Burstein, M. Pegram, A. M. Storniolo, V. M. Salazar, J. E. Maleski, X. Lin, N. Spector, S. H. Stein, M. S. Berger; Duke Univ Medcl Ctr, Durham, NC; Dana-Farber Cancer Inst, Boston, MA; Univ of CA, Los Angeles, Los Angeles, CA; Indiana Univ Cancer Ctr, Indianapolis, IN; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Research Triangle Park, NC*

Background: Lapatinib is an oral tyrosine kinase inhibitor that potently inhibits both ErbB1 and ErbB2 tyrosine kinase activity. Results of two Phase II trials in metastatic breast cancer (MBC) suggest activity of lapatinib in trastuzumab (T) pretreated patients. The main objective of this report was a combined biomarker analysis from these two large studies to evaluate correlations between clinical parameters, tissue/serum biomarker expression and response to lapatinib. **Methods:** Eligible patients had MBC with disease progression following T-containing regimens in the 1st phase II study and were anthracycline, taxane, capecitabine and T exposed in the 2nd phase II study. Tumor tissues were obtained on each patient from the time of most recent biopsy. Using standard IHC techniques, tumors were stained for: ErbB1–4, IGF1R, truncated ErbB2 (p95), heregulin and p-Erk 1/2. Sequential quanitation of extra-cellular domain (ECD) for both ErbB1 and ErbB2 were obtained. **Results:** Investigator reported efficacy data on the first 81 patients from the combined trials demonstrates a total of 19 patients progression-free at 16 weeks of which 7 achieved an objective response (CR or PR). The mean T exposure in the 1st study was 46 weeks and in the 2nd study 84 weeks. As of Dec 2004, both studies have completed accrual with a total of 215 patients. For the initial 37 tumors analyzed, IHC data indicate only 6/37 patients overexpressed both ErbB1 and ErbB2. To date, over 100 tumor tissues have been collected and tested for ErbB1–4, IGF1R, p95, heregulin, and p-Erk 1/2. Initial data suggest that expression levels of ER, PR and ErbB1 may be related to lapatinib response in T pre-treated patients. Declines of ErbB2 ECD at both week 4 and week 8 appear to predict response to lapatinib. A multivariate analysis for response predictors, including all collected tumors, sequential ECD levels and clinical parameters will be performed. **Conclusions:** Inhibition of both ErbB1 and ErbB2 with lapatinib represents a promising approach in the treatment of MBC. This analysis of potential predictive molecular phenotypes for response to lapatinib in T-resistant tumors will be the most extensive to date.

3005 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

Pharmacodynamic study of BAY 43–9006 in patients with metastatic renal cell carcinoma. *P. J. O'Dwyer, M. Rosen, M. Gallagher, B. Schwartz, K. T. Flaherty; Univ of Pennsylvania, Philadelphia, PA; Bayer Pharmaceuticals Corp, West Haven, CT*

Background: BAY 43–9006 (BAY) is a novel signal transduction inhibitor that prevents tumor cell proliferation and angiogenesis through blockade of the Raf/MEK/ERK pathway at the level of Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR-β. In preclinical models BAY administration is associated with decreased microvessel density and area in colon and breast cancer xenografts. We investigated alterations in tumor perfusion and vascular permeability associated with BAY using dynamic contrast-enhanced MRI (DCE-MRI). **Methods:** BAY was given from day 1 to 28 of a 28 day cycle at 400 mg bid. DCE-MRI was performed at baseline and after a median of 6.1 weeks (range 2.7–10.9 weeks). The rate constant for gadolinium transfer from the vasculature to the interstitium (Ktrans) and volume fraction of the tissue extracellular and extravascular space (Ve) were calculated for an index lesion for each patient and were normalized for the arterial input function. Response was assessed with CT scans after 12 weeks, then every 8 weeks for four months, then every 12 weeks using WHO criteria. **Results:** 17 renal cell carcinoma patients (pts) (median age 59, PS 0–1) have been enrolled on this pharmacodynamic study and 16 underwent baseline and follow-up MRIs. Data are available from both scans for 12 patients. 65% of patients had clear cell histology and had a median of 1 prior therapy (range 0–6). As in previous studies, BAY was well-tolerated at this dose and schedule. Responses using WHO criteria included 7 partial responses (ORR 41%), 7 minor responses (25–50% reduction), 2 stable disease and 1 progression prior to 12 weeks. Median time to progression has not been reached, but is at least 10.8 months. Among the 12 patients with data from both DCE-MRIs, Ktrans declined by 60.9% on average (95% CI 45.5–76.4%), and Ve declined by 23.4% (95% CI 4.8–41.9%). Both high Ktrans at baseline, and percent decline in Ktrans, correlated with time to progression. **Conclusions:** BAY 43–9006 is well-tolerated as a single-agent and is associated with significant alterations in measures of vascular permeability and tumor perfusion in patients with renal cell carcinoma. Preliminary evidence is adduced that therapeutic efficacy is a consequence of angiogenesis inhibition.

3006 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

Pharmacodynamic analysis of target receptor tyrosine kinase activity and apoptosis in GIST tumors responding to therapy with SU11248. *D. W. Davis, D. J. McConkey, J. V. Heymach, J. Desai, S. George, J. Jackson, C. L. Bello, C. Baum, D. R. Shalinsky, G. D. Demetri; Univ of Texas MD Anderson Cancer Ctr, Houston, TX; Dana-Farber Cancer Inst, Boston, MA; Pfizer Global Research and Development, La Jolla, San Diego, CA*

Background: Most GIST lesions contain activating mutations in the receptor tyrosine kinases, KIT and/or PDGFR. SU11248 is an oral, multitargeted tyrosine kinase inhibitor of KIT, PDGFR, and VEGFR-1, -2 and -3 active against imatinib-resistant GIST. We report here effects of SU11248 on endothelial and tumor compartments in GIST. **Methods:** Paired tumor biopsies were obtained from 19 GIST patients (pts) undergoing phase 1/2 therapy with SU11248 (Proc. ASCO 22:A3001, 2004). Biopsies were collected at baseline before and after at least 14d of treatment with SU11248 in the first cycle of treatment. Biopsies were examined using immunofluorescence coupled with laser scanning cytometry to quantify endothelial and tumor cell apoptosis, microvessel density (MVD), and the phosphorylation of PDGR-β and other RTKs. **Results:** Eight of 19 pairs of tumor samples came from patients who had clinical benefit (CB), defined as either partial response (PR) by RECIST criteria or stable disease (SD) for >6 months and 11 from pts with progressive disease (PD). Compared with baseline, tumors from pts with CB had a significant decrease of 15.0±0.03 % (SD; $p=0.016$, t-test) in phosphorylated PDGFR-β activity in the tumor cell compartment whereas tumors in non-responders had an increase in PDGFR-β activity of 11.0±0.17%. Two pts had PR and six had SD, corresponding to a 23 and 11% decrease in phosphorylated PDGFR-β activity, respectively ($p<0.05$). Overall, tumors in pts with CB displayed a 3.6- and 6-fold ($p<0.05$) increase in endothelial and tumor cell apoptosis, respectively. In contrast, tumors in pts with PD had little or no change in endothelial and tumor cell apoptosis from baseline. **Conclusions:** PDGFR-β phosphorylation was significantly decreased in tumor biopsies from GIST pts treated with SU11248 who had CB but not in those who had PD. Activities of other target RTKs are under investigation and will be presented. These data demonstrate that SU11248 inhibits PDGFR-β activity in addition to other RTKs in GIST. We hypothesize that SU11248 exerts direct antitumor and indirect antiangiogenic effects in GIST as the basis for its anticancer efficacy.

3007 **Oral Presentation, Sun, 1:00 PM - 4:00 PM**

A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors. *J. Tabernero, F. Rojo, H. Burris, E. Casado, T. Macarulla, S. Jones, S. Dimitrijevic, K. Hazell, N. Shand, J. Baselga, for the study group; Vall d'Hebron Univ Hosp, Barcelona, Spain; Sarah Cannon Cancer Ctr, Nashville, TN; Novartis Oncology, Basel, Switzerland*

Background: Everolimus (E), an oral derivative of rapamycin, inhibits mTOR, a protein kinase downstream of PI3K and Akt, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of E is associated with reduction of mTOR downstream phosphorylated(p)-S6 (p-S6) and p-4E-BP1, and occasionally with increase in upstream p-Akt. This study explores safety, PK and MPD changes in tumor at different doses and schedules of E to define the recommended dose for further development. **Methods:** Pts with advanced solid tumors were treated in successive cohorts of E: weekly 20, 50 and 70 mg or daily 5 and 10 mg. Dose escalation depended on dose limiting toxicity (DLT) rate during the first 4-week period. Pre- and on-treatment steady-state (24hr post-dose and, for the weekly schedule, 5 days post-dose) tumor biopsies were obtained from each pt. Tumor tissue was evaluated by immunohistochemistry (IHC) for p-S6, p-4E-BP1 and p-Akt expression by a pathologist blinded for the biopsy sequence. **Results:** 33 pts have been treated with 6–8 pts in each cohort. Grade 3 DLT occurred in 5 pts comprising stomatitis (1 pt at 10 mg daily, 2 at 70 mg weekly), neutropenia and hyperglycemia (1 pt each at 70 mg weekly). There were one partial response (colon cancer) and 2 stabilizations of >4 months (renal cell and breast cancer). MPD studies (see table) demonstrated an almost complete inhibition of p-S6 at all doses and schedules ($p=0.001$). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥50 mg weekly. **Conclusions:** This phase I study shows that E, at the doses and schedules studied, results in intratumoral inhibition of mTOR signaling. Based on the toxicity profile and the MPD findings, a dosage of 10 mg daily can be recommended for further phase II-III development with E as a single agent.

Schedule/Dose	Mean p-S6 inhibition (%)	Mean p-4E-BP1 inhibition (%)	Mean p-Akt activation (%)
Daily 5 mg (n=3)	100	48	22.2
Daily 10 mg (n=6)	92.5	58.2	45.5
Weekly 20 mg (n=5)	96.7	5.9	32.7
Weekly ≥50 mg (n=6)	100	63.8	63.1

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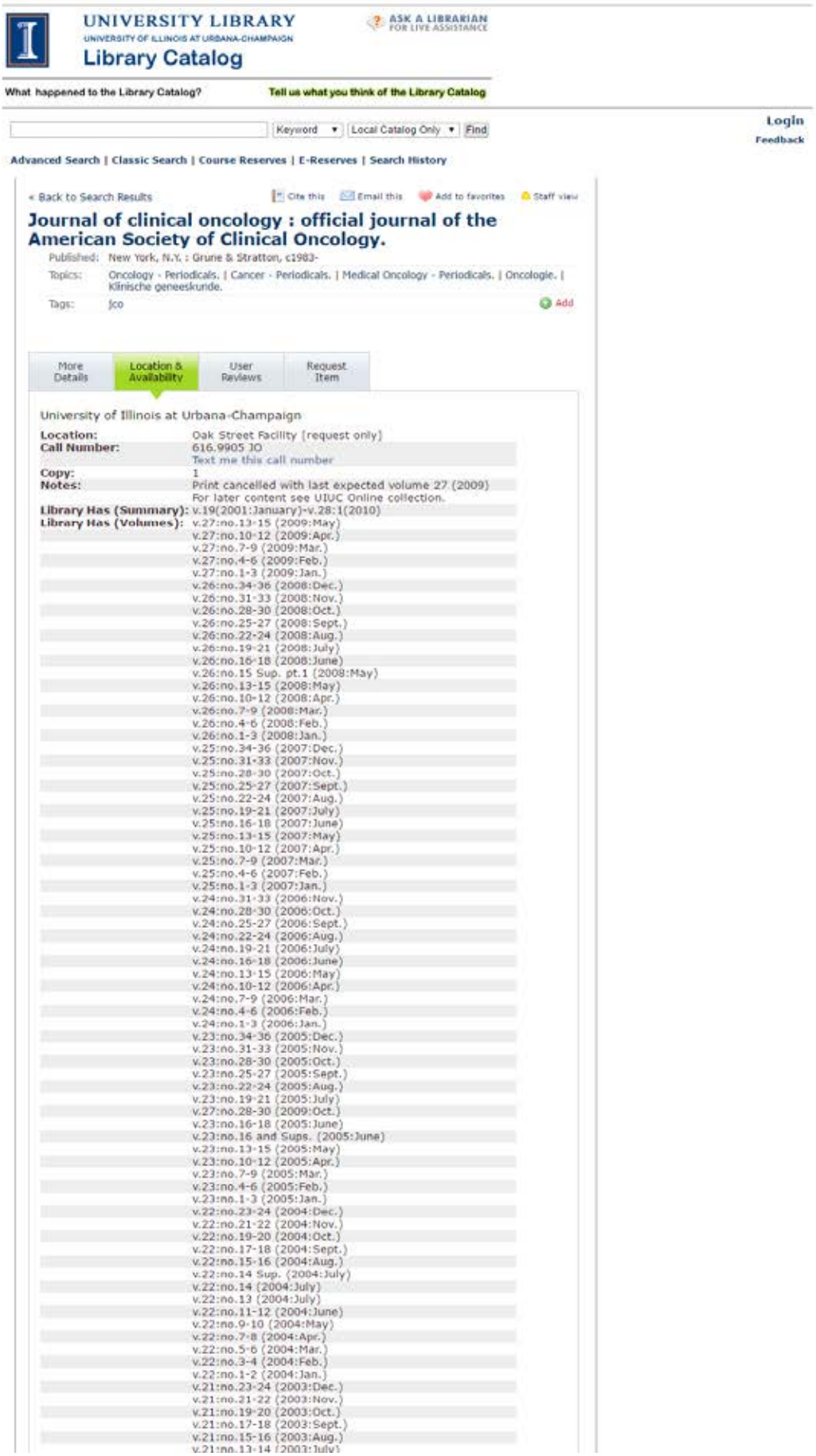

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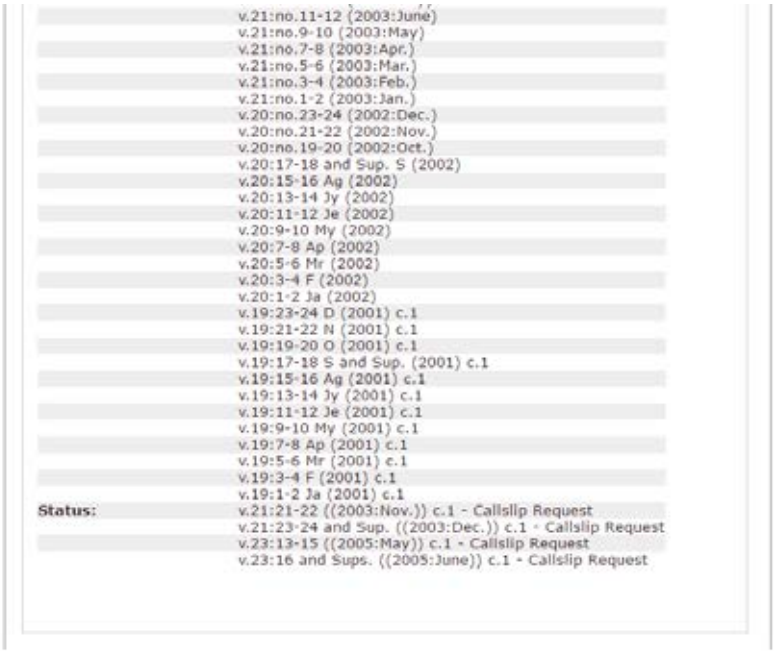

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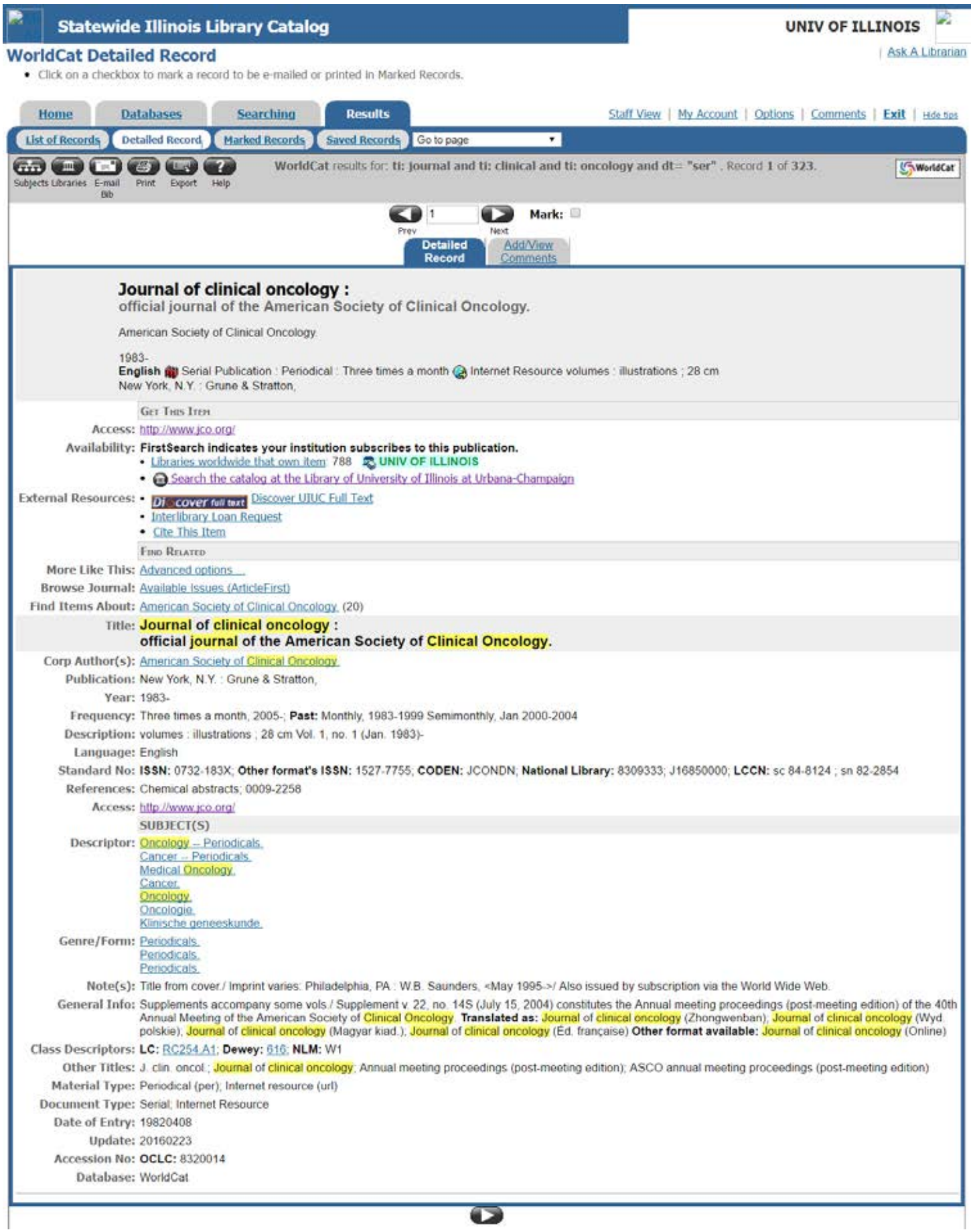

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Year: 1983-

Frequency: Three times a month, 2005-; **Past:** Monthly, 1983-1999 Semimonthly, Jan 2000-2004

Description: volumes : illustrations ; 28 cm Vol. 1, no. 1 (Jan. 1983)-

Language: English

Standard No: **ISSN:** 0732-183X; **Other format's ISSN:** 1527-7755; **CODEN:** JCONDN; **National Library:** 8309333; J16850000; **LCCN:** sc 84-8124 ; sn 82-2854

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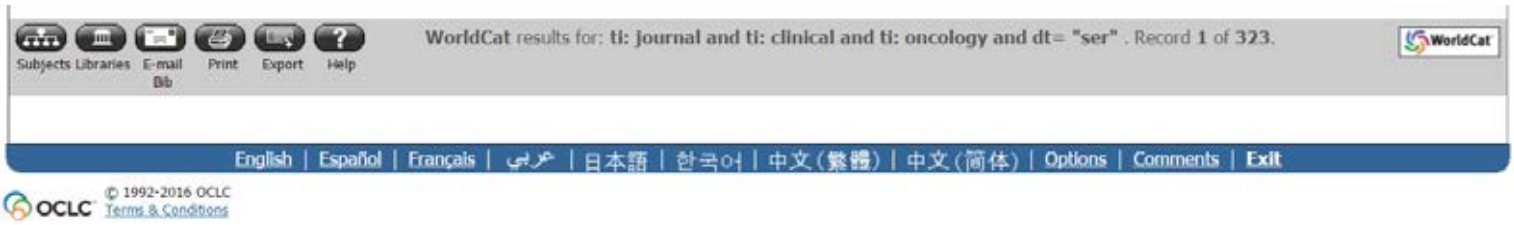

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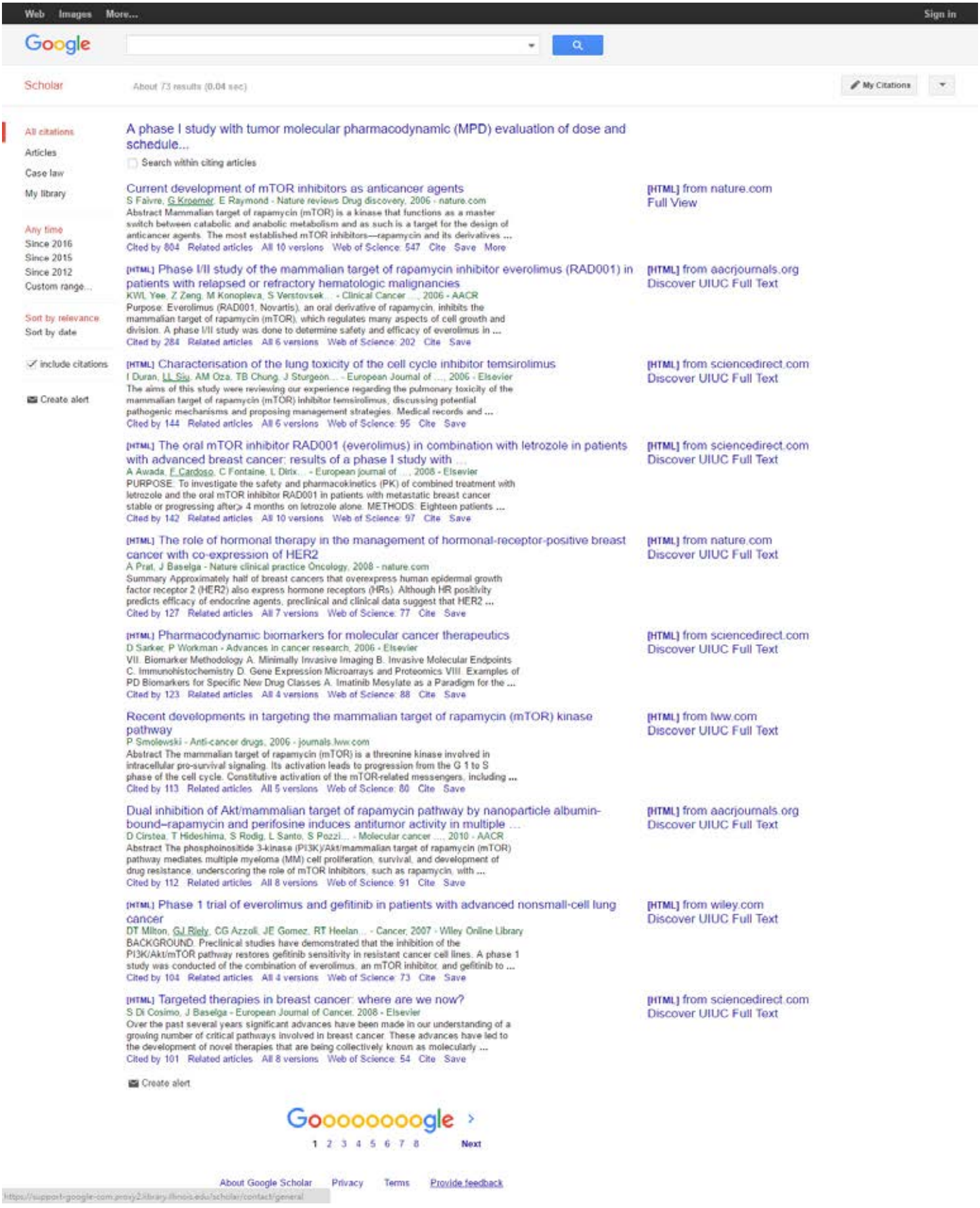

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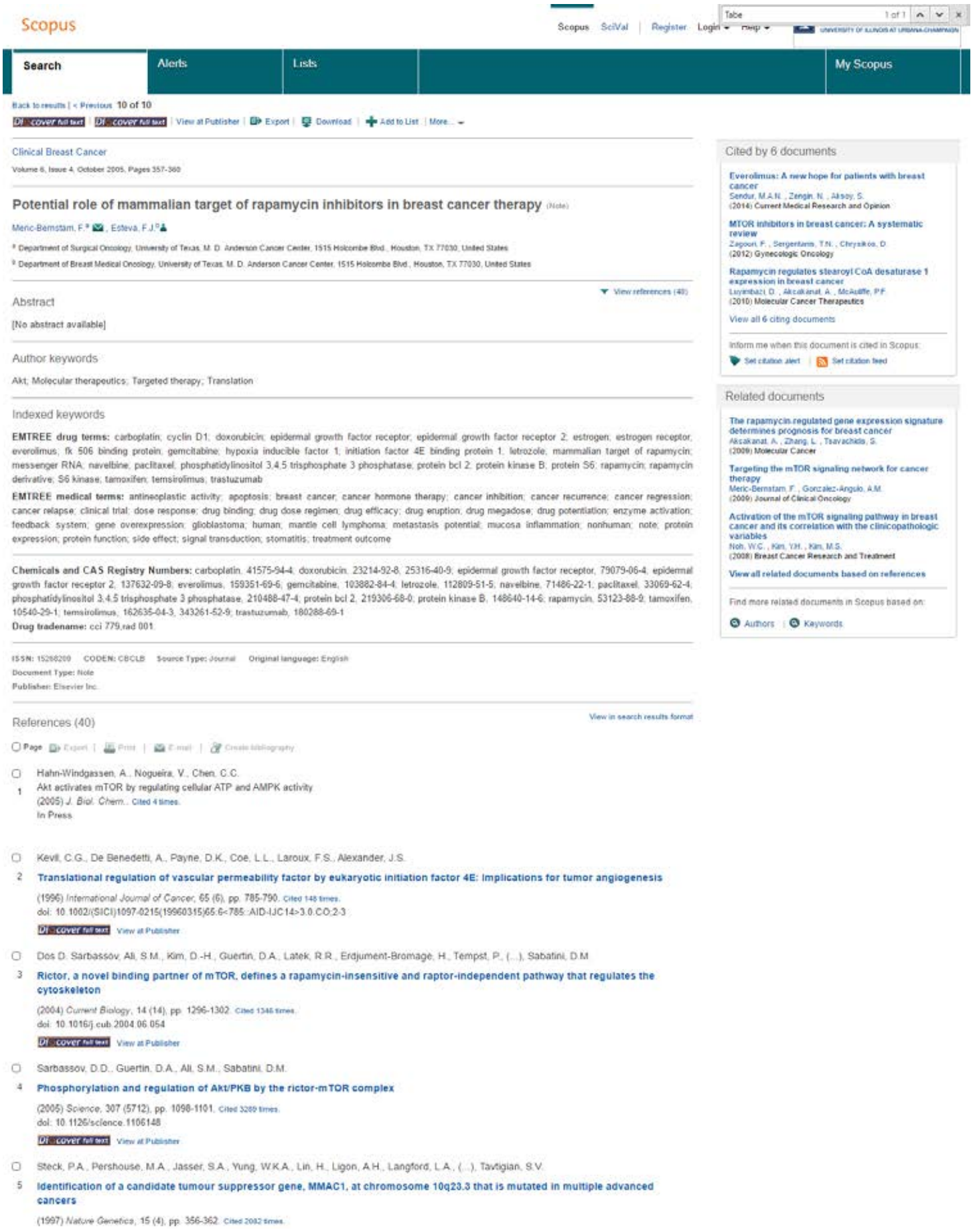

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Clinical Breast Cancer

Volume 6, Issue 4, October 2005, Pages 357-360

Potential role of mammalian target of rapamycin inhibitors in breast cancer therapy (Note)

Meric-Bernstam, F.[a], Esteva, F.J.[b]

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[b] Department of Breast Medical Oncology, University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States

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Abstract

[No abstract available]

Author keywords

Akt; Molecular therapeutics; Targeted therapy; Translation

Indexed keywords

EMTREE drug terms: carboplatin; cyclin D1; doxorubicin; epidermal growth factor receptor; epidermal growth factor receptor 2; estrogen; estrogen receptor; everolimus; fk 506 binding protein; gemcitabine; hypoxia inducible factor 1; initiation factor 4E binding protein 1; letrozole; mammalian target of rapamycin; messenger RNA; navelbine; paclitaxel; phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase; protein bcl 2; protein kinase B; protein S6; rapamycin; rapamycin derivative; S6 kinase; tamoxifen; temsirolimus; trastuzumab

EMTREE medical terms: antineoplastic activity; apoptosis; breast cancer; cancer hormone therapy; cancer inhibition; cancer recurrence; cancer regression; cancer relapse; clinical trial; dose response; drug binding; drug dose regimen; drug efficacy; drug eruption; drug megadose; drug potentiation; enzyme activation; feedback system; gene overexpression; glioblastoma; human; mantle cell lymphoma; metastasis potential; mucosa inflammation; nonhuman; note; protein expression; protein function; side effect; signal transduction; stomatitis; treatment outcome

Chemicals and CAS Registry Numbers: carboplatin, 41575-94-4; doxorubicin, 23214-92-8, 25316-40-9; epidermal growth factor receptor, 79079-06-4; epidermal growth factor receptor 2, 137632-09-8; everolimus, 159351-69-6; gemcitabine, 103882-84-4; letrozole, 112809-51-5; navelbine, 71486-22-1; paclitaxel, 33069-62-4; phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase, 210488-47-4; protein bcl 2, 219306-68-0; protein kinase B, 148640-14-6; rapamycin, 53123-88-9; tamoxifen, 10540-29-1; temsirolimus, 162635-04-3, 343261-52-9; trastuzumab, 180288-69-1

Drug tradename: cci 779,rad 001

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References (40)

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1 Hahn-Windgassen, A., Nogueira, V., Chen, C.C.
Akt activates mTOR by regulating cellular ATP and AMPK activity
(2005) J. Biol. Chem., Cited 4 times.
In Press

2 Kevil, C.G., De Benedetti, A., Payne, D.K., Coe, L.L., Laroux, F.S., Alexander, J.S.
Translational regulation of vascular permeability factor by eukaryotic initiation factor 4E: implications for tumor angiogenesis
(1996) International Journal of Cancer, 65 (6), pp. 785-790. Cited 148 times.
doi: 10.1002/(SICI)1097-0215(19960315)65:6<785::AID-IJC14>3.0.CO;2-3
View at Publisher

3 Dos D. Sarbassov, Ali, S.M., Kim, D.-H., Guertin, D.A., Latek, R.R., Erdjument-Bromage, H., Tempst, P., (...), Sabatini, D.M
Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton
(2004) Current Biology, 14 (14), pp. 1296-1302. Cited 1346 times.
doi: 10.1016/j.cub.2004.06.054
View at Publisher

4 Sarbassov, D.D., Guertin, D.A., Ali, S.M., Sabatini, D.M.
Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex
(2005) Science, 307 (5712), pp. 1098-1101. Cited 3289 times.
doi: 10.1126/science.1106148
View at Publisher

5 Steck, P.A., Pershouse, M.A., Jasser, S.A., Yung, W.K.A., Lin, H., Ligon, A.H., Langford, L.A., (...), Tavtigian, S.V.
Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers
(1997) Nature Genetics, 15 (4), pp. 356-362. Cited 2082 times.

Cited by 6 documents

Everolimus: A new hope for patients with breast cancer
Sendur, M.A.N., Zengin, N., Aksoy, S.
(2014) Current Medical Research and Opinion

MTOR inhibitors in breast cancer: A systematic review
Zagouri, F., Sergentanis, T.N., Chrysikos, D.
(2012) Gynecologic Oncology

Rapamycin regulates stearoyl CoA desaturase 1 expression in breast cancer
Luyimbazi, D., Akcakanat, A., McAuliffe, P.F.
(2010) Molecular Cancer Therapeutics

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(2009) Journal of Clinical Oncology

Activation of the mTOR signaling pathway in breast cancer and its correlation with the clinicopathologic variables
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Perren, A., Weng, L.-P., Boag, A.H., Ziebold, U., Thakore, K., Dahia, P.L.M., Komminoth, P., (...), Eng, C.

6 **Immunohistochemical evidence of loss of PTEN expression in primary ductal adenocarcinomas of the breast**

(1999) *American Journal of Pathology*, 155 (4), pp. 1253-1260. Cited 292 times.

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Rhei, E., Kang, L., Bogomolniy, F., Federici, M.G., Borgen, P.I., Boyd, J.

7 **Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in primary breast carcinomas**

(1997) *Cancer Research*, 57 (17), pp. 3657-3659. Cited 229 times.

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Khan, S., Kumagai, T., Vora, J., Bose, N., Sehgal, I., Koeffler, P.H., Bose, S.

8 **PTEN promoter is methylated in a proportion of invasive breast cancers**

(2004) *International Journal of Cancer*, 112 (3), pp. 407-410. Cited 80 times.
doi: 10.1002/ijc.20447

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Tsutsui, S., Inoue, H., Yasuda, K., Suzuki, K., Higashi, H., Era, S., Mori, M.

9 **Reduced expression of PTEN protein and its prognostic implications in invasive ductal carcinoma of the breast**

(2005) *Oncology*, 68 (4-6), pp. 398-404. Cited 75 times.
doi: 10.1159/000086981

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Saal, L.H., Holm, K., Maurer, M., Memeo, L., Su, T., Wang, X., Yu, J.S., (...), Parsons, R.

10 **PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma**

(2005) *Cancer Research*, 65 (7), pp. 2554-2559. Cited 532 times.
doi: 10.1158/0008-5472.CAN-04-3913

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Zhou, B.P., Hu, M.C.-T., Miller, S.A., Yu, Z., Xia, W., Lin, S.-Y., Hung, M.-C.

11 **HER-2/neu blocks tumor necrosis factor-induced apoptosis via the Akt/NF-κB pathway**

(2000) *Journal of Biological Chemistry*, 275 (11), pp. 8027-8031. Cited 300 times.
doi: 10.1074/jbc.275.11.8027

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Cui, X., Zhang, P., Deng, W., Oesterreich, S., Lu, Y., Mills, G.B., Lee, A.V.

12 **Insulin-like growth factor-I inhibits progesterone receptor expression in breast cancer cells via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway: Progesterone receptor as a potential indicator of growth factor activity in breast cancer**

(2003) *Molecular Endocrinology*, 17 (4), pp. 575-588. Cited 158 times.
doi: 10.1210/me.2002-0318

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Chung, J., Bachelder, R.E., Lipscomb, E.A., Shaw, L.M., Mercurio, A.M.

13 **Integrin (α6β4) regulation of eIF-4E activity and VEGF translation: A survival mechanism for carcinoma cells**

(2002) *Journal of Cell Biology*, 158 (1), pp. 165-174. Cited 147 times.
doi: 10.1083/jcb.200112015

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Avdulov, S., Li, S., Michalek, V., Burrichter, D., Peterson, M., Perlman, D.M., Manivel, J.C., (...), Polunovsky, V.A.

14 **Activation of translation complex eIF4F is essential for the genesis and maintenance of the malignant phenotype in human mammary epithelial cells**

(2004) *Cancer Cell*, 5 (6), pp. 553-563. Cited 215 times.
doi: 10.1016/j.ccr.2004.05.024

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Bärlund, M., Forozan, F., Kononen, J., Bubendorf, L., Chen, Y., Bittner, M.L., Torhorst, J., (...), Kallioniemi, A.

15 **Detecting activation of ribosomal protein S6 kinase by complementary DNA and tissue microarray analysis**

(2000) *Journal of the National Cancer Institute*, 92 (15), pp. 1252-1259. Cited 212 times.

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Li, B.D.L., McDonald, J.C., Nassar, R., De Benedetti, A.

16 **Clinical outcome in stage I to III breast carcinoma and eIF4E overexpression**

(1998) *Annals of Surgery*, 227 (5), pp. 756-763. Cited 79 times.
doi: 10.1097/00000658-199805000-00016

Discover full text View at Publisher

Noh, W.-C., Mondesire, W.H., Peng, J., Jian, W., Zhang, H., Dong, J., Mills, G.B., (...), Meric-Bernstam, F.

17 **Determinants of Rapamycin Sensitivity in Breast Cancer Cells**

(2004) *Clinical Cancer Research*, 10 (3), pp. 1013-1023. Cited 214 times.
doi: 10.1158/1078-0432.CCR-03-0043

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Attachment 4f: Index record for a documenting citing Tabernero

Zhou, X., Tan, M., Hawthorne, V.S., Klos, K.S., Lan, K.-H., Yang, Y., Yang, W., (...), Yu, D.

18 **Activation of the Akt/mammalian target of rapamycin/4E-BP1 pathway by ErbB2 overexpression predicts tumor progression in breast cancers**

(2004) *Clinical Cancer Research*, 10 (20), pp. 6779-6788. Cited 217 times.
doi: 10.1158/1078-0432.CCR-04-0112

Discover full text View at Publisher

Majumder, P.K., Febbo, P.G., Bikoff, R., Berger, R., Xue, Q., McMahon, L.M., Manola, J., (...), Sellers, W.R.

19 **mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways**

(2004) *Nature Medicine*, 10 (6), pp. 594-601. Cited 673 times.
doi: 10.1038/nm1052

Discover full text View at Publisher

Yu, K., Toral-Barza, L., Discafani, C., Zhang, W.-G., Skotnicki, J., Frost, P., Gibbons, J.J.

20 **mTOR, a novel target in breast cancer: The effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer**

(2001) *Endocrine-Related Cancer*, 8 (3), pp. 249-258. Cited 356 times.
doi: 10.1677/erc.0.0080249

Discover full text View at Publisher

Mondesire, W.H., Jian, W., Zhang, H., Ensor, J., Hung, M.-C., Mills, G.B., Meric-Bernstam, F.

21 **Targeting mammalian target of rapamycin synergistically enhances chemotherapy-induced cytotoxicity in breast cancer cells**

(2004) *Clinical Cancer Research*, 10 (20), pp. 7031-7042. Cited 216 times.
doi: 10.1158/1078-0432.CCR-04-0361

Discover full text View at Publisher

Raymond, E., Alexandre, J., Faivre, S., Vera, K., Materman, E., Boni, J., Leister, C., (...), Armand, J.-P.

22 **Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer**

(2004) *Journal of Clinical Oncology*, 22 (12), pp. 2336-2347. Cited 413 times.
doi: 10.1200/JCO.2004.08.116

Discover full text View at Publisher

Witzig, T.E., Geyer, S.M., Ghobrial, I., Inwards, D.J., Fonseca, R., Kurtin, P., Ansell, S.M., (...), Kaufmann, S.H.

23 **Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma**

(2005) *Journal of Clinical Oncology*, 23 (23), pp. 5347-5356. Cited 399 times.
doi: 10.1200/JCO.2005.13.466

Discover full text View at Publisher

Galanis, E., Buckner, J.C., Maurer, M.J., Kreisberg, J.I., Ballman, K., Boni, J., Peralba, J.M., (...), Walsh, D.J.

24 **Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: A north central cancer treatment group study**

(2005) *Journal of Clinical Oncology*, 23 (23), pp. 5294-5304. Cited 525 times.
doi: 10.1200/JCO.2005.23.622

Discover full text View at Publisher

Atkins, M.B., Hidalgo, M., Stadler, W.M., Logan, T.F., Dutcher, J.P., Hudes, G.R., Park, Y., (...), Sherman, M.L.

25 **Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma**

(2004) *Journal of Clinical Oncology*, 22 (5), pp. 909-918. Cited 799 times.
doi: 10.1200/JCO.2004.08.185

Discover full text View at Publisher

Chan, S., Scheulen, M.E., Johnston, S., Mross, K., Cardoso, F., Dittrich, C., Eiermann, W., (...), Moore, L.

26 **Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer**

(2005) *Journal of Clinical Oncology*, 23 (23), pp. 5314-5322. Cited 368 times.
doi: 10.1200/JCO.2005.66.130

Discover full text View at Publisher

Baker, A.F., Dragovich, T., Ihle, N.T., Williams, R., Fenoglio-Preiser, C., Powis, G.

27 **Stability of phosphoprotein as a biological marker of tumor signaling**

(2005) *Clinical Cancer Research*, 11 (12), pp. 4338-4340. Cited 108 times.
doi: 10.1158/1078-0432.CCR-05-0422

Discover full text View at Publisher

Barlund, M., Monni, O., Kononen, J., Cornelison, R., Torhorst, J., Sauter, G., Kallioniemi, O.-P., (...), Kallioniemi, A.

28 **Multiple genes at 17q23 undergo amplification and overexpression in breast cancer**

(2000) *Cancer Research*, 60 (19), pp. 5340-5344. Cited 150 times.

Discover full text View at Publisher

Gera, J.F., Mellinghoff, I.K., Shi, Y., Rettig, M.B., Tran, C., Hsu, J.-H., Sawyers, C.L., (...), Lichtenstein, A.K.

29 **AKT Activity Determines Sensitivity to Mammalian Target of Rapamycin (mTOR) Inhibitors by Regulating Cyclin D1 and c-myc Expression**

(2004) *Journal of Biological Chemistry*, 279 (4), pp. 2737-2746. Cited 248 times.
doi: 10.1074/jbc.M309999200

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Discover full text View at Publisher

Dong, J., Peng, J., Zhang, H., Mondesire, W.H., Jian, W., Mills, G.B., Hung, M.-C., (...), Meric-Bernstam, F.

30 **Role of glycogen synthase kinase 3β in rapamycin-mediated cell cycle regulation and chemosensitivity**

(2005) *Cancer Research*, 65 (5), pp. 1961-1972. Cited 64 times.
doi: 10.1158/0008-5472.CAN-04-2501

Discover full text View at Publisher

Dong, D., Ko, B., Baumeister, P., Swenson, S., Costa, F., Markland, F., Stiles, C., (...), Lee, A.S.

31 **Vascular targeting and antiangiogenesis agents induce drug resistance effector GRP78 within the tumor microenvironment**

(2005) *Cancer Research*, 65 (13), pp. 5785-5791. Cited 116 times.
doi: 10.1158/0008-5472.CAN-05-0754

Discover full text View at Publisher

Hashemolhosseini, S., Nagamine, Y., Morley, S.J., Desrivières, S., Mercep, L., Ferrari, S.

32 **Rapamycin inhibition of the G1 to S transition is mediated by effects on cyclin D1 mRNA and protein stability**

(1998) *Journal of Biological Chemistry*, 273 (23), pp. 14424-14429. Cited 264 times.
doi: 10.1074/jbc.273.23.14424

Discover full text View at Publisher

Neshat, M.S., Mellinghoff, I.K., Tran, C., Stiles, B., Thomas, G., Petersen, R., Frost, P., (...), Sawyers, C.L.

33 **Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR**

(2001) *Proceedings of the National Academy of Sciences of the United States of America*, 98 (18), pp. 10314-10319. Cited 608 times.
doi: 10.1073/pnas.171076798

Discover full text View at Publisher

Shi, Y., Gera, J., Hu, L., Hsu, J.-H., Bookstein, R., Li, W., Lichtenstein, A.

34 **Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779**

(2002) *Cancer Research*, 62 (17), pp. 5027-5034. Cited 223 times.

Discover full text View at Publisher

Sun, S.-Y., Rosenberg, L.M., Wang, X., Zhou, Z., Yue, P., Fu, H., Khuri, F.R.

35 **Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition**

(2005) *Cancer Research*, 65 (16), pp. 7052-7058. Cited 527 times.
doi: 10.1158/0008-5472.CAN-05-0917

Discover full text View at Publisher

Tabernero, J., Rojo, F., Burris, H.

36 A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors
(2005) *J. Clin. Oncol.*, 23 (16 SUPPL.), p. 193s. Cited 54 times.
(Abstract #3007)

Nagata, Y., Lan, K.-H., Zhou, X., Tan, M., Esteva, F.J., Sahin, A.A., Klos, K.S., (...), Yu, D.

37 **PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients**

(2004) *Cancer Cell*, 6 (2), pp. 117-127. Cited 1136 times.
doi: 10.1016/j.ccr.2004.06.022

Discover full text View at Publisher

DeGraffenried, L.A., Friedrichs, W.E., Russell, D.H., Donzis, E.J., Middleton, A.K., Silva, J.M., Roth, R.A., (...), Hidalgo, M.

38 **Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt activity**

(2004) *Clinical Cancer Research*, 10 (23), pp. 8059-8067. Cited 259 times.
doi: 10.1158/1078-0432.CCR-04-0035

Discover full text View at Publisher

Boulay, A., Rudloff, J., Ye, J., Zumstein-Mecker, S., O'Reilly, T., Evans, D.B., Chen, S., (...), Lane, H.A.

39 **Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer**

(2005) *Clinical Cancer Research*, 11 (14), pp. 5319-5328. Cited 221 times.
doi: 10.1158/1078-0432.CCR-04-2402

Discover full text View at Publisher

(2005)

40 National Institutes of Health [Website]. Available at Accessed: October 9
http://www.clinicaltrials.gov/ct/gui/show/NCT00088393

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— SUPPLEMENT TO —

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2005 ASCO Annual Meeting Proceedings

41st Annual Meeting
May 13-17, 2005
Orange County Convention Center
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2005 Annual Meeting Proceedings Part I

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American Society of Clinical Oncology
41st Annual Meeting

2005 Abstracts

Abstract Session Descriptions for Scheduled Presentations

Oral Abstract Presentation Sessions

Oral Abstract Presentation Sessions include didactic presentations of the abstracts determined by the Scientific Program Committee to be of the highest scientific merit. Experts in the field serve as Discussants to place the findings into perspective. The Plenary Sessions include the abstracts selected by the Scientific Program Committee as having significant findings.

Integrated Education Sessions

Integrated Education Sessions provide a forum for science in oncology, combining the presentation of selected abstracts on a specific topic with didactic lectures. Experts in the field place the studies in the appropriate context based on the strength of the evidence and critically discuss the conclusions in terms of their applicability to clinical practice.

Poster Discussion Sessions

Poster Discussion Sessions highlight selected abstracts of clinical research in poster format. The posters are grouped by topic or by the questions posed as a result of the research findings. The posters are on display for a specified time, followed by a discussion session in which experts provide commentary on the research findings.

General Poster Sessions

General Poster Sessions include selected abstracts of clinical research in poster format. The posters are grouped by topic and are on display for a specified time.

Publication Abstracts

Publish only abstracts were selected to be published in conjunction with the Annual Meeting, but not to be presented at the Meeting.

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2005 Annual Meeting and for publication. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Pocket Program or ASCO.org.

Dates and times are subject to change.
All modifications will be posted on *ASCO.org* (www.asco.org).

Letter from the Editor

The *2005 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) contains more than 2,000 abstracts selected by the ASCO Scientific Program Committee for presentation at the 41st Annual Meeting of the American Society of Clinical Oncology, held May 13-17, 2005, in Orlando, Florida, and more than 1,400 abstracts selected for publication. The abstracts are categorized by scientific track and ordered numerically within each track by presentation type: Plenary; Integrated Education Session; Oral Presentation; Poster Discussion; General Poster; and Publication. The scientific program uses a 500-series classification system (e.g., Plenary abstracts are numbered 1-12; Breast Cancer, 500-999; Cancer Prevention 1,000-1,500). The Table of Contents lists the abstract number ranges for abstracts scheduled for presentation.

This year, ASCO has once again accepted late-breaking abstract submissions for the Meeting. These abstracts feature the results of major phase III trials for which final data were not available at the time of ASCO's regular abstract submission deadline. In order to facilitate Annual Meeting planning, the late-breaking abstract "placeholders"—without the final results and conclusions—are included in this supplement. The final late-breaking abstracts will be included in the *2005 ASCO Annual Meeting Proceedings Part II* (a supplement to the *Journal of Clinical Oncology*), which will be available onsite at the Annual Meeting on Saturday, May 14, 2005, and will be mailed to JCO subscribers with the June 1, 2005, issue of JCO.

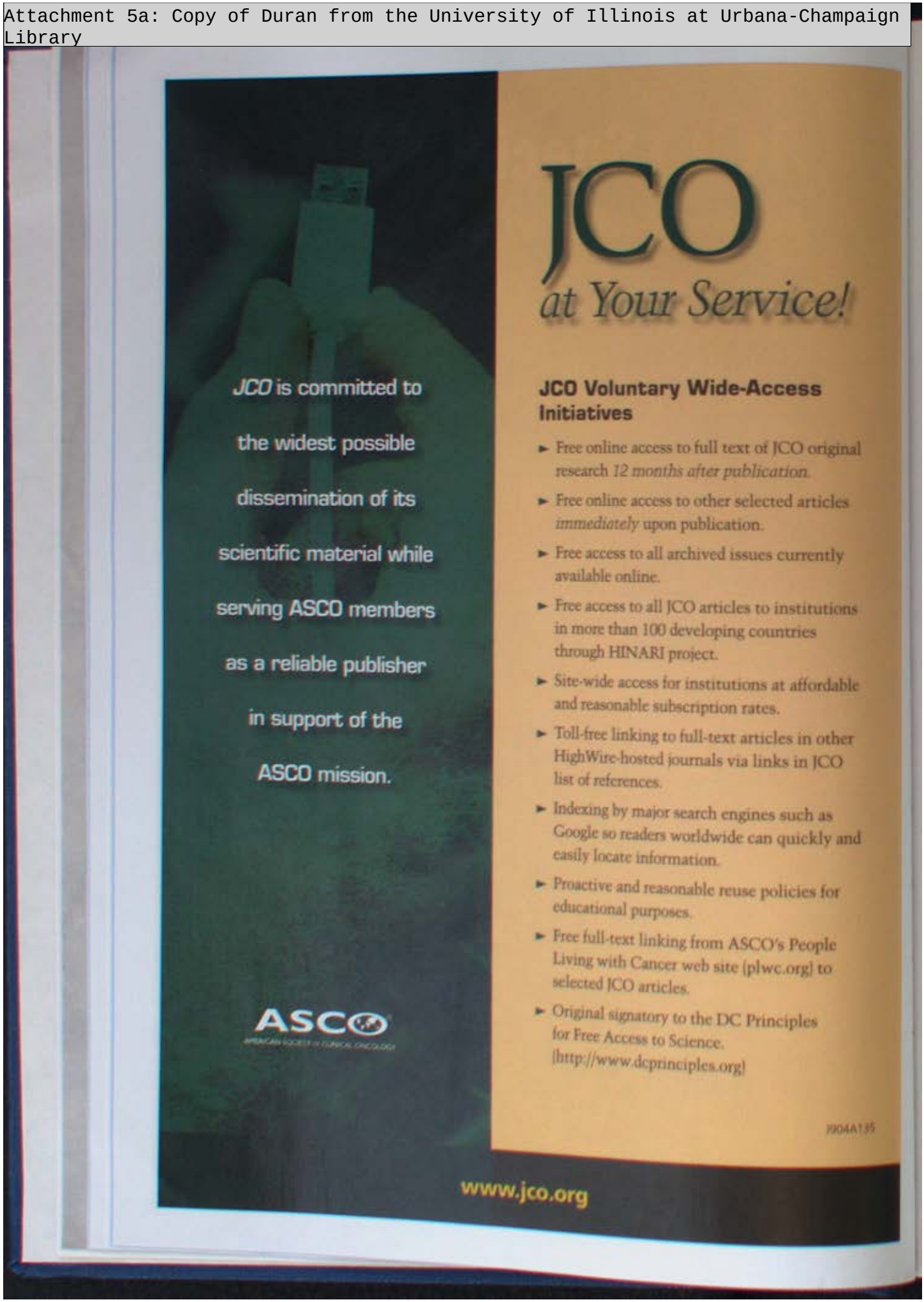
The *2005 ASCO Annual Meeting Proceedings* serves as the publication of record for citation of abstracts. The following is a sample citation:

T. Fama, M. Wood, H. Muss: Patient preferences for adjuvant treatment of early-stage breast cancer. J Clin Oncol 23:61s, 2005 (suppl, abstr 733)

An additional advantage of publishing the *Annual Meeting Proceedings I* and *II* as supplements to JCO is that the abstracts are housed as part of www.jco.org. Readers can search online by keyword, author, etc, not only within the abstracts themselves but also in conjunction with other JCO content. The abstracts are housed additionally on www.asco.org and can be accessed through the Virtual Meeting.

We encourage you, as always, to provide us with any feedback that will augment the quality of information contained in our publications. Should you have any questions or comments about the usefulness, format, and indexes pertaining to the abstracts, please feel free to contact us at abstracts@asco.org.

Steven M. Grunberg, MD
Proceedings Editor



ASCO ABSTRACTS POLICY

ASCO has formalized the following confidentiality policy governing the use of information contained in abstracts of the ASCO *2005 Annual Meeting Proceedings Part I* (a Supplement to the *Journal of Clinical Oncology*), which contains all abstracts to be presented at the 2005 Annual Meeting, all publish-only abstracts, and late-breaking abstract "placeholders" (without final results and conclusions). Abstracts are short, preliminary summaries of research that are used by ASCO to determine whether or not a study is accepted into its Annual Meeting program. These 300 word or less summaries typically include preliminary data that, subsequent to their submission to ASCO, are analyzed in the months leading up to the Annual Meeting. Therefore, these abstracts do not necessarily contain the final results or conclusions that are reported at the Meeting.

In an effort to ensure that premature research data are not publicly reported prior to the scientific review at the Annual Meeting, ASCO has instituted the following confidentiality policy governing the use of the information contained in this publication. The Society's official Embargo Policy, designed to ensure the integrity of the information that is communicated from the ASCO Annual Meeting, is also published below. Both the Confidentiality Policy and the Embargo Policy are in effect until they are lifted, on an abstract-by-abstract basis, as stated in each of the respective policies below.

CONFIDENTIALITY AGREEMENT

The information contained in the ASCO *2005 Annual Meeting Proceedings Part I* (individually, the Abstracts, and collectively, the Proceedings) is confidential information until its public release. Distribution of this information in advance of public release is solely for the purpose of preparing for and planning Annual Meeting activities.

Until the public release of this information, this information must be kept confidential. Specifically, and without limiting the generality of your agreement to maintain the confidentiality of the Abstracts, you agree that:

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- You will not use the information contained in any Abstract for any purpose other than the purpose set forth above, including but not limited to trading in the securities of any issuer or providing the information to others who may use it for securities trading purposes, until after the opening of trading on the second trading day following the date the Abstract is made public at the Annual Meeting or on www.asco.org.

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For purposes of this Confidentiality Agreement, Abstracts are considered to have been made public at the time when the embargo on them has been lifted under the official Embargo Policy below.

ASCO EMBARGO POLICY

All abstracts presented at the Annual Meeting are embargoed until the beginning of the Scientific Session containing the research, with the following exceptions:

- Abstracts in ASCO's Official Press Program: Embargoes lift at the beginning of the News Briefing, or the beginning of the Scientific Session containing the research, whichever comes first.
- Publish-Only Abstracts: For abstracts published in the *2005 ASCO Annual Meeting Proceedings* but not scheduled for presentation, embargoes lift at the official start of the meeting at 1:00 PM (EST) on Friday, May 13, 2005.
- Late-Breaking Abstracts (LBAs): Embargoes on all ASCO-designated LBAs lift at 7:45 AM (EST) on Saturday, May 14, 2005.

3089 **Publication Only**

Flexible dosing schedules of panitumumab (ABX-EGF) in cancer patients. *R. Arends, B. B. Yang, G. Schwab, P. Lockbaum, C. Funelas, L. Roskos; Abgenix, Inc., Fremont, CA; Amgen Inc., Thousand Oaks, CA*

Background Panitumumab is a fully human monoclonal antibody directed against the EGFr. In a Phase 1 trial in patients with colorectal, NSCL, renal, prostate, pancreatic, or esophageal cancer, the optimum weekly dose was determined to be 2.5 mg/kg (Roskos et al, ASCO 2002, Abstract 362). To allow for more convenient dosing, every 2 week (Q2W) or every 3 week (Q3W) dosing intervals were evaluated in the same Phase 1 trial. **Methods:** PK data from weekly doses in the range of 0.1 mg/kg to 5 mg/kg were fitted by a 2-compartment model with elimination of panitumumab occurring simultaneously via a Michaelis-Menten pathway and a first-order linear pathway. This model was used to simulate Q2W and Q3W regimens achieving serum trough panitumumab concentrations around 50 μg/mL, as was measured for the steady-state trough levels at the 2.5 mg/kg weekly dose. The model predicted that the trough concentration after three doses of 6 mg/kg Q2W or 9 mg/kg Q3W would be 53 and 47 μg/mL respectively. Patients were enrolled in 6 mg/kg Q2W (n=17) and 9 mg/kg (n=23) cohorts, with intensive PK sampling after the first and the third doses. **Results** Preliminary results indicate mean (SE) trough concentrations for 6 mg/kg Q2W and 9 mg/kg Q3W regimens after 3 doses were 49 (4) and 45 (8) μg/mL, respectively, consistent with simulations. The inter-individual variability in PK was low in both cohorts at CV ≤ 20%. After a single dose the mean (SD) Cmax was 147 (25) and 227 (45) μg/mL for the Q2W and the Q3W regimen respectively and the mean (SD) AUClast was 853 (173) and 1627 (293) μg*day/mL for the Q2W and the Q3W regimens respectively. Both regimens were generally well tolerated with a safety profile comparable to 2.5 mg/kg weekly. **Conclusion** Panitumumab administered at 6 mg/kg Q2W or 9 mg/kg Q3W resulted in exposure and tolerability profiles comparable to 2.5 mg/kg weekly, demonstrating the ability to dose panitumumab flexibly for enhanced patient convenience. Panitumumab exhibited predictable PK, with low inter- and intra-patient variability.

3090 **Publication Only**

Dose escalation and pharmacokinetic (pk) study of E 7389, a microtubule-binding drug in patients (pts) with advanced solid tumors. *K. K. Desai, S. Goel, A. Mita, S. Silberman, J. Sicam, S. Woeppel, M. Macapinlac, K. Berg, E. Rowinski, S. Mani; Albert Einstein Cancer Ctr; Montefiore Medcl Ctr, Bronx, NY; Cancer Treatment and Research Ctr, San Antonio, TX; Eisai Medcl Research, Ridgefield Park, NJ; Jacobi Medcl Ctr; Albert Einstein Cancer, Bronx, NY*

Background: E7389 is a synthetic analog of halichondrin B, which was isolated from the marine sponge *Halichondria okadai*. It has a unique profile of tubulin interactions and exhibits broad anti-proliferative activity at nanomolar concentrations. We performed a phase I study using a weekly infusional schedule for 3 weeks with a week rest. **Methods:** Patients (pts) at two centers were treated using an accelerated titration design with intra-patient dose escalation, and switched to a standard escalation upon observation of a dose limiting toxicity (DLT). E7389 was administered on days 1, 8 and 15 as a 1-hour intravenous infusion every 28 days (1 cycle) in 5 dose cohorts at doses ranging from 0.25-1.4 mg/m^2. Pts underwent extensive PK sampling on days 1 and 15 of the first cycle. **Results:** 23 pts were enrolled: median (range) age was 56 (34-78) years and they received 50 (1-6) cycles. Overall performance status was ≥ 80% and diagnoses consisted of colon (5), lung (3), cervical (2), ovarian (2), or other (11). DLT (grade 3 fatigue) was observed in one patient at 0.5 mg/m^2, resulting in expansion of the cohort. At the highest dose level tested (1.4 mg/m^2), 3 patients developed grade 3/4 neutropenia, resulting in missed doses, and were considered DLTs based on protocol criteria (see table below). One pt died of interstitial pneumonitis after two cycles at 1 mg/m^2. No other toxicity ≥ grade 3 was observed in this trial. Of the 12 pts evaluable for response, 1 (cervical cancer) had a partial response and another (uterine cancer) had stable disease for > 8 cycles. **Conclusion:** In this weekly regimen of E7389 every 4 weeks, neutropenia was the DLT at the 1.4 mg/m^2 dose level. Alternative schedules of infusion to explore better hematological tolerability are planned. PK data and updated safety and efficacy will be presented.

Dose level	Dose mg/m2	# cycles	# patients	# DLT/evaluable patients
1	0.25	2	2	0/2
2	0.5	19	6	1/7 (fatigue)
3	0.7	13	4	0/4
4	1.0	7	3	0/3
5	1.4	9	6	3/5 (neutropenia)

3091 **Publication Only**

Suicide gene therapy using adenovirus encoded nitroreductase and CB1954 in patients with locally relapsed prostate cancer. *P. Patel, V. Mautner, P. F. Searle, J. G. Young, D. Hull, J. Ellis, D. M. A. Wallace, H. Y. Leung, L. S. Young, N. D. James; Univ of Birmingham, Birmingham, United Kingdom; ML Labs PLC, Leicestershire, United Kingdom; Univ Hosp, Birmingham, Birmingham, United Kingdom; Univ of Newcastle, Newcastle Upon Tyne, United Kingdom*

Background: Bacterial nitroreductase (ntr) converts the weak monofunctional alkylating agent CB1954 into a highly cytotoxic bifunctional alkylating agent effective in replicating and quiescent cells. We have previously reported phase I safety and biodistribution studies using intraprostatic injection of a replication defective adenovirus encoding ntr (CTL102). Immunohistochemistry of resected prostate demonstrated dose-related ntr staining in tumour, glandular epithelium and stroma. Increasing the injection volume achieved more widespread ntr expression. We now report a phase I clinical trial in prostate cancer using direct intraprostatic injection of CTL102 + intravenous prodrug CB1954. **Methods:** Patients with biopsy-confirmed local disease and rising PSA underwent 4 TRUS-guided intraprostatic injection of CTL102 in escalating total doses, from $5x10^{10}$ to $1x10^{12}$ particles with iv CB1954 24mg/m^2 48 hours post injection. Primary endpoints were safety and tolerability; secondary endpoints were efficacy by PSA & biopsy. **Results:** 11 patients with biopsy-confirmed locally relapsed PCa have been treated with virus and prodrug combination (virus particle dose $5x10^{10}$ n=3, 10^{11} n=3, $5x10^{11}$ n=3, 10^{12} n=2). Both virus and prodrug injections were well tolerated with no significant toxicity apart from a transient transaminitis at day 8 in 7 patients and mild lymphopenia at day 1 in 9 patients. 10 patients had flu-like symptoms at week one. At month 3, 3/8 patients had stable disease and a further 2/8 patients had a PSA reduction of >10% without any additional treatment from baseline. Mean time to PSA progression (>10% rise in PSA from baseline) was 20.6 weeks (95%CI 13.4, 27.8). Two-thirds of patients remain PSA progression free at 6 months. **Conclusions:** Direct intraprostatic injection of CTL102 followed by iv CB1954 is feasible and safe. Dose limiting toxicity has not been observed; although efficacy has been a secondary endpoint, there are some encouraging initial results and a further study is underway.

3092 **Publication Only**

A phase II study of imatinib mesylate in prostate cancer patients with evidence of biochemical relapse following definitive radical retropubic prostatectomy or radiation therapy. *G. K. Bajaj, E. Garrett-Mayer, R. Drew, V. J. Sinibaldi, M. Gaver, R. Pili, S. Denmeade, M. A. Carducci, M. Eisenberger, T. L. Deweese; Johns Hopkins Hosp, Baltimore, MD*

Background: Biochemical recurrence of prostate cancer after definitive or salvage local therapy in the absence of metastatic disease represents a group of men well suited for a novel therapeutic intervention. Imatinib mesylate (Gleevec) is a protein-tyrosine kinase inhibitor which has previously been tested in men with androgen-independent and metastatic prostate cancer. This phase II study was undertaken to determine the safety and efficacy of imatinib mesylate in men with biochemical relapse of non-metastatic, androgen-sensitive prostate cancer following local therapy. Patients and **Methods:** Twenty-seven patients were treated with imatinib mesylate 400mg twice daily for 12 months or until evidence of disease progression or dose limiting toxicity. All patients had evidence of biochemical progression with a rising PSA after definitive radiation therapy, prostatectomy, or prostatectomy and salvage radiation therapy. Three patients (11%) completed less than 4 weeks of therapy and were not evaluable. **Results:** Of the 24 patients evaluated for a biochemical response, six patients (22%) demonstrated a stable PSA over the course of treatment; two patients (7%) experienced a partial response to treatment as defined by a PSA decline of greater than 50% for at least 4 weeks duration. Duration of response in these two patients was 5 months and 12 months. Sixteen patients (59%) demonstrated progressive disease as defined by a 25% or greater increase in PSA above the baseline value at study entry. There was no association between overall PSA response and changes in serum testosterone level. The proportion of patients achieving a partial response in PSA while on therapy did not significantly differ from the null rate of 5% using a two-sided exact binomial test (P=0.394; 95% CI 0.9% - 24.3%). There was no irreversible NIH-CTC Grade 3 or 4 toxicities. Grade 3 and 4 toxicity included leukopenia (3.7%), elevation in SGOT (7.4%) and SGPT (7.4%), and rash (18.5%). **Conclusions:** Imatinib mesylate delivered at a dose of 400mg twice daily is associated with acceptable toxicity and limited ability to confer a PSA response in this patient population.

3093 **Publication Only**

Tariquidar (XR9576) is a potent and effective P-glycoprotein (Pgp) inhibitor but can be administered safely with chemotherapy. *M. E. Menefee, C. Fan, W. Edgerly, D. Draper, C. Chen, R. Robey, F. Balis, W. D. Figg, S. Bates, A. T. Fojo; NIH/NCI, Bethesda, MD*

Background: Inhibition of P-glycoprotein (Pgp) as a means to improve chemotherapeutic efficacy remains a valid but unproven hypothesis. Two recent trials in patients with lung cancer using the Pgp inhibitor, tariquidar (XR9576), closed prematurely due to toxicity concerns. We report our experience using tariquidar with chemotherapy. **Methods:** Patients with refractory or metastatic adrenocortical cancer (ACC) received tariquidar on days 1 & 3 with a 96-hour infusion of doxorubicin, vincristine, and etoposide with mitotane (X-MAVE) every 21 days. Patients with refractory ovarian, cervical & lung cancer received tariquidar with a docetaxel infusion every 21 days. Study participants had two ^{99m}Tc-sestamibi scans. Time-activity curves were generated and areas under the curve calculated to compare ^{99m}Tc-sestamibi accumulation at baseline to that 1 h after tariquidar. Rhodamine efflux from CD56+ cells was measured before and after tariquidar to assess Pgp inhibition. **Results:** To date, 15 patients with ACC have received 71 cycles of X-MAVE, and 16 patients with ovarian, cervical or lung cancer have received 66 cycles of docetaxel. Grade 3 non-hematologic toxicities (# of cycles) observed with X-MAVE include: abdominal pain/constipation (4), arthralgia (4), nausea/vomiting (2), diarrhea (1), esophagitis (1), fatigue (6), hand-foot reaction (1), and hyponatremia (3); those with docetaxel include: diarrhea (1), dyspnea (1) fatigue (6), hyponatremia (3), pain (3) and tearing (2). ^{99m}Tc-sestamibi accumulation increased 39 to 129%, compared to a mean increase of 106% in the liver, in 6 of 8 patients with ACC whose lesions could be visualized. Quantitation for the 10 such patients with ovarian, cervical or lung cancer is ongoing. Rhodamine efflux from CD56+ cells assayed in 30 patients was reduced by a mean of 85% after tariquidar and was sustained even after 48 h. Pharmacokinetic sampling before and after tariquidar has been performed. **Conclusions:** Tariquidar is a potent and highly effective Pgp inhibitor that can be administered safely with a combination of doxorubicin, etoposide and vincristine or with docetaxel. The efficacy in patients with refractory cancers continues to be evaluated.

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Background: The thioxanthone analog, SR271425, is a novel cytotoxic DNA-interacting agent with a broad spectrum of antitumor activity in preclinical murine tumor models. This clinical trial aims to determine tolerability and toxicities of SR271425 as a 1-hour single intravenous dose repeated weekly for 2 weeks followed by 1 week rest, to determine the maximum tolerated dose (MTD), recommended phase II dose (RPIID), and to assess its pharmacokinetic profile. **Methods:** A modified Fibonacci dose escalation design is being used. A single intravenous dose of SR271425 is administered over 1-hour weekly for 2 weeks, followed by 1 week rest, in a variety of refractory solid tumors. Of note, in the rabbit model, QTc prolongation, related to Cmax, has been reported at doses >660mg/m^2. Therefore, all patients are undergoing cardiology assessment with serial ECGs, which are assessed by a central reviewer. **Results:** To date, 17 patients have been treated at 5 dose levels (ranges, 64–675 mg/m^2/week). The mean age is 53 (range 24 -74 years) and ECOG performance status is 0–2. Grade 1–2 toxicities including QTc prolongation, nausea/vomiting/constipation, and fatigue have been observed. The pharmacokinetics of SR271425 following weekly dosing were consistent with that observed previously in a single dose ascending study with SR271425. Both Cmax and AUC (day 1) increased in a dose dependent manner. As would be predicted from the drugs short half-life (6.7 h), no systemic accumulation was observed as assessed by Cmax and C_{ss} values on Day 1 versus Day 8. Stable disease has been observed in 3 patients. **Conclusions:** Preliminary data on this ongoing study suggests that SR271425 administered at split, weekly doses will likely allow greater cumulative exposure without significant toxicity.

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Letter from the Editor

The *2005 ASCO Annual Meeting Proceedings Part I* (a supplement to the *Journal of Clinical Oncology*) contains more than 2,000 abstracts selected by the ASCO Scientific Program Committee for presentation at the 41st Annual Meeting of the American Society of Clinical Oncology, held May 13-17, 2005, in Orlando, Florida, and more than 1,400 abstracts selected for publication. The abstracts are categorized by scientific track and ordered numerically within each track by presentation type: Plenary; Integrated Education Session; Oral Presentation; Poster Discussion; General Poster; and Publication. The scientific program uses a 500-series classification system (e.g., Plenary abstracts are numbered 1-12; Breast Cancer, 500-999; Cancer Prevention 1,000-1,500). The Table of Contents lists the abstract number ranges for abstracts scheduled for presentation.

This year, ASCO has once again accepted late-breaking abstract submissions for the Meeting. These abstracts feature the results of major phase III trials for which final data were not available at the time of ASCO's regular abstract submission deadline. In order to facilitate Annual Meeting planning, the late-breaking abstract "placeholders"—without the final results and conclusions—are included in this supplement. The final late-breaking abstracts will be included in the *2005 ASCO Annual Meeting Proceedings Part II* (a supplement to the *Journal of Clinical Oncology*), which will be available onsite at the Annual Meeting on Saturday, May 14, 2005, and will be mailed to JCO subscribers with the June 1, 2005, issue of JCO.

The *2005 ASCO Annual Meeting Proceedings* serves as the publication of record for citation of abstracts. The following is a sample citation:

T. Fama, M. Wood, H. Muss: Patient preferences for adjuvant treatment of early-stage breast cancer. J Clin Oncol 23:61s, 2005 (suppl, abstr 733)

An additional advantage of publishing the *Annual Meeting Proceedings I* and *II* as supplements to JCO is that the abstracts are housed as part of www.jco.org. Readers can search online by keyword, author, etc, not only within the abstracts themselves but also in conjunction with other JCO content. The abstracts are housed additionally on www.asco.org and can be accessed through the Virtual Meeting.

We encourage you, as always, to provide us with any feedback that will augment the quality of information contained in our publications. Should you have any questions or comments about the usefulness, format, and indexes pertaining to the abstracts, please feel free to contact us at abstracts@asco.org.

Steven M. Grunberg, MD
Proceedings Editor

3093 **Publication Only**

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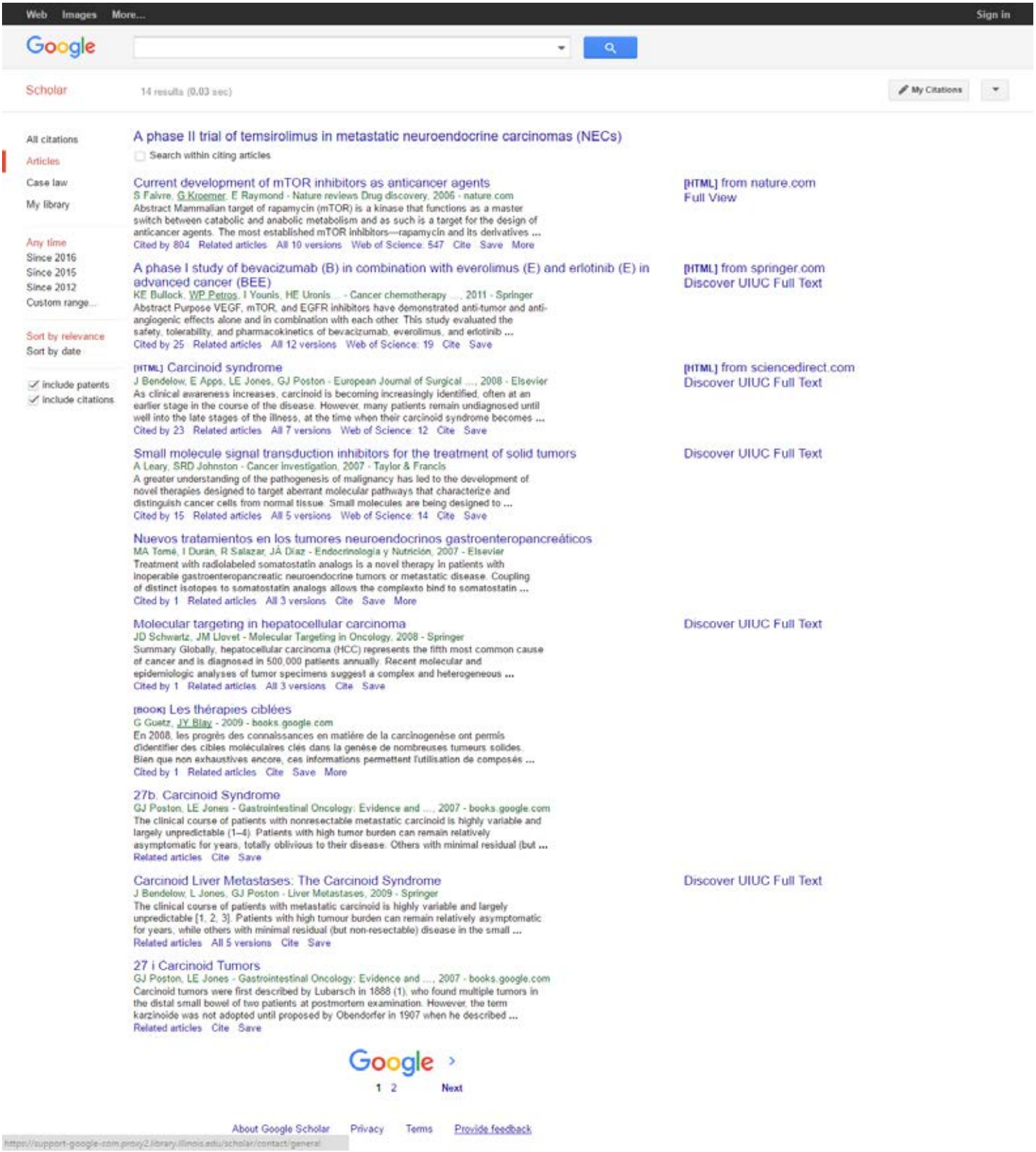
Attachment 5c: Google Scholar list of documents citing Duran



УДК 616.8-006-085

СОВРЕМЕННЫЕ ПОДХОДЫ ЛЕКАРСТВЕННОГО ЛЕЧЕНИЯ ГЕНЕРАЛИЗОВАННЫХ ФОРМ НЕЙРОЭНДОКРИННЫХ ОПУХОЛЕЙ. СИМПТОМАТИЧЕСКАЯ ТЕРАПИЯ СИНДРОМОВ ПРИ НЕЙРОЭНДОКРИННЫХ НЕОПЛАЗИЯХ

ГУН НИИ онкологии им. проф. Н.Н.Петрова, Санкт-Петербург

Р.В. Орлова, А.В. Новик

Нейроэндокринные опухоли представляют собой гетерогенную группу заболеваний, что требует дифференцированного подхода к их лечению.

Нейроэндокринные опухоли (НЭО) – гетерогенная группа новообразований, происходящих из эндокринного эпителия эктодермы [4], который представлен в различных органах и тканях человека (легкие, гипофиз, поджелудочная железа, печень и т.д.). Для данного типа опухолей важное значение в клинической картине играет не только наличие опухоли как объемного образования, но и её воздействие на различные системы организма путем секреции биологически активных веществ – аминов и полипептидов, обладающих функцией гормонов. В настоящее время в установлении нейроэндокринного происхождения опухоли ведущую роль играет иммуногистохимическая характеристика (нейрон-специфическая энолаза, хромогранин А, синаптофизин) и обнаружение в клетках специфических продуктов секреции. Ввиду различной функциональной активности данных опухолей (могут быть функционально активными и неактивными), различии в естественной истории их роста и возможностях их лечения по последней морфофункциональной классификации ВОЗ выделяют следующие группы НЭО [8].

1. Высокодифференцированные НЭО (доброкачественные или низкой. степени злокачественности).
2. Низкодифференцированные (мелкоклеточные) карциномы.
3. Смешанные экзокринно-эндокринные карциномы.

Первая группа характеризуется низким пролиферативным потенциалом, способностью секретировать разнообразные биологически активные вещества и низкой чувствительностью к химиотерапии. К данной группе могут быть отнесены:

– карциноиды (К) различного происхождения (эмбриогенетически развивающиеся в производных передней, средней и задней кишки),
– опухоли из хромаффинных клеток (феохромоцитома),
– медуллярная карцинома щитовидной железы.

Вторая группа представлена высокозлокачественными опухолями с высоким пролиферативным потенциалом, чувствительными к химиотерапии и лучевой терапии. К этой группе может быть отнесен мелкоклеточный рак лёгкого (МЛР).

Для третьей группы характерно наличие клеток как с экзокринной, так и с эндокринной секреторной функцией. К ней относятся различные опухоли поджелудочной железы (ОПЖ); исключение составляют карциноиды. Чувствительность к химиотерапии у данного типа опухолей умеренная [8].

Учитывая системное воздействие опухоли на организм, при лечении НЭО необходимо обращать особое внимание на лечение симптомов заболевания, так как одной из основных целей терапии любой диссеминированной опухоли является увеличение продолжительности качественной жизни.

Ввиду чрезвычайной схожести терапевтических подходов к лечению НЭО в каждой из указанных групп целесообразно рассмотреть терапию наиболее часто встречающихся представителей данного типа неоплазий, а также симптоматической терапии ряда паранеопластических синдромов и дистантных проявлений НЭО.

Противоопухолевое лечение Высокодифференцированные НЭО

Карциноиды

Учитывая в целом индолентное течение данной опухоли (хотя в некоторых случаях возможно и достаточно агрессивное её поведение), хирургический подход в настоящее время остаётся основным даже при распространенных формах НЭО. Всем пациентам, у которых возможно удаление опухоли, необходимо проводить операцию [7, 8]. В данном случае циторедуктивные вмешательства позволяют, наряду с контролем симптомов и повышением качества жизни, увеличить длительность ремиссии и улучшить прогноз [8].

Отдельно необходимо остановиться на лечении поражений печени при карциноидах. Это связано с высокой частотой метастатического поражения данного органа и резким ухудшением прогноза у этой группы больных. Эмболизация и химиоэмболизация метастазов, радиочастотная абляция и криодеструкция, как в сочетании с системной терапией, так и без таковой, показали свою целесообразность в некоторых исследованиях. По данным, обобщенным G.A. Kaltsas [8], локальные методы воздействия на метастазы в печени позволяют достичь регресса карциноида в 35–80 % случаев, при этом контроль симптомов достигается у 50–100 % больных, причем, даже в тех случаях, когда опухоль полностью не удалена.

Дистанционная лучевая терапия, с учетом низкой пролиферативной активности неоплазий данной группы, оказалась неэффективной [8].

Наряду с локальными методами воздействия на опухоль, безусловный приоритет в лечении диссеминированного карциноида остаётся за системной терапией. На протяжении последних 20 лет активно изучалась эффективность цитостатиков и их комбинаций. Результаты этих исследований приведены в табл. 1.

Таблица 1

Активность цитостатиков в лечении нейроэндокринных опухолей [1, 6–9, 12]

Препарат	Частота объективного ответа (%)		
	Карциноид	НЭО поджелудочной железы	Мелкоклеточный рак
Монотерапия			
Доксорубицин	21	20	25
Фторурацил	26		
Дакарбазин	16–29	9	
Препараты платины	7	9	63
Алкилирующие агенты (циклофосфамид, ифосфамид)	9	10	22–57
Этопозид	5	6	82
Стрептозотоцин	30	36–54	Нет данных
Винкаалкалоиды	Нет данных	Нет данных	26–40
Таксаны	0–11		22–45
Иринотекан	Нет данных		50
Топотекан			39–75
Гемцитабин			27
Полихимиотерапия			
Стз+F	3–40	45–68	Нет данных
Стз+С	26		
Стз+А	40	20–69	
Интерферон-альфа + F	7	14	
Д+F	11		
CCNU+F	17	40	
Д+эпирубицин+ F	10	26,7	
F+A+P	10	20	
Стз+С+F	22		
Стз+С+F+А	30		
Стз+А + интерферон-альфа	10–30%		
EP	0	14	62–63
Топ+ Е	Нет данных		14–55
EP + Тр			50
EP, чередующийся с Топ+Тр			77 (62–89)
P+Топ			73 (39–94)
EP + Г			72,2 (56,5–85,0)
Рс+Тр+Н			71
EP, чередующийся с Топ			64 (48–79)
EP+К			77–84
Топ+Тр			28–77

Сокращения: А – доксорубицин, Е – этопозид, Стз – стрептозотоцин, Р – цисплатин, Рс – карбоплатин, Тр – паклитаксел, Топ – топотекан, Н – ифосфамид, F – фторурацил, Д – дакарбазин, К – иринотекан, С – циклофосфамид, Г – гемцитабин.

Как видно из приведенной таблицы, эффективность монотерапии колеблется в пределах 0–30%. Однако и полихимиотерапия не показала никаких преимуществ перед ней. Необходимо отметить, что недостаточная чувствительность к химиотерапии характерна для большинства НЭО высокой степени дифференцировки. Лишь при лечении некоторых опухолей этой группы полихимиотерапия позволяет достичь удовлетворительных результатов. Так, стандартом лечения крупноклеточного нейроэндокринного рака лёгкого являются схемы на основе препаратов платины [8].

С введением в клиническую практику аналогов соматостатина и интерферонов началась новая эра в лечении карциноида. Активность данных препаратов представлена в табл. 2. В рандомизированных исследованиях, показано, что биотерапия позволяет увеличить как выживаемось больных, так и качество их жизни, поскольку позволяет контролировать симптомы заболевания практически у всех пациентов [8].

Достаточно высокая клиническая эффективность биотерапии по сравнению с химиотерапией объясняется двояким механизмом действия: с одной стороны, блокированием активности веществ, продуцируемых опухолью, что позволяет контролировать симптомы заболевания, с другой стороны, активацией апоптоза (аналогами соматостатина) и повышением активности bcl-2 (производными интерферона), что обеспечивает туморостатический эффект [7].

К сожалению, исследования первых препаратов этой группы, таких как соматостатин, показали возможность развития резистентности к терапии [8]. В первую очередь это связывают с изменением функционирования рецепторов соматостатина в опухолевых клетках. В целом, повышение доз препарата не приводит к преодолению этого эффекта. Данное явление наблюдается в среднем через 12 мес от начала терапии, что безусловно требует её изменения. Другим недостатком соматостатина является быстрое выведение его из организма, что приводит к необходимости введения препарата 3 и более раз в день. В настоящее время созданы аналоги более длительного действия, такие как лартреотид и SOM-230. Их использование позволяет применить большие дозы препарата при более редком его введении, что дает возможность преодолевать или предотвращать резистентность к терапии [8]. Рандомизированные исследования показали отсутствие различий между указанными лекарствами и соматостатином по эффективности, что делает данную терапию наиболее привлекательной в настоящее время [14].

Преимущество комбинации соматостатина и интерферона-альфа перед монотерапией этими препаратами изучалось во многих исследованиях. В первых работах по изучению комбинации данных препаратов были получены многообещающие результаты. Однако в последующих рандомизированных исследованиях они не подтвердились. Интересно отметить, что, несмотря на отсутствие различий в показателях выживаемости, контроля за симптомами заболевания и противоопухолевой эффективности, в исследовании L. Kolby и соавт. [10] показано снижение риска прогрессирования опухоли при применении комбинации интерферона и соматостатина. Учитывая гораздо менее выгодный профиль токсичности интерферона, необходимость более частого введения препарата (еженедельно для пегелированного интерферона и 1 раз в месяц для пролонгированных форм аналогов соматостатина) и отсутствие перекрёстной резистентности между указанными лекарственными средствами, интерферон остается препаратом выбора для второй линии терапии карциноида.

Таким образом, при карциноиде стандартом терапии является применение соматостатина 200–400 мг/сут или его аналогов, например, лартреотида аутогеля 120 мг ежемесячно, соматостатина-ЛАР 30–60 мг 1 раз в 3–4 нед. Для интерферона оптимальной дозой является 3–9 млн. МЕ ежедневно или через день или (в случае пегелированных форм) 90–100 мкг в неделю [8].

Низкая противоопухолевая активность всех вышеперечисленных препаратов стимулировала поиск путей повышения её эффективности. Но ни комбинированная химиотерапия, ни иммунотерапия, ни химиоиммунотерапия не улучшили результаты лечения [7]. Повышение доз биотерапевтических агентов, хотя и позволяло улучшить контроль симптомов, но не реализовалось в увеличении выживаемости или частоты регрессов опухоли [8].

Многообещающие результаты предоставляет системная лучевая терапия выскодифференцированных НЭО. Использование радиоиодина при опухолях щитовидной железы привело к созданию нескольких препаратов, механизм действия которых основан на захвате опухолью вещества, меченного радиоактивным изотопом. Эффективность данных препаратов представлена в табл. 3.

Активно изучающиеся в настоящее время ингибиторы сигнальной трансдукции показали свою активность в лечении карциноида. В исследованиях, представленных на ASCO в 2005 г., M. Kulke и соавт. [11] и I. Duran и соавт. [5] показали противоопухолевую активность SU11248- поливалентного ингибитора EGFR, c-kit и PDGF и темзиро-

Таблица 2

Эффективность биотерапии при нейроэндокринных опухолях

Препарат	Объективный ответ (%)/симптоматический эффект	
	Карциноид	НЭО поджелудочной железы
Интерферон-альфа	0–22/50–80	0–50/70
Октреотид	0–16/60–90	0–17/70
Ланреотид	0–8/40–90	Нет данных
Интерферон-альфа + октреатид	0/100	
Интерферон-альфа + гамма	0/50	

Таблица 3

Эффективность системной лучевой терапии у больных НЭО [8]

Препарат	Объективный ответ, %	
	Карциноид, НЭО поджелудочной железы	РЩЖ
^{131}*I-MIBG*	15	24
^{111}*In* Октреотид	27	Не исследовались
^{90}*Y* Октреотид	23	
^{90}*Y* лартреотид	20	
[^{177}*Lu-DOTA Tyr*^{3}]-*октреатид*	39	

Примечание. РЩЖ – медуллярный рак щитовидной железы.

лимуса – ингибитора mTOR. Перспективным также представляется изучение препарата соматостатина, конъюгированного с доксорубицином, однако результатов клинических исследований этого препарата нет [8].

Медуллярная опухоль щитовидной железы

Относясь к высокодифференцированным опухолям, медуллярный рак щитовидной железы обладает теми же особенностями, что и другие представители этой группы. Хирургический метод является основным не только при первичной опухоли, но и при местном рецидиве заболевания. Как и при карциноиде, эффективность монотерапии колеблется от 0 до 30%. Преимущество при этом отдается терапии с использованием доксорубицина. Химиотерапия не приводит к увеличению выживаемости, однако, позволяет у отдельных больных получить длительные ремиссии. Системная лучевая терапия с использованием метайодбензилгуанидина (табл. 3) обладает гораздо большей эффективностью, позволяя достичь клинически значимых результатов (регресс или стабилизация опухоли, контроль симптомов) у большинства пролеченных больных [8].

Хромаффинные опухоли

Данный тип НЭО имеет некоторое сходство с опухолями нервной ткани, такими как нейробластома, в связи с чем имеются различия в терапии представителей данной группы. Чрезвычайно важным аспектом терапии является симптоматическое лечение сопутствующих симптомов. Вся другая терапия должна проводиться в сочетании с использованием подобных препаратов [8].

Хирургический метод лечения является основным даже при диссеминированном процессе. Циторедуктивные операции позволяют не только достичь лучшего контроля за симптомами заболевания, но и в ряде случаев увеличивают эффективность последующего системного лечения.

Схожесть опухоли с нейробластомой привела к попытке применения химиотерапии, такой как CVD (циклофосфамид, винкристин и дакарбазан). В обзоре, представленном G.A. Kaltas и соавт. [8], приведены результаты нескольких исследований по оценке эффективности этой комбинации. И, хотя количество наблюдений крайне незначительно, можно говорить об умеренной противоопухолевой активности (около 50%) и высоком значении лечения по контролю симптомов заболевания.

Значимое место в лечении также занимает системная лучевая терапия (табл. 3) с использованием препарата метайодбензилгуанидина (*^{131}I-MIBG*) [8].

2. Низкодифференцированные и недифференцированные опухоли

Мелкоклеточный рак

К данному типу относятся высокоагрессивные, интенсивно пролиферирующие опухоли. Для них проявления самой опухоли выходят на первое место в клинической картине, хотя отдаленные симптомы также встречаются довольно часто. Важной характеристикой этих опухолей является раннее метастазирование, высокая частота поражения головного мозга. Большинство из данных заболеваний высокочувствительны к химиотерапии. Наиболее ярким представителем данной группы опухолей является мелкоклеточный рак лёгкого. Основные принципы его терапии могут быть распространены и на другие локализации низкодифференцированных и недифференцированных НЭО, в том числе с неясной первичной локализацией очага [8, 12].

Многочисленные клинические исследования, проведенные после внедрения в практику препаратов платины, позволили выбрать комбинированную терапию на основе этих препаратов стандартом лечения. Метаанализ, обобщивший 18-летний опыт применения этих комбинаций [3], показал не только высокий уровень объективных ответов, но и явные преимущества в выживаемости больных. Изучение новых цитостатиков и их комбинаций со стандартной химиотерапией в настоящее время не показали значимых преимуществ по сравнению с существующим лечением. В настоящее время активно ведётся поиск новых схем терапии. Большие надежды возлагаются на использование такого препарата, как иринотекан.

Как и при многих других онкологических заболеваниях, при мелкоклеточном раке изучался путь интенсификации лечения больных. В исследованиях, обобщенных Tjan-Heijnen и соавт. в 2002 г., а затем Ardizzoni и соавт. в 2003 г., рассматривались следующие аспекты интенсификации терапии: 1) повышение интенсивности

дозы – уменьшение продолжительности интервалов между циклами; 2) повышение дозы препаратов – высокодозная терапия с поддержкой стволовыми клетками и 3) увеличение количества циклов; 4) комбинация этих подходов. Было показано, что определяющим для увеличения показателей выживаемости является количество циклов химиотерапии (6 лучше, чем 3; выживаемость увеличивается на 3 мес). Исследования по повышению интенсивности дозы были противоречивы. Учитывая токсичность высокодозных режимов и отсутствие достоверной разницы в отдаленных результатах лечения, эта химиотерапия не рекомендуется для лечения подобных заболеваний [6]. В настоящее время данный подход остаётся сугубо экспериментальным и его дальнейшие перспективы неясны.

Отдельную задачу представляет собой терапия метастатического поражения головного мозга при мелкоклеточной НЭО. Анатомо-физиологические особенности головного мозга, такие как ограниченный объем пространства внутри черепной коробки, наличие гематоэнцефалического барьера и многочисленных функционально и жизненно важных зон, обусловливают резкое ухудшение прогноза пациентов и ставят лечение этих поражений первоочередной задачей. В случае наличия единичных удалимых поражений хирургический подход целесообразен и желателен. При множественном поражении головного мозга возможна неполная циторедукция с последующей лучевой терапией или/и химиотерапией [6]. Несмотря на то, что при метастатическом поражении значительно повышается проницаемость гематоэнцефалического барьера для цитостатиков [13], по нашему мнению, предпочтительнее использовать препараты, проникающие через него (ломустин, темозоламид, тениопозид). Особо следует подчеркнуть важность профилактического облучения головного мозга при полном регрессе опухоли, поскольку, по результатам метаанализа нескольких рандомизированных исследований, такой подход продлевает жизнь больных [15].

Дистанционная лучевая терапия занимает важное место в лечении низкодифференцированных и недифференцированных НЭО в отличие от высокодифференцированных,. При диссеминированном процессе её можно проводить как на зоны остаточной опухоли, так и на метастазы, особенно в головном мозге. Достаточно широкое распространение получило сочетание химиотерапии с лучевой терапией, когда после нескольких циклов лекарственного лечения проводятся сеансы облучения, после чего химиотерапия возобновляется.

3. Смешанные экзокринно–эндокринные карциномы

НЭО поджелудочной железы

Как и при других НЭО, локальные методы играют важную роль в лечении данного типа опухолей, так как циторедуктивные операции и химиоэмболизация позволяют достичь удовлетворительных результатов лечения [8]. Химиотерапия позволяет у большинства больных контролировать симптомы заболевания, при этом у половины из них наблюдается регресс опухоли (табл.1). Наиболее приоритетными режимами являются комбинации стрептозотоцина или любого производного нитрозомочевины с доксорубицином или фторпиримидинами. Биотерапия с использованием аналогов соматостатина также эффективна у данной группы больных и в целом используется как стандарт терапии [8] наряду с применением симптоматического лечения, речь о котором пойдет ниже.

Симптоматическое лечение

Паранеопластические синдромы

Паранеопластические синдромы – симптомокомплексы, возникающие под воздействием опухоли вследствие ряда причин [2]:

– продукции опухолью биологически активных веществ (по этому признаку НЭО делятся на гормонально-активные и неактивные),

– снижения уровня существующих веществ, что приводит к возникновению патологических симптомов,

– ответа организма пациента на наличие опухолевого процесса.

В табл. 4 представлены некоторые из указанных симптомов [2, 8], ассоциированных с НЭО, и их лечение. Основной терапией для всех указанных состояний является лечение первичной опухоли, которое позволяет успешно контролировать симптомы заболевания.

Таблица 4

Паранеопластичесеие синдромы, ассоциированные с НЭО

Синдром	Опухоль	Симптомы	Лечение (в дополнение к терапии первичной опухоли)
Синдром эктопической продукции АКТГ (синдром Кушинга)	Мелкоклеточный рак	Миопатия, слабость, снижение мышечной массы, гиперпигментация, гипокалиемия	Кетоконазол 400–1200 мг/сут Метирапон 500–4000 мг/сут Аминоглютотемил 500–2000 мг/сут Митотан 4–12 мг/сут Сандостатин 300–1500 мкг/сут
Диарея	Карциноид (в составе карциноидного синдрома), VIP-ома	Частый водянистый обильный стул	Лоперамид. Глюкокортикоиды (для VIP-омы)
Артериальная гипертензия	Феохромоцитома	Повышение АД, плохо контролирующееся обычными антигипертензивными препаратами	Альфа-адреноблокаторы, блокаторы кальциевых каналов

Продолжение табл. 4

Синдром	Опухоль	Симптомы	Лечение (в дополнение к терапии первичной опухоли)
Синдром Золлингера – Эллисона	Гастринома	Язвы желудка и двенадцатиперстной кишки	Ингибиторы протонной помпы (омепразол) и антагонисты Н2-гистаминовых рецепторов (циметидин, ранитидин)
Синдром неадекватной продукции АДГ	Рак лёгкого	Гипонатриемия, слабость, анорексия, головные боли, незначительные нарушения памяти, слабость, судороги. В тяжелых случаях – расстройство сознания до комы	Ограничение жидкости при Na<130 мкмоль/л до 500 мл/сут, демеклоциклин 600–1200 мг/сут за 2–3 приёма
Синдром гипогликемии	Инсулинома	Потливость, тремор, слабость, нарушение зрения, ощущение голода, дисфазия, парестезии в углах рта, тревога, страх. В тяжелых случаях – гипогликемическая кома	Введение глюкозы, диазоксид 50–300 мг/сут, возможно использование верапамила, глюкокортикоидов
Белок-теряющая энтеропатия	Различные НЭО	Снижение уровня белков в плазме, редко периферические отеки	Ограничение в диете жиров, переливание белковых препаратов
Кахексия	Различные НЭО	Снижение массы тела, анорексия, тошнота	Мегейс в высоких дозах (360–480 мг/сут)
Нефротический синдром	Различные НЭО	Отеки, протеинурия, артериальная гипертензия	Петлевые диуретики
Генерализованный мланоз	Меланома, АКТГ-продуцирующие опухоли	Диффузная серо-коричневая пигментация	
Паранеопластический кератоз	Плоскоклеточный рак пищевода, лёгкие. Голова и шея	Псориазоподобный кератоз конечностей	
Erythema gyratum repens	Лёгкое, молочная железа, гастроинтестинальные	Эритема с шелушением и зудом	
Necrolytic migratory erythema	Глюкагонома	Циркулярные и спиральные волдыри, эритема с эрозиями на лице, животе, конечностях	
Приливы	Карциноиды (в составе карциноидного синдрома), медуллярный рак щитовидной железы	Периодическое покраснение головы и шеи	Диета с исключением привоцирующих высвобождение гистамина веществ, например острых, цитрусовых и т.д.
Поражение сердечно-сосудистой системы	Карциноид (в составе карциноидного синдрома)	Аритмии, сердечная недостаточность	Диуретики
Поражение ЦНС: энцефаломиелит паранеопластическая дегенерация мозжечка лимбический энцефалит	Герминогенные опухоли Мелкоклеточный рак лёгкого	Симптомы зависят от уровня поражения	Специального лечения не существует вазоактивные препараты (кавинтон, эуфиллин)
Поражение сетчатки	Мелкоклеточный рак лёгкого, меланома	Светобоязнь, скотомы, понижение цветового и ночного зрения. Снижение остроты зрения	Глюкокортикоиды
Поражение периферических нервов: моторная нейропатия сенсорная нейропатия сенсомоторная нейропатия	Мелкоклеточный рак (моторная или сенсомоторная), лимфопролиферативные заболевания (сенсорная)	Нарушение чувствительности, атаксия, снижение рефлексов	Нет эффективного лечения
Нейромышечные поражения: миастения Лимберта-Итона дерматомиозит полимиозит	Мелкоклеточный рак лёгкого	Слабость и повышенная мышечная утомляемость, изменения при миографии, повышение мышечной КФК	Кортикостероиды, иммуносупрессивные агенты, Диаминопиридин, монотерапия или в сочетании с пиридостигмином

Заключение

Обобщая вышесказанное, необходимо отметить следующее

1. НЭО являются гетерогенной группой опухолей, характеризующихся как местным воздействием объема опухоли, так и отдаленным воздействием её на организм.

2. В лечении высокодифференцированных опухолей и смешанных экзо-эндокринных опухолей ведущая роль принадлежит локальным методам лечения. Биотерапия с применением аналогов соматостатина и интерферона позволяет контролировать симптомы большинства гормонально-активных НЭО и является стандартом лечения этой группы опухолей.

3. Химиотерапия с препаратами платины является стандартом при лечении низкодифференцированных и недифференцированных НЭО.

На рисунке показан алгоритм лечения НЭО, который, по нашим представлениям, позволяет добиться наилучших результатов в лечении данного типа опухолей.

Алгоритм терапии НЭО.

Литература

1. *Ansell S.M., Pitot H.C., Burch P.A. et al.* J.A Phase II study of high-dose paclitaxel in patients with advanced neuroendocrine tumors // Cancer –2001. – Vol. 91 (8). – P. 1543-1548.

2. *Arnold S.M., Patchell R., LowyA.M., Foon K.A.* Paraneoplastic Syndromes // Cancer: Principles and Practice of Oncology. 6th edition. – 2001.– Chapter 47.

3. *Berghmans T., Paesmans M., Mascaux C. et al.* A meta-analysis of the role of etoposide (VP16) and cisplatin (CDDP) in small cell lung cancer (SCLC) with a methodology assessment // Europ. Cancer. – 1999. – Vol. 35 (suppl. 4).

4. *Berman J.J.* Tumor classification: molecular analysis meets Aristotle // BMC Cancer. – 2004. – Vol. 4 (10).

5. *Duran I., Le L., Saltman D., Kortmansky J. et al.* A phase II trial of temsirolimus in metastatic neuroendocrine carcinomas (NECs) // ASCO. – 2005. – Abstr. 3096.

6. *Hansen H.* Small Cell Lung Cancer // European Society for Medical Oncology 5x5x5 course «Lung cancer and thoracic tumors». – St. Peterburg, 2005. – P. 11-22.

7. *Jensen R.T. and Doherty J.M.* Carcinoid Tumors and the Carcinoid Syndrome // Cancer: Principles and Practice of Oncology on CD-ROM.-6 edition. – 2000. – Chapter 38.6.

8. *Kaltsas G.A., Besser G.M., Grossman A.B.* The Diagnosis and Medical Management of Advanced Neuroendocrine Tumors // Endocrin. Rev. – 2004. – Vol. 25 (3). – P. 458-511.

9. *Kegel T., Grothe W., Jordan K. et al.* Paclitaxel, carboplatin and etoposid (TCE) in the treatment of advanced neuroendocrine tumours // ASCO. – 2005. – Abstr. 4263.

10. *Kolby L., Persson G., Franzen S., Ahren B.* Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours // Brit. J. Surg. – 2003. – Vol. 90 (6). – P. 687-693.

11. *Kulke M., Janes J.H., Meropol N.J. et al.* A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs) // J. Clin. Oncol. – 2005. – Abstr. 4008.

12. *Miranda F.T., Singel D.R., Hainsworth J.D. et al.* Paclitaxel/carboplatin/etoposide (PCE) therapy for advanced poorly differentiated neuroendocrine (PDNE) carcinoma: A Minnie Pearl Cancer Research Network phase II trial // ASCO. – 2005. – Abstr. 4058.

13. *Murren J., Glatstein E, Pass H.I.* Small Cell Lung Cancer // Cancer: Principles and Practice of Oncology on CD-ROM. – 6th edition. – 2000. – Chapter 31.3.

14. *O'Toole D., Ducreux M., Bommelaer G. et al.* Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance // Cancer. – 2000. – Vol. 88 (4). – P. 770-776.

15. The Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission (Cochrane Review) // *The Cochrane Library*, Issue. – Chichester, UK: John Wiley & Sons, Ltd., 2000.

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