UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.
Petitioner

v.

NOVARTIS AG
Patent Owner

Case IPR2016-_____
U.S. Patent No. 9,006,224

DECLARATION OF MARK J. RATAIN, M.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,006,224

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I, Mark J. Ratain, M.D., resident of Chicago, Illinois, hereby declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

1. I have been retained by Par Pharmaceutical, Inc. ("Par") to provide my opinion concerning the validity of U.S. Patent No. 9,006,224 (Exhibit 1001; "the '224 patent") in support of Par's Petition for *Inter Partes* Review of the '224 patent ("'224 Petition").

2. I graduated from Harvard University *magna cum laude* in 1976 with an A.B. in Biochemical Sciences. I obtained my M.D. from Yale University School of Medicine in 1980. I completed my internship and residency at the Johns Hopkins Hospital in Baltimore, MD from 1980-1983. I completed a fellowship in Hematology/Oncology at the Department of Medicine at the University of Chicago from 1986-1988.

3. In 1986, I joined the Department of Medicine, Section of Hematology/Oncology and Committee on Clinical Pharmacology at the University of Chicago as an Instructor and become a Professor in that department in 1995. In 2002, I became the Leon O. Jacobson Professor in the Department of Medicine, Section of Hematology/Oncology and Committee on Clinical Pharmacology and Pharmacogenomics, and Comprehensive Cancer Center at the University of Chicago.

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4. In 1991, I became the Director of the Developmental Therapeutics Program at the Cancer Research Center at the University of Chicago. In 1992, I became Chairman of the Committee on Clinical Pharmacology and Pharmacogenomics at the University of Chicago. In 1995, I became Co-Director of the Clinical and Experimental Therapeutics Program of the Cancer Research Center at the University of Chicago. In 1999, I became the Associate Director for Clinical Sciences at the Comprehensive Cancer Center at the University of Chicago. In 2010, I became the founding Director of the Center for Personalized Therapeutics and Chief Hospital Pharmacologist at the University of Chicago.

5. I have received numerous honors and awards over my career. These include election to the Association of American Physicians in 2007, and awards from multiple institutions (MD Anderson Cancer Center, University of North Carolina, University of Nebraska, University of Utah), foundations (Pharmaceutical Research and Manufacturer's Association of America Foundation) and professional societies (American Association of Pharmaceutical Scientists, American Society for Clinical Pharmacology and Therapeutics, American Society of Clinical Oncology, American College of Clinical Pharmacology).

6. I have also had extensive involvement with the American Society of Clinical Oncology (ASCO), dating back to 1990 when I was appointed Chair of ASCO's Audit and Finance Committee. I was subsequently elected to the position

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of Secretary-Treasurer of ASCO, and served in that capacity as an Officer and Director from 1994 to 1997. I also served as the Chair of ASCO's Continuing Medical Education Committee from 1997 to 1999. In my capacities as Committee Chair, Officer, and Director, I participated actively in ASCO Board meetings and am familiar with ASCO's policy and lobbying efforts to modify Medicare reimbursement policies for oral oncology drugs during the period from 1990 to 1999.

7. I have served as a research reviewer for a number of committees and working groups at the National Institutes of Health, as well as for several cancer societies and state departments of health.

8. I have served as an editor for numerous journals, including Journal of Clinical Oncology (Investigational New Drugs (1995 to present; Editorial Board); Pharmacogenetics and Genomics (2005 to present; Co-Editor-in-Chief); and Clinical Cancer Research (1994 to 2002 and 2012 to present; Editorial Board and Associate Editor).

9. I have written more than 400 articles in peer-reviewed journals. I am additionally a named inventor on five United States and two foreign patents.

10. I have extensive experience in clinical pharmacokinetics and development of cancer therapeutics, including chemotherapeutic agents, other small molecules (e.g., targeted compounds) and biologics. I have been involved in

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the design, conduct and analysis of clinical phase I, phase II, and phase III trials for cancer therapeutics, including studies of rapamycin and its derivatives. Many of these studies have been conducted in our Developmental Therapeutics Clinic (at the University of Chicago), which was previously known as the Advanced Solid Tumors Clinic. (I have served as the director of that clinic since its founding more than 20 years ago.)

11. My curriculum vitae is attached as Exhibit 1004. My work in this matter is being billed at my standard rate of $750 per hour, with reimbursement for necessary and reasonable expenses. My compensation is not in any way contingent upon the outcome of any *Inter Partes* Review. I have no financial or personal interest in the outcome of this proceeding or any related litigation.

II. UNDERSTANDING OF THE GOVERNING LAW

A. Invalidity by Obviousness

12. I am informed by counsel for Par that obviousness is analyzed from the perspective of a hypothetical person of ordinary skill in the art at the time of the alleged invention. I am also informed by counsel for Par that a person of ordinary skill in the art is presumed to have been aware of all pertinent prior art at the time of the alleged invention.

13. I am informed by counsel for Par that 35 U.S.C. § 103 governs the determination of obviousness. According to 35 U.S.C. § 103:

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> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

14. I am also informed by counsel for Par that the first three factors to be considered in an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; and (3) the level of ordinary skill in the pertinent art. I have also been informed by counsel for Par that when a patent claims a genus, that claim is obvious if a single embodiment falling within the scope of the claims is obvious.

15. I am also informed by counsel for Par that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In such a circumstance, when a patent simply arranges

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old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious.

16. I am also informed by counsel for Par that certain factors, sometimes known as "secondary considerations," must be considered, if present, when in an obviousness determination. These secondary considerations include: (i) long-felt need, (ii) unexpected results, (iii) skepticism of others of the invention, (iv) teaching away from the invention, (v) commercial success, (vi) praise by others for the invention, and (vii) copying by other companies.

17. I am also informed by counsel for Par that the earliest patent application leading to the '224 Patent was filed on November 21, 2005. I have therefore analyzed obviousness as of that day or somewhat before, understanding that as time passes, the knowledge of a person of ordinary skill in the art will increase.

B. Interpreting Claims Before the Patent Office

18. I understand that *Inter Partes* Review is a proceeding before the United States Patent & Trademark Office ("PTO") for evaluating the validity of issued patent claims. I understand that in an *Inter Partes* Review a claim term is given the broadest reasonable interpretation that is consistent with the patent's specification. I understand that a patent's "specification" includes all the figures,

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discussion, and claims within the patent. I understand that the PTO will look to the specification to see if there is a definition for a given claim term, and if not, will apply the broadest reasonable interpretation from the perspective of a person of ordinary skill in the art at the time in which the alleged invention was made. I present a more detailed explanation of the interpretation of certain terms in the '224 patent in the section titled "Claim Construction" below.

C. Materials Relied on in Forming My Opinions

19. In forming my opinions, I have relied on the '224 patent's claims, specification, and file history, on the prior art exhibits to the '224 Petition, any other materials cited in this declaration, and my own experience, expertise, and knowledge of the person of ordinary skill in the art in the relevant timeframe.

III. THE PERSON OF ORDINARY SKILL IN THE ART OF THE '224 PATENT

20. The claims of the '224 patent are directed to treating pancreatic neuroendocrine tumors in patients by administering the rapamycin, (i.e., rapamycin or a derivative thereof) 40-O-(2-hydroxyethyl)-rapamycin.

21. Based on this, in my opinion, a person of ordinary skill in the art in November 2005 would have had, at a minimum:

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a. a medical degree (e.g., MD) with several years of specific experience in medical oncology, which generally includes board certification, as well as knowledge of oncology drug development and clinical pharmacology; or

b. a Ph.D. in cancer biology, molecular biology, medicinal chemistry, or a related field with several years of experience in oncology drug development and clinical pharmacology, including evaluating cancer therapeutics in *in vitro* and/or *in vivo* assays, as well as familiarity with the practice of medical oncology.

This description is approximate, and a higher level of education or skill might make up for less experience, and vice-versa.

IV. PERSPECTIVE APPLIED IN THIS DECLARATION

22. I believe that I would qualify as a person of at least ordinary skill in the art in November 2005, and that I have a sufficient level of knowledge, experience, and education to provide an expert opinion in the field of the '224 patent.

23. Because of my work experience and the earlier date on which I received my medical degree, by November 2005 my own level of skill likely exceeded the ordinary level of skill in the art. In the mid-2000s, I served as Professor at the University of Chicago, supervised and worked with those of ordinary skill in the art, and served on editorial boards for multiple journals

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specializing in cancer research. Accordingly, I am well acquainted with the actual performance of a person of ordinary skill in the art as defined above, and can approach technical issues from the perspective of such a person.

24. My opinions in this declaration are based on the perspective of a person of ordinary skill in the art as of November 2005. This is true even if the testimony is stated in the present tense. Each of the statements below reflects my opinion based on my review of the prior art, the disclosures of the '224 patent, its file history, and the challenged claims.

V. OVERVIEW OF THE '224 PATENT

A. Disclosure of the '224 Patent

25. The '224 patent claims methods of treating advanced pancreatic neuroendocrine tumors (pNETs) by administering everolimus as a monotherapy after failure of cytotoxic chemotherapy. Everolimus is the common name for 40-O-(2-hydroxyethyl)-rapamycin. '224 patent at 1:46-47. The '224 patent also refers to everolimus as Compound A. *Id.* at 11:66-67.

26. Claim 1 of the '224 patent recites

> A method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need thereof a therapeutically effective amount of 40-O-(2-hydroxyethyl)-rapamycin as a

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monotherapy and wherein the tumors are advanced after failure of cytotoxic chemotherapy.

27. Claim 2 of the ’224 patent recites

The method of claim 1, wherein a unit dose of 40-O-(2-hydroxyethyl)-rapamycin is 10 mg/day.

28. Claim 3 of the ’224 patent recites

The method of claim 1 wherein the tumor is islet cell tumor.

29. According to the ’224 patent specification, rapamycin and other mTOR inhibitors, including everolimus, inhibit mTOR activity through a complex with FKBP12. Rapamycin and its derivatives, including everolimus, have potent antiproliferative properties which make them useful for cancer chemotherapy, particularly for advanced solid tumors. Ex. 1001, ’224 patent at 2:35-40.

30. pNETs comprise only 1-2% of pancreatic tumors and, according to the ’224 patent specification, a recent review showed that the 5 year survival rate of patients with pNETs was merely 55.3%. *Id.* at 2:49-54, 3:7-12.

31. According to the ’224 patent, it was found that mTOR inhibitors like rapamycin and everolimus are useful for the treatment of pNETs. *Id.* at 7:10-11.

32. The ’224 patent does not include any data demonstrating the activity of everolimus, or any other rapamycin derivative or mTOR inhibitor, in treating

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any tumor, including pNET, either in human patients or in preclinical laboratory experiments.

33. The ’224 patent describes two *in vitro* assays for assessing the antiproliferative activity of mTOR inhibitors such as everolimus. *Id.* at 25:54-26:20. First, the specification describes incubating two cancer cell lines with mTOR inhibitors alone or in combination with other antineoplastic agents and measuring IC_{50} values to determine the antiproliferative effect of the compounds and/or combinations. *Id.* at 25:54-26:10. Second, the specification describes measuring the phosphorylation of S6, for example by using the p70S6 kinase I assay, as a measure of mTOR inhibition. *Id.* at 26:11-20.

34. The ’224 specification also describes *in vitro* studies to assess everolimus’s ability to restore activity of endocrine agents in cells resistant to endocrine agent treatment. *Id.* at 26:21-27.

35. Finally, the ’224 specification describes four clinical trials to investigate the activity of everolimus. First, the specification describes administering 5 mg of everolimus daily to patients with carcinoid or islet cell cancer either alone or in combination with the somatostatin analogue Sandostatin LAR. *Id.* at 26:29-36. The active ingredient of Sandostatin LAR is octreotide acetate, and it was approved for the treatment of symptoms of VIPomas, a type of pNET in 1998. Ex. 1060.

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36. The specification describes evaluating the response of the treatment and obtaining synergistic effects from the combination. *Id.* Second, the specification describes administering 5 mg or 10 mg daily (5 to 70 mg weekly) alone or in combination with Sandostatin LAR to patients with advanced midgut carcinoid tumors. *Id.* at 26:37-55. The specification describes evaluating the progression free survival, overall survival, carcinoid-associated symptoms, "pharmakinetics and pharmadynamics [*sic*]." *Id.* at 26:46-49. Third, the specification describes administering 10 mg/day of everolimus to patients with advanced pNET after failure of cytotoxic chemotherapy. *Id.* at 26:56-60. Finally, the specification describes administering 10 mg/day everolimus to patients with secretory pancreatic tumors in combination with Sandostatin LAR. *Id.* at 26:61-64.

37. The '224 patent specification does not include any data demonstrating the preclinical or clinical activity of everolimus or any other mTOR inhibitor in pNETs. The specification provides no data demonstrating the activity of everolimus or any other mTOR inhibitor in laboratory models of pNET or in any human patient populations diagnosed with pNET.

B. Prosecution History of the '224 Patent

38. I have reviewed the prosecution history of the '224 patent and present a short overview of it.

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39. All originally-pending claims in the application for the '224 patent were initially rejected as anticipated by O'Reilly et al. (Proceedings of the American Association of Cancer Research Annual Meeting, 03/2002, Vol. 43, pg. 71) ("O'Reilly"; Ex. 1030) and Weckbecker (WO 97/47317) ("Weckbecker"; Ex. 1053). (Ex. 1002 at 2/16/2011 Non-Final Rejection at 4-6). Those originally-filed claims included within their scope therapy with 40-O-(2-hydroxyethyl)-rapamycin combined with other therapies for the treatment of endocrine tumors. (Ex. 1002 at 5/19/2008 Prelim. Am. at 4-5.)

40. The Examiner stated that O'Reilly teaches that 40-O-(2-hydroxyethyl)-rapamycin has demonstrated anti-proliferative activity in human tumors and is an inhibitor of pancreatic tumor growth *in vivo*. Ex. 1002 at 2/16/2011 Non-Final Rejection at 4-5.

41. The Examiner further stated that Weckbecker teaches a combination of a rapamycin and a derivative of somatostatin (a hormone that regulates the endocrine system) for the prevention and treatment of cell hyperproliferation, and that rapamycin derivative are known to inhibit cancer. Ex. 1002 at 2/16/2011 Non-Final Rejection at 5. The Examiner also stated that Weckbecker identifies 40-O-(2-hydroxyethyl)-rapamycin as a preferred rapamycin compound and that the combination of a somatostatin analogue and a rapamycin can be used for preventing or treating endocrine tumors. *Id.* at 5-6.

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42. In response, the Applicants amended the claims to recite 40-O-(2-hydroxyethyl)-rapamycin. Ex. 1002, 8/2/2011 Am. at 2. The Applicants argued that O'Reilly does not disclose or suggest 40-O-(2-hydroxyethyl)-rapamycin for treating endocrine or pancreatic neuroendocrine tumors. *Id.* at 3-4. The Applicants further argued that Weckbecker only refers to gastroenteropancreatic (GEP) tumors and does not disclose treating endocrine tumors or pancreatic neuroendocrine tumors. *Id.* at 4.

43. The Examiner then issued a Final Rejection, stating that the claims as amended were still anticipated by O'Reilly and were obvious in light of Weckbecker. Ex. 1002, 10/13/2011 Final Rejection at 2-4.

44. The Applicants appealed and entered a request for continued examination, arguing that the claims were not anticipated by O'Reilly on the grounds that it did not disclose 40-O-(2-hydroxyethyl)-rapamycin as a treatment for endocrine tumors or pancreatic neuroendocrine tumors in humans, which a person of ordinary skill in the art would distinguish from each other and from other pancreatic cancers and tumors, such as adenocarcinomas. Ex. 1002, 1/13/2012 Response After Final Action at 3-5; Ex. 1002, 2/6/2012 Request for Continued Examination at 5-7.

45. The Applicants submitted a declaration from the co-inventor, Dr. Lebwohl, highlighting the distinction between the various cancer types. Ex. 1002,

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9/24/2013 Lebwohl Affidavit at 2-3. Dr. Lebwohl additionally stated in his declaration that a clinical study of 40-O-(2-hydroxyethyl)-rapamycin in patients with pNETs indicated that 40-O-(2-hydroxyethyl)-rapamycin "more than doubled the time without tumor growth and reduced the risk of pNET progression in patients by 65% when compared with placebo." *Id.* at 2.

46. The Examiner then issued a Non-Final Rejection. The Examiner was persuaded by Dr. Lebwohl's declaration that the pending claims were not anticipated by the O'Reilly abstract given that O'Reilly did not differentiate between pancreatic tumors and tumor cells derived from pancreatic neuroendocrine tumors. Ex. 1002, 05/09/2014 Non-Final Rejection at 2. However, the Examiner maintained the obviousness rejection based on Weckbecker in view of Arnold et al. *Id.* at 5-8. The Examiner stated that Weckbecker teaches treatment of gastroenteropancreatic neuroendocrine (GEP) tumors. *Id.* at 6. The Examiner further stated that Arnold teaches that GEP tumors are also called neuroendocrine tumors. *Id.* at 7. Therefore, the Examiner stated that a person of ordinary skill in the art would have been motivated to combine Weckbecker and Arnold and administer a rapamycin derivative together with somatostatin to treat neuroendocrine tumors. *Id.* at 7-8.

47. Following this rejection, the Applicants amended the claims, limiting the scope to include only the treatment of advanced pancreatic neuroendocrine

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tumors using 40-O-(2-hydroxyethyl)-rapamycin as a monotherapy after failure of cytotoxic chemotherapy. Ex. 1002, 11/7/2014 Am. at 2.

48. The Examiner issued a Notice of Allowance on January 30, 2015. Ex. 1002, Notice of Allowance at 3-4.

49. Importantly, Boulay 2004 (discussed below) was submitted to the Patent Office during prosecution, but the Examiner never discussed or relied upon it. Oberg 2004, O'Donnell, Duran, and Tabernero (discussed below) were neither submitted to the Patent Office nor considered by the Examiner during prosecution of the '224 patent. Further, Dr. Lebwohl's declaration did not present any data comparing 40-O-(2-hydroxyethyl)-rapamycin's activity with that of rapamycin or temsirolimus.

VI. CLAIM CONSTRUCTIONS

A. Legal Standard

50. I understand that in an *Inter Partes* Review a claim term is given the broadest reasonable construction in light of the patent specification and prosecution history as understood by a person of ordinary skill in the art at the time of the alleged invention. I understand that this claim construction standard is broader than what a district court would apply in litigation.

51. I applied this broadest reasonable construction standard to my review of the claims of the '224 patent discussed below.

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B. "pancreatic neuroendocrine tumor"

52. The term "pancreatic neuroendocrine tumor" is used in challenged claim 1 of the '224 patent.

53. A person of ordinary skill in the art would have generally understood "pancreatic neuroendocrine tumor," as used in claim 1 of the '224 patent, to have the customary meaning that is consistent with its use and definition in the '224 patent specification. A person of ordinary skill in the art would understand that a neuroendocrine tumor is an abnormal growth of cells of the nervous or endocrine systems within or proximal to the pancreas. These tumors may be malignant or benign. Malignant tumors are frequently identified as carcinomas.

54. A person of ordinary skill in the art would understand that not all neuroendocrine tumors occur in the pancreas and that not all pancreatic cancers are neuroendocrine tumors. (Ex. 1020, Kaltsas et al., "The Diagnosis and Medical Management of Advanced Neuroendocrine Tumors," *Endocrine Rev.* 25:458-511 (June 2004) ("Kaltsas"); Ex. 1019, Levy and Wiersema, "Pancreatic neoplasms," *Gastrointestinal Endoscopy Clin. N. Am.* 15:117-142 (2005) ("Levy").) Rather, the majority of pancreatic cancers are adenocarcinomas, or abnormal growths of the cells of the pancreas that produce digestive enzymes. (Ex. 1019, Levy.)

55. The '224 patent specification indicates that "Endocrine, e.g. neuroendocrine tumors (NETs), are found in the endocrine system. . . . Pancreatic

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neuroendocrine tumors (islet cell tumors), which were formerly classified as APUDomas (tumors of the amine precursor uptake and decarboxylation system), comprise less than half of all neuroendocrine tumors and only 1-2% of all pancreatic tumors. Pancreatic NETs can arise either in the pancreas (insulinomas, glucagonomas, nonfunctioning pancreatic NETs, pancreatic NETs causing hypercalcemia) or at both pancreatic and extrapancreatic sites (gastrinomas, VIPomas, somatostatinomas, GRFomas)." Ex. 1001, '224 patent at 2:41-58.

56. The '224 patent specification states that "Pancreatic neuroendocrine tumors as indicated herein e.g. include islet cell tumors, APUDomas, insulinomas, glucagonomas, nonfunctioning pancreatic NETS, pancreatic NETs associated with hypercalcemia, gastrinomas, VIPomas, somatostatinomas, GRFomas." Ex. 1001, '224 patent at 8:13-17.

57. Accordingly, in my opinion, the broadest reasonable construction of the term "pancreatic neuroendocrine tumors" is "abnormal growths of cells of the nervous or endocrine systems in the pancreas, including, e.g., islet cell tumors, APUDomas, insulinomas, glucagonomas, nonfunctioning pancreatic NETS, pancreatic NETs associated with hypercalcemia, gastrinomas, VIPomas, somatostatinomas, GRFomas."

C. "advanced tumors"

58. The term "advanced" is used in challenged claim 1 of the '224 patent.

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59. A person of ordinary skill in the art would understand the term "advanced tumors" to have the customary meaning that is consistent with the specification. As used by those of skill in the field of oncology, an "advanced tumor" is a tumor that is unresectable or metastatic. *See, e.g.*, Ex. 1023, Moertel et al., "Streptozocin-Doxorubicin, Streptozocin-Fluorouracil, or Chlorozotocin in the Treatment of Advanced Islet-Cell Carcinoma," *NEJM* 326(8):519-523 (Feb. 20, 1992) at 520 (describing the patients with advanced islet cell carcinoma as having been identified with "proof of unresectable or metastatic islet-cell carcinoma"). This is consistent with the '224 patent specification, which correlates "advanced" tumors with "metastatic or unresectable." Ex. 1001, '224 patent, 26:57-58 ("measurable advanced (metastatic or unresentable [*sic*, unresectable]) pancreatic neuroendocrine tumors"). An unresectable tumor is one that is unable to be completely removed by surgery. (This definition is also consistent with that used in the context of our aforementioned Advanced Solid Tumor Clinic.)

60. Accordingly, in my opinion, the broadest reasonable construction of the term "advanced tumors" is tumors that are "metastatic or unresectable."

D. "unit dose"

61. The term "unit dose" is used in challenged claim 2 of the '224 patent.

62. A person of ordinary skill in the art would have understood "unit dose" to have its customary meaning that is consistent with the specification. As

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used by those in the field, a "unit dose" is a single dose administered at one time, as compared to a "divided dose" which is a dose that is administered in separate portions over a period of time. This is consistent with the '224 patent specification which indicated that a "divided dose[]" is one that is administered "up to four times a day." '224 patent at 10:27-36.

63. Accordingly, in my opinion, the broadest reasonable construction of the term "unit dose" is "a dose administered as a single unit."

E. "islet cell tumor"

64. The term "islet cell tumor" is used in challenged claim 3 of the '224 patent.

65. A person of ordinary skill in the art would have generally understood "islet cell tumor," as used in claim 3 of the '224 patent, to have the customary meaning that is consistent with its use and definition in the specification. A person of ordinary skill in the art would understand that an islet cell tumor is another name for a pancreatic neuroendocrine tumor. Pancreatic NETs are also termed islet cell tumors. (*E.g.*, Ex. 1007, Buetow et al., "Islet cell tumors of the Pancreas: Pathologic-Imaging Correlation Among Size, Necrosis and Cysts, Calcification, Malignant Behavior, and Functional Status," *AJR. American journal of roentgenology*, 165.5:1175-1179 (1995) ("Buetow") at 1176, Table 1 (collating data for "Islet Cell Tumors" such as insulinoma, gastrinoma, glucagonoma,

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somatostatinoma, VIPoma).) Islet cell tumors may be malignant or benign. Malignant tumors are frequently identified as carcinomas.

66. The ’224 patent specification indicates that “Pancreatic neuroendocrine tumors (islet cell tumors), which were formerly classified as APUDomas (tumors of the amine precursor uptake and decarboxylation system), comprise less than half of all neuroendocrine tumors and only 1-2% of all pancreatic tumors.” Ex. 1001, ’224 patent at 2:41-58. The ’224 patent specification therefore equates pancreatic neuroendocrine tumors with islet cell tumors, consistent with how a person of ordinary skill would understand this term.

67. Accordingly, in my opinion, the broadest reasonable construction of the term “islet cell tumors” is “abnormal growths of cells of the nervous or endocrine systems within the pancreas.”

VII. STATE OF THE PRIOR ART TO THE ’224 PATENT

68. The ’224 patent involves several common concepts that were well known to those working in antineoplastic drug development in the mid-2000s. Below, I explain how the technical context of the ’224 patent informs my opinion on the level of skill of a person of ordinary skill at the time of the alleged invention of the ’224 patent.

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A. The Prior Art Taught Rapamycin and Its Derivatives Were Potent Immunosuppressants and Antitumor Agents

69. Rapamycin, clinically known as sirolimus, was originally isolated from a soil sample from Easter Island in the early 1970s. After rapamycin was discovered, scientists quickly discovered that it had potent antifungal and antibiotic properties. (U.S. Patent No. 3,929,992 ("the '992 patent") at 1:40-47, 7:34-47 (Ex. 1040); Martel R. et al., "Inhibition of the immune response by rapamycin, a new antifungal antibiotic," *Can. J. Physiol. Pharmacol.* 55:48-51 (1977) (Ex. 1021).) Throughout the 1980s, scientists continued to investigate the activities and uses of rapamycin, identifying all of the following properties: treating and/or preventing organ or tissue transplant rejection, multiple sclerosis, rheumatoid arthritis, and diabetes. (*See, e.g.*, Morris, "Rapamycins: Antifungal, Antitumor, and Immunosuppressive Macrolides," *Transplantation Rev.*, 6(1):39-87 (1992) ("Morris") at 39-42, 52-64 (Ex 1022).) This extensive work on the use of rapamycin in preventing organ transplant rejection, the early stages of which were exhaustively detailed in Morris (*id.* at 55-64), led to its approval for that indication in 1999. (Ex. 1008, 1999 Rapamune Approval Letter.) Morris assembled a timeline of the variety of research conducted on rapamycin in its first fifteen years:

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Table 1. History of RPM Drug Development: The First 15 Years

Discovery	*Year*	*References*
Isolation from Easter Island (Rapa Nui) soil sample and characterization of antimicrobial activity	1975	Vezina, Kudelski, and Sehgal[46] Sehgal, Baker, and Vezina[47]
In vivo use: Toxicity Pharmacokinetics Bioavailability Antifungal activity	1978	Baker, Sidorowicz, Sehgal, et al[48]
Immunosuppression of autoimmune disease	1977	Martel, Klicius, and Galet[49]
Elucidation of structure	1980	Findlay and Radics[50]
Antitumor activity described	1981	Douros and Suffness[51]
Immunosuppression of allograft rejection		
RPM alone	1989	Morris and Meiser[1] Calne, Collier, Lim, et al[2]
RPM in combination with CsA	1990	Meiser, Wang, and Morris[1]
Differentiation of effects of RPM and FK506 on immune cells in vitro	1989 1990	Tocci, Matkovich, Collier, et al[27] Metcalfe and Richards[28] Dumont, Staruch, Koprak, et al[29]
Differentiation of effects of RPM and FK506 on immune system in vivo	1990	Morris, Wu, and Shorthouse[1]
Demonstration of binding of RPM to FK506 binding protein	1989	Harding, Galat, Uehling, et al[52]

(Ex. 1022, Morris at 42 (Table 1) (RPM denotes rapamycin).)

70. Starting in the 1970s, rapamycin was also investigated as an antitumor agent. (U.S. Patent No. 4,885,171 ("the '171 patent") (Ex. 1042); Eng C. et al., "Activity of Rapamycin (AY-22,989) Against Transplanted Tumors," *J. Antibiotics* 37(10):1231-1237 (1984) (Ex. 1013).) The '171 patent, which claims priority to an application filed in 1978, describes methods of treating certain cancers or tumors with rapamycin, including lymphatic leukemia, colon tumors, mammary tumors, "melanocarcinomas," and ependymoblastomas. (Ex. 1041, '171 patent at 2:7-4:14.) Specifically, the '171 patent includes data showing that rapamycin reduces tumor size and prolongs survival time of tumor-bearing

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mammals with these types of cancers. (*Id.*) From these earliest explorations of rapamycin as an antitumor agent, researchers continued to study rapamycin in various cancer and tumor models. (*E.g.*, U.S. Patent No. 5,206,018 at 5:48-6:15 (Ex. 1044) (additionally describing rapamycin's activity in treating skin carcinomas and malignant central nervous system carcinomas); Guba M et al., "Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor," *Nat. Med.* 8:128 (2002) (Ex. 1015).)

71. In 1999, Grewe et al. described rapamycin's activity as an antitumor agent in two pancreatic cancer cell lines, MiaPaCa-2 and Panc-1. (Ex. 1014, Grewe M et al., "Regulation of Cell Growth and Cyclin D1 Expression by the Constitutively Active FRAP-p70^{s6K} Pathway in Human Pancreatic Cancer Cells," *Cancer Res.* 59:3581-3587 (1999) at Abstract, 3582-85.) Additionally, in 2004, Oberg suggested "Rapamycin" as a treatment for neuroendocrine tumors of the gastrointestinal tract, including the pancreas. (Ex. 1027, Oberg K, "Treatment of neuroendocrine tumors of the gastrointestinal tract," *Oncologia* 27(4):185-189 (2004) at 60.)

72. By the late 1970s and early 1980s, the promising activity of rapamycin sparked interest in making small or minor modifications to the chemical structure of rapamycin in order to identify additional rapamycins with similar

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biological activity to the parent compound. (*See, e.g.*, Ex. 1041, U.S. Patent No. 4,650,803 ("Stella"); Ex. 1045, U.S. Patent No. 5,233,036 ("Hughes"); Ex. 1043, U.S. Patent No. 5,100,883 ("Schiehser").) In 1992, Sandoz Ltd. (a division of Novartis AG, the assignee of the '224 patent) disclosed 40-O-(2-hydroxyethyl)-rapamycin, a rapamycin derivative formed by substituting the hydroxyl group at rapamycin's C-40 position with a 2-hydroxyethyl group. (Ex. 1048, U.S. Patent No. 5,665,772 ("the '772 patent") at 1:10-2:30.) The literature has alternatively referred to this rapamycin derivative as everolimus, RAD001, SDZ RAD, and RAD. (*E.g.*, Ex. 1033, Rao R. et al., "Mammalian Target of Rapamycin (mTOR) Inhibitors as Anti-Cancer Agents," *Curr. Cancer Drug Targets*, 4:621-635 (2004) ("Rao"), at 621.) Sandoz and Novartis patents have occasionally referred to 40-O-(2-hydroxyethyl)-rapamycin as Compound A. (Ex. 1001, '224 patent at 11:66-67.) I will primarily refer to 40-O-(2-hydroxyethyl)-rapamycin as everolimus in this declaration.

73. In 1992, temsirolimus, a hydroxyester derivative of rapamycin, was disclosed by American Home Products Corporation. (U.S. Patent No. 5,362,718 ("the '718 patent") (Ex. 1046).) Temsirolimus has also been referred to in the literature as CCI-779. (*E.g.*, Ex. 1033, Rao at 621.)

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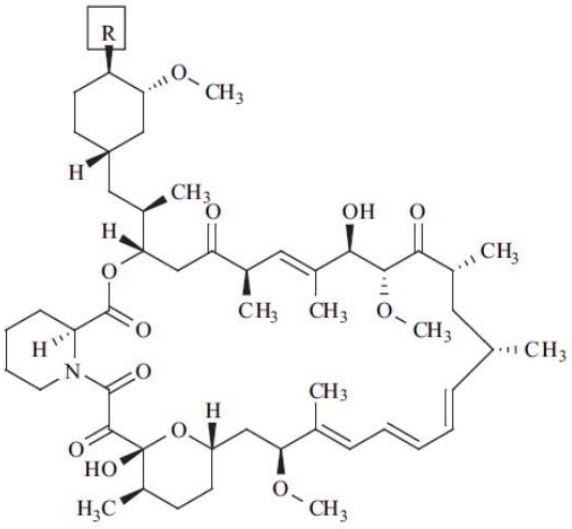
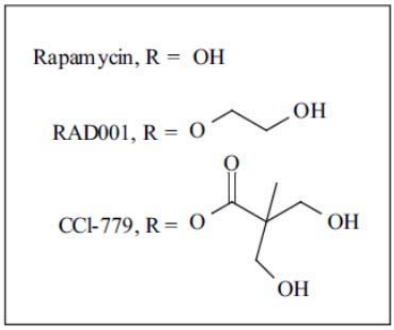
74. As of November 2005, other rapamycins had also been developed. (*E.g.*, Ex. 1047, U.S. Patent No. 5,391,730; Ex. 1049, U.S. Patent No. 7,091,213 (disclosing class of derivatives including Ariad's ridaforolimus/deforolimus).)

75. Of all the disclosed derivatives of rapamycin, as of November 2005, everolimus and temsirolimus had been studied the most exhaustively since their disclosures in 1992, both clinically and in the laboratory. (Ex. 1012, Dutcher, "Mammalian Target of Rapamycin Inhibition," *Clin. Cancer Res.*, 10:6382s-6387s (Sept. 15, 2004); Ex. 1017, Huang and Houghton, "Inhibitors of mammalian target of rapamycin as novel antitumor agents: From bench to clinic," *Curr Op Invest Drugs*, 3:295-304 (2002) ("Huang 2002").) The chemical structures of rapamycin, everolimus (RAD001), and temsirolimus (CCI-779) are shown below. (Ex. 1033, Rao at 622, Fig. 1.)





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76. As expected, the prior art taught that, like rapamycin, the derivative everolimus possesses immunosuppressant properties. For example, Sandoz Ltd. described this derivative's properties as "particularly useful" for the "[t]reatment and prevention of organ or tissue transplant rejection" and "of autoimmune disease and of inflammatory conditions" and the "[t]reatment of proliferative disorders, e.g. tumors, hyper-proliferative skin disorder and the like." (Ex. 1048, '772 patent at 3:22-4:10; *see also* Schuler W et al., "SDZ RAD, A New Rapamycin Derivative: Pharmacological Properties In Vitro and In Vivo," *Transplantation* 64(1):36-42 (July 1997) ("Schuler") (Ex. 1036).) Everolimus was also identified as having been developed to "overcome the formulation problems" of rapamycin and to have a "more favorable pharmacokinetic properties," which would "promise to provide a clinical advantage, i.e., it should be easier to handle and to monitor . . . in clinical practice." *Id.* at 36-37, 41. Like everolimus, temsirolimus was also reported to have immunosuppressant activity, similar to rapamycin. (*See* Ex. 1046, '718 patent at 4:50-6:60.)

77. When compared to rapamycin, the derivative everolimus was reported in the prior art to have slightly lower pharmacological properties *in vitro* but comparable properties to rapamycin *in vivo*. (Ex. 1036, Schuler at Abstract.) Everolimus was also reported in the prior art to have slightly increased bioavailability and a shorter half-life than rapamycin. (Ex. 1009, Dancey J,

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"Clinical development of mammalian target of rapamycin inhibitors," *Hematol Oncol Clin N Am*, 16:1101-1114 (2002) ("Dancey"), at 1105-06.) As early as 1997, Schuler reported that everolimus "is a new, orally active rapamycin-derivative that is immunosuppressive and that efficiently prevents graft rejection in rat models . . . [and] had therefore been selected for development." (Ex. 1036, Schuler at Abstract; Ex. 1005, Boulay A, 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 Res*, 64:252–61 (2004) ("Boulay 2004") at 252 ("[Everolimus], an orally bioavailable derivative of rapamycin, . . . demonstrates potent antiproliferative effects against a variety of mammalian cell types. . . . As a result of these properties, [everolimus] is being clinically developed both as an immunosuppressant . . . and as a novel therapeutic in the fight against human cancer.")

78. As had been done for rapamycin, the prior art described the investigations into the anticancer and antitumor activities of the derivatives everolimus and temsirolimus. (Ex. 1016, Hidalgo M. et al., "The rapamycin-sensitive signal transduction pathway as a target for cancer therapy," *Oncogene* 19:6680-6686 (2000) ("Hidalgo") (temsirolimus); Ex. 1055, WO02066019 (everolimus and temsirolimus); Ex. 1050, U.S. Patent No. 8,410,131 (everolimus);

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Ex. 1054, WO0240000 ("Dukart") (temsirolimus); Ex. 1005, Boulay 2004 (everolimus).) Thus, by November 2005, everolimus had been reported in the literature as a promising clinical candidate for development both for its immunosuppressant properties as well as its antitumor activity.

79. Unlike rapamycin, by November 2005, early clinical trials of everolimus (then known as RAD001) in human cancer patients had been reported, concluding that everolimus was "well tolerated", with evidence of activity against solid tumors. Ex. 1029, O'Donnell A et al., "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 tumors," *Proc. Am. Soc. Clin. Oncol.* 22:200(803ab) (2003) ("O'Donnell"). O'Donnell further reported that everolimus showed promising antitumor activity as measured by monitoring of cancer biomarkers and tumor imaging. (*Id.*) O'Donnell further indicated that these results in human cancer patients correlate with the antitumor effects in rodent models. (*Id.*) Indeed, the first clinical trial of rapamycin administered to human cancer patients was not reported until the 2006 ASCO Meeting (by Dr. Antonio Jimeno), and was invited to be presented orally by ASCO's Program Committee because of its perceived novelty. (Ex. 1064, Jimeno A. et al., "Pharmacodynamic-guided, modified continuous reassessment method (mCRM)-based, dose finding study of rapamycin

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in adult patients with solid tumors," *J. Clin. Oncol.* 24(18S):3020 (2006).) In fact, around the same time the University of Chicago had been awarded a grant (on which I was a co-investigator)for a clinical trial of rapamycin as an antineoplastic agent and specifically recall this 2006 presentation being the first public disclosure of rapamycin administered to cancer patients. As of November 2005, no dosing information or any clinical safety or efficacy assessments had been published reporting the effect of administering rapamycin to patients for the treatment of cancer. When considering administering cancer therapies to patients, a person of skill in the art would prefer to administer compounds with reported dosing, safety, and efficacy data in clinical studies over compounds with unknown dosing, safety, and efficacy information for human patients.

80. Like everolimus, temsirolimus had also been reported to have anticancer properties both in preclinical models and in human patients. Dukart describes temsirolimus as an antineoplastic agent, "particularly for neoplasms which are refractory to standard therapy, or for whom standard therapy is not appropriate." (Ex. 1054, Dukart at 2:5-7.) Temsirolimus was reported to reduce tumor mass when administered to renal tumors engrafted in nude mice, a standard preclinical model. (*Id.* at 4:10-25.) Two phase I clinical trials in human patients had been conducted, administering temsirolimus to patients with solid tumors and lymphomas. Results indicated that temsirolimus reduced tumor size in patients

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with a variety of cancers, including renal carcinoma, soft tissue carcinoma, breast cancer, neuroendocrine cancer of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, and colon cancer. (*Id.* at 5:1-6:26.)

81. Temsirolimus was reported to have "comparable potency and specificity" for the biological target of rapamycin "but with a longer half-life" as compared to rapamycin. (Ex. 1034, Sawyers C, "Will mTOR inhibitors make it as cancer drugs?," *Cancer Cell*, 4:343-348 (Nov. 2003) ("Sawyers"), at 344.) Sawyers further reported that temsirolimus "show[s] promising results" as an anticancer agent for advanced stage kidney cancer and "warrant[s] a phase III randomized trial that is underway." (*Id.*) Early studies indicated that rapamycin and temsirolimus "share a mechanism of action that is distinct from other cancer therapeutics," and both have been reported to be "similar in activity." (Ex. 1009, Dancey at 1106-08.)

82. By the time of the earliest priority date of the '224 patent, the prior art demonstrated that rapamycin and its derivatives everolimus and temsirolimus were well known to have similar immunosuppressant and biological properties, including promising anticancer activity.

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B. The Prior Art Taught the Mechanism of Action for the Immunosuppressant and Antitumor Activity of Rapamycin and Its Derivatives

83. By the early 2000s, significant progress had been made in elucidating the mechanisms of action and biological pathway of rapamycin and its derivatives, including everolimus. At that time, it was well known that rapamycin binds to FKBP12 (FK-Binding Protein 12), and that this rapamycin-FKBP12 complex inhibits the activity of the protein mTOR (mammalian Target of Rapamycin). (Ex. 1037, Tolcher, A., "Novel Therapeutic Molecular Targets for Prostate Cancer: the mTOR Signaling Pathway and Epidermal Growth Factor Receptor," *J. Urology* 171:S41-S44 (Feb. 2004) ("Tolcher") at S41-S42; Ex. 1005, Boulay 2004 at 252 ("[Everolimus], like rapamycin, binds with high affinity to a ubiquitous intracellular receptor, the immunophilin FKBP12. This complex specific interacts with . . . mTOR . . ., inhibiting downstream signaling events."))

84. Tolcher taught that mTOR was known to play a role in the Akt/PI3 kinase signal transduction pathway, which mediates proliferative signals and had been identified as "an attractive target for chemoprevention drug development." (Ex. 1037, Tolcher at S41-S42.)

85. The prior art further taught that the FKBP12-rapamycin complex inhibited the progression through the G1 phase of the cell cycle in osteosarcoma, liver, and T cells, as well as interfered with mitogenic signaling pathways involved

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in G1 progression. (*See* Ex. 1006, Brown E et al., "A mammalian protein targeted by G1-arresting rapamycin-receptor complex," *Nature* 369:756-758 (1994) ("Brown") at 756.)

86. Prior art disclosed that it was this activity—the inhibition of mTOR by the rapamycin-FKBP12 complex—that was responsible for the antiproliferative properties of rapamycin and its derivatives, including everolimus and temsirolimus. (*See, e.g.*, Ex. 1009. Dancey at 1104-05; Ex. 1039, Vignot et al., "mTOR-targeted therapy of cancer with rapamycin derivatives," *Annals of Oncol.* 16:525-537 (2005) ("Vignot") at Abstract; Ex. 1033, Rao at 622; Ex. 1005, Boulay 2004 at 252 ("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."); *id.*at 253 ("Because mTOR couples nutrient/growth factor availability to cell growth and proliferation in a variety of cell types, there is potential for developing rapamycin derivatives such as [everolimus] as novel inhibitors of the deregulated cell growth characteristic of human cancers.").)

87. By the early 2000s, significant research had been published identifying mTOR inhibitors, in particular rapamycin and its derivatives, as a class of cancer agents that would allow for targeted antiproliferative activity. (Ex. 1039, Vignot; Ex. 1033, Rao; Ex. 1005, Boulay 2004 at 252-53.)

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88. In particular, "rapamycin and its analogues [had been shown to] antagonize tumor growth induced by the loss of the PI3K antagonist, PTEN." (Ex. 1039, Vignot at 525.) Thus, cancer and malignancies related to activated P70S6K/AKT and/or loss of PTEN expression were expected to be sensitive to rapamycin and its analogs. (Ex. 1039, Vignot at 525, 529-30; Ex. 1033, Rao at 622, 626; Ex. 1024, M. Neshat et al., "Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR," *PNAS* 98:10314-10319 (2001).)

89. As seen below, the prior art taught that abnormalities in the Akt/PI3-mTOR pathway had been implicated in a number of different human cancers (Ex. 1009, Dancey at Table 1):

Table 1
Abnormalities in the phosphatidyl-inositol 3 kinase/Akt-mTOR pathway in human cancers

Abnormality	Function	Tumors
Growth factor receptors (eg, EGFR, PDGFR, IGF-R, IL-2)	Oncogene	Lung, bladder, ovary, endometrium, cervix, prostate carcinomas, glioma, lymphoma
PI3 kinase	Oncogene	Ovary
PTEN	Tumor suppressor gene	Prostate, endometrium, breast carcinomas, melanoma
Akt	Oncogene	Breast, gastric, ovary, pancreas, prostate carcinomas
eIF-4E	Oncogene	Breast, bladder, and head, and neck carcinomas; lymphoma
Cyclin D	Oncogene	Mantle cell lymphoma; breast, head and neck carcinomas
P16	Tumor suppressor gene	Familial melanoma, pancreas carcinomas

Abbreviations: EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; IGF-R, insulin-like growth factor receptor; IL-2, interleukin-2 PI3, phosphoisinositol-3; eIF-4E, eukaryotic initiation factor-4E.

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90. The prior art further taught that the mTOR and FKBP12 binding domains of rapamycin, everolimus, and temsirolimus were identical. (*E.g.*, Ex. 1006, Brown 1994 (identifying the mTOR binding domain of rapamycin) and Ex. 1035, S.L. Schreiber, "Chemistry and Biology of the Immunophilins and Their Immunosuppressive Ligands," *Science*, 251:283-287 (1991) (identifying the FKBP12 binding domain and "effector domain" for activity of the complex).)

91. The figure below depicts the binding domains of rapamycins for mTOR and FKBP12 and highlights the structural differences between rapamycin and everolimus and temsirolimus. The rapamycin derivatives everolimus and temsirolimus differ from rapamycin only where circled in red, removed from the known binding sites of mTOR and FKBP12 to the rapamycin structure. (*See* Ex. Vignot at 528, Figure 4; Ex. 1018, S. Huang et al., "Rapamycins: Mechanism of Action and Cellular Resistance," *Cancer Biol. & Ther.* 2:222-232 (2003) ("Huang 2003") at Figure 1.)

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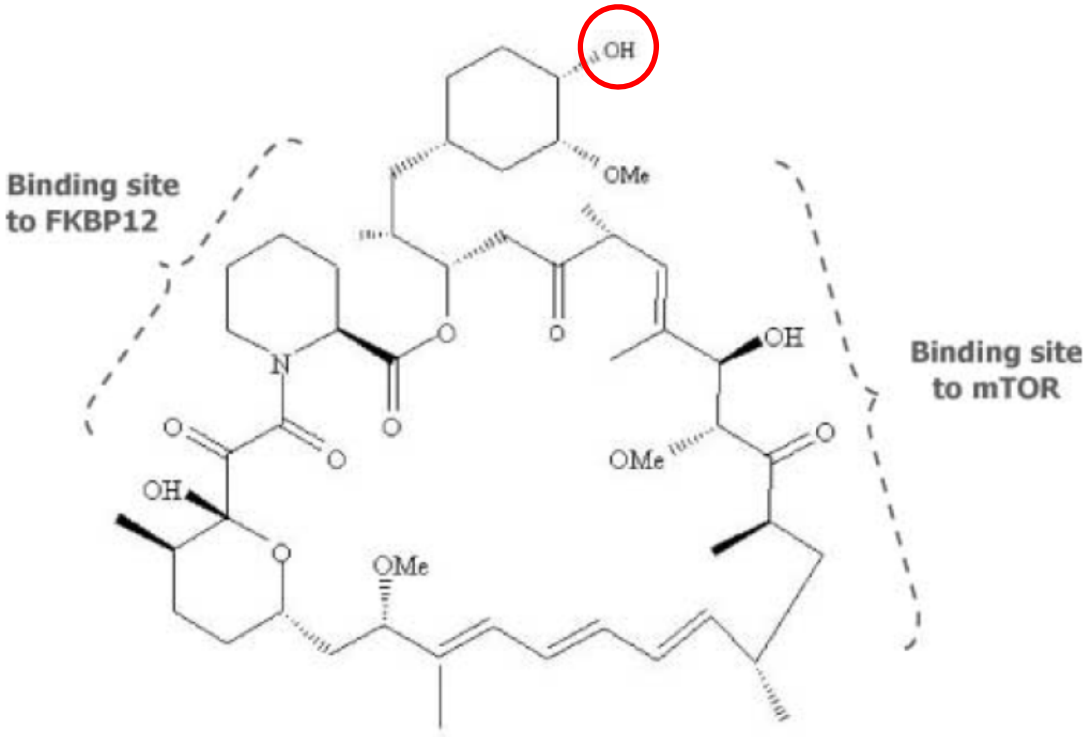

92. A person of ordinary skill in the art in the early 2000s would have expected these compounds to have similar biological activity within the mTOR signaling cascade given their activity as mTOR inhibitors and the reported similar immunosuppressant and antiproliferative properties reported in the literature. (*See, e.g.*, Ex. 1018, Huang 2003 at Abstract; Ex. 1033, Rao at Abstract; Ex. 1005, Boulay 2004 at 252-53; Ex. 1039, Vignot.)

C. Understanding and Classification of NETs

93. Neuroendocrine tumors (NETs) are a heterogeneous group of tumors or neoplasms originating from various glands and organs and have been postulated to originate from a common precursor cell population. (Ex. 1020, Kaltsas at 458.) NETs originate from neuroendocrine cells in the pituitary, parathyroids,

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neuroendocrine adrenal gland, endocrine islets within the thyroid and pancreas, and endocrine cells of the digestive and respiratory tract. (*Id.*) NETs have been classified via their organ or tissue of origin as well as the degree of differentiation (e.g., "well-differentiated," "poorly differentiated"). (*Id.* at 458-459; Ex. 1052, B. Wiedenmann & U. Pape, "From Basic to Clinical Research in Gastroenteropancreatic Neuroendocrine Tumor Disease—The Clinician-Scientist Perspective," *Neuroendocrinology* 80:94-98 (2004) ("Wiedenmann") at 94-95.)

94. All neuroendocrine carcinomas are neuroendocrine tumors, however some neuroendocrine tumors are benign and therefore not neuroendocrine carcinomas.

95. NETs of the gastrointestinal tract and pancreas include carcinoids and pancreatic neuroendocrine tumors (e.g., gastrinoma, insulinoma, glucagonoma, VIPoma). (Ex. 1026, K. Oberg, "Management of neuroendocrine tumors," *Ann. Oncology* 15:iv293-298 (2004) ("Oberg 2004b"), at iv293.) Pancreatic NETs are also termed islet cell tumors. (*E.g.*, Ex. 1007, Buetow at 1176, Table 1 (collating data for "Islet Cell Tumors" such as insulinoma, gastrinoma, glucagonoma, somatostatinoma, VIPoma).)

96. NETs of the pancreas are rare, occurring in approximately 1 in 100,000, representing 1-2% of all pancreatic neoplasms. (Ex. 1028, Oberg and Eriksson, "Endocrine tumours of the pancreas," *Best Practice & Res. Clin.*

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Gastroent., 19(5):753-781, at 753 (Oct. 2005) ("Oberg & Eriksson").) Poorly differentiated endocrine carcinomas are sometimes misdiagnosed as pancreatic cancer (i.e., adenocarcinoma). (*Id.* at 755.) In contrast to other human tumors, the activation of an oncogene is not a common event in pancreatic NETs. (*Id.*) Genetic analysis has identified a number of genetic alterations in pancreatic NETs, including alterations in the PTEN gene. (*Id.* at 755-756, Table 1.)

97. PTEN protein has been found to be expressed in pancreatic islets. (Ex. 1051, L. Wang et al., "Differential Expression of the PTEN Tumor Suppressor Protein in Fetal and Adult Neuroendocrine Tissues and Tumors: Progression Loss of PTEN Expression in Poorly Differentiated Neuroendocrine Neoplasms," *App. Immunohistochemistry & Mol. Morphology*, 10:139-146 (2002) ("Wang 2002") at 139, 141, 144.) Poorly differentiated neuroendocrine carcinomas have been shown to have significantly reduced PTEN expression. (Ex. 1051, Wang 2002 at 140, Table 1, 144.) Further, pNETs have been shown to have altered PTEN behavior compared to normal islet cells, suggesting that decreased PTEN activity may play a role in the initiating events for pNETs. (Ex. 1031, A. Perren, et al. "Mutation and expression analyses reveal differential subcellular compartmentalization of PTEN in endocrine pancreatic tumors compared to normal islet cells," *The American Journal of Pathology* 157(4):1097-1103 (2000) at 1101-02.)

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98. PTEN protein regulates the mTOR signaling cascade by inhibiting the activation of Akt. (Ex. 1033, Rao at Fig. 2.) Cancer cells with decreased expression of PTEN have hyperactivation of mTOR signaling, and this constitutive activation of mTOR signaling contributes to tumorigenesis. (*Id.* at 623.) For this reason, mTOR inhibitors, such as rapamycin and its derivatives like everolimus, would have been expected to exert antitumor effects in tumor cells with hyperactivation of mTOR signaling. (*Id.* at 624.)

99. As of November 2005, treatment of NETs frequently involved multiple approaches including surgery and the use of standard cytotoxic chemotherapies. (*E.g.*, Ex. 1027, Oberg 2004 at 57-59.) In fact, cytotoxic treatment was considered the "gold standard" for treating NETs, most commonly a combination of streptozotocin plus 5-fluorouracil or doxorubicin." (*Id.*at 58-59.) Thus, pNETs were frequently treated with cytotoxic therapies, although surgery was known to be "the only approach that can achieve a complete cure in patients with NE tumours." (*Id.* at 57.) Somatostatin analogs, such as octreotide, had been shown to cause regression in some patients with pancreatic NETs, but regression was observed in a limited number of patients and very few were shown to have complete tumor regression. (Ex. 1062, C. Clements & E. Elias, "Regression of Metastatic VIPoma with Somatostatin Analogue SMS 201-995," *The Lancet* 325(8433):874-875 (April 13, 1985); Oberg 2004 at 59.) Treatment of these

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tumors remained difficult. (*See* Clements.) For these reasons, patients with unresectable pNETs (*i.e.*, patients whose tumors could not be removed or cured via surgery) would be administered cytotoxic chemotherapies but upon failure with that treatment or other limited available treatments, alternative treatments or approaches were needed.

VIII. THE PRIOR ART RELIED UPON

A. Oberg 2004

100. Oberg K, "Treatment of neuroendocrine tumors of the gastrointestinal tract," *Oncologia* 27(4):185-189 (2004) ("Oberg 2004"), published in April 2004. (Ex. 1027.) Oberg 2004 describes NETs as including "endocrine pancreatic tumor" and describes treatment of NET with Sandostatin LAR®. (*Id.*) Sandostatin LAR® was approved for use in VIPomas, a particular type of pNET. (Ex. 1060, Sandostatin LAR® label (Nov. 1998) at 7.) Therefore, a person of ordinary skill in the art would understand that Oberg 2004 includes the treatment of pNETs in the discussion of the treatment of NETs.

101. Oberg 2004 identifies that the "clinical management of metastatic NE tumors requires a multimodal approach." (*Id.* at 57.) Therefore, Oberg 2004 identifies and discusses the treatment of metastatic NETs. A person of skill in the art thus would understand that Oberg 2004's description of treating NETs includes the treatment of advanced NETs.

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102. Oberg 2004 graphically outlines the choices for therapy of NETs (*id.* at Fig. 1):

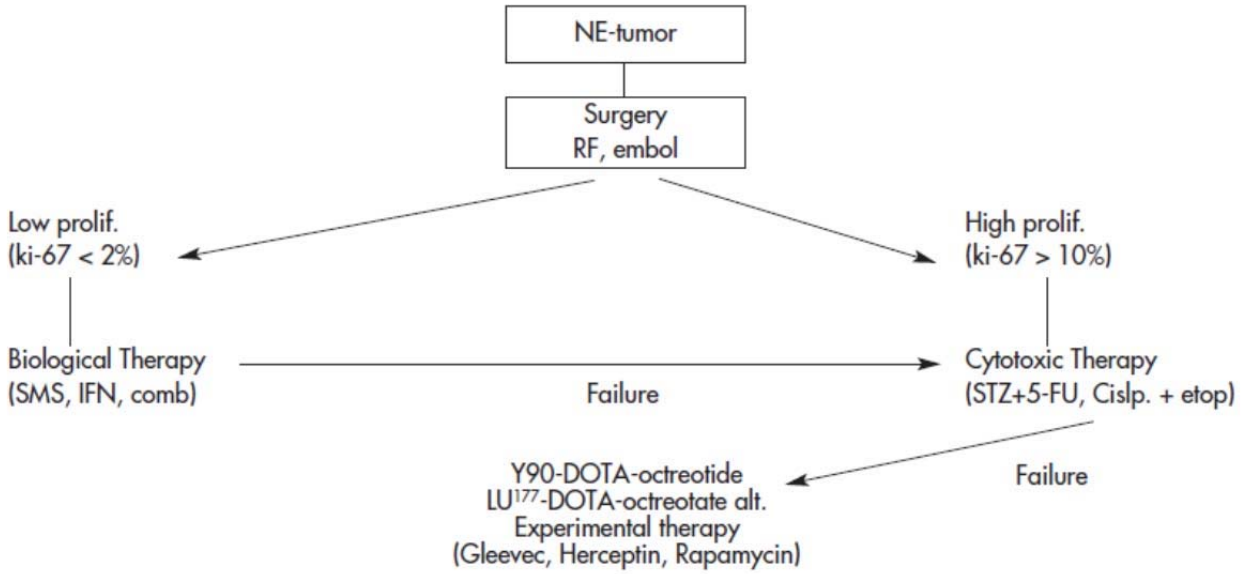

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

103. From this figure, a person of ordinary skill in the art would understand that in treating NET—including pNET—surgery would be the first option. If surgery was not successful or unavailable (and thus the tumor were unresectable), a person of ordinary skill in the art would next try biological therapies, such as interferon (IFN) or somatostatin inhibitors (SMS) for low proliferative tumors, and would try cytotoxic therapy (*e.g.*, chemotherapeutics) for high proliferative tumors and low proliferative tumors that failed to respond to biological therapies. Finally, for unresectable NETs—including unresectable pNETs—that did not respond to any of these therapies, Oberg teaches that a person of ordinary skill in the art should use a handful of other experimental therapies, including a rapamycin. Thus,

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Oberg teaches that administering a rapamycin after failure of cytotoxic chemotherapy would be an appropriate treatment for human patients with advanced NETs, including advanced pNETs.

104. Oberg 2004 states that "[a]nother 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." (*Id.* at 60.) Oberg 2004 identifies that "Rapamycin" "may block signal transduction through the m-TOR pathway." (*Id.* at 60.) Thus, Oberg 2004 identifies that "Rapamycin", as an inhibitor of "the m-TOR pathway" (m-TOR is a commonly used abbreviation for mammalian target of rapamycin), is an "interesting new compound" for the treatment of advanced NETs, including advanced pNETs. (*See id.*) As discussed above, as of November 2005, there were no reported clinical data of the administration of sirolimus (i.e., the parent rapamycin compound) to human cancer patients, and thus no specific data regarding dosing, safety, or efficacy of sirolimus for the treatment of any tumors. (*See* ¶ 79, above.) Therefore, a person of ordinary skill in the art would have understood the reference to "Rapamycin" in Oberg 2004 for the treatment of NETs to encompass the class of rapamycin compounds (as disclosed in Huang 2003) that had been reported to be safely administered to human cancer patients, namely everolimus (RAD001) and temsirolimus (CCI-779). A skilled artisan

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would have preferred to administer a compound with known dosing, safety, and efficacy information from clinical studies over a compound with no reported dosing or safety information for human cancer patients.

105. These teachings from Oberg 2004 are echoed in Wiedenmann 2004 (Ex. 1052), which published in October 2004.

106. Wiedenmann 2004 describes the (then) current state of treatment for neuroendocrine tumors, including neuroendocrine tumors of the pancreas. (Ex. 1052, Wiedenmann at 94-95.)

107. Wiedenmann states that "chemotherapy has only partially been effective in two NET groups: in pancreatic as well as in undifferentiated NETs." (*Id.* at 95.)

108. Wiedenmann describes that "other pharmaceutical agents . . . are currently evaluated in numerous clinical, oncological trials for non-NET indications. These include targeted therapies such as . . . rapamycin interfering with nuclear replication and membrane transport/secretion." (*Id.* at 97.) Wiedenmann states that these "new targeted therapies offer new hope especially in the field of angiogenesis, nuclear replication, cellular adhesion and signal transduction" "in order to improve current, rather limited treatment options especially in metastatic NET disease." (*Id.*) Thus, Wiedenmann confirms the

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interest in rapamycins for the treatment of advanced NETs described in Oberg 2004.

B. Boulay 2004

109. Boulay 2004 (Ex. 1005) published in January 2004.

110. Boulay discloses that everolimus was "being clinically developed" as "a novel therapeutic in the fight against human cancer." (Boulay 2004 at 252.) Specifically, Boulay notes the concurrent clinical trials of everolimus in humans with cancer, as well as recent reports with other "rapamycin derivatives," specifically temsirolimus. (*Id.* at 259-260.) Therefore, Boulay 2004 suggests everolimus for the administration of human cancer patients.

111. Boulay 2004 describes that everolimus has significant tumor activity against CA20948 tumors in rats. (*Id.* at Abstract, 254.)

112. CA20948 is a rat tumor line used as a model for pNET in laboratory studies. (*See* Ex. 1010, De Jong et al., "Therapy of neuroendocrine tumors with radiolabeled somatostatin-analogues." *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* 43: 356-366 (1999) ("De Jong") at Abstract, 357.) CA20948 is a not a common preclinical model; in other words, it is not a broadly applicable model and not typically used in standard *in vivo* screening analyses for anticancer/antitumor activity. It is a rare study that utilizes this model, which is a chemically-induced experimental pNET model. (Ex. 1010, De Jong.) A person of

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ordinary skill in the art would have understood that antitumor activity in this pNET model would support clinical development in pNET. Indeed, De Jong simultaneously discloses sequential preclinical and clinical studies of a somatostatin receptor-targeted agent in two rat pancreatic CA20948 tumor models (flank and liver injections) and 30 patients with advanced "mostly neuroendocrine progressing tumors", and specifically suggests that patients with GEP tumors (a class of tumors that includes pNETs) are candidates for this treatment on the basis of the reported data. (Ex. 1010, De Jong at 366.)

113. Boulay 2004 discloses that everolimus administered daily to CA20948 tumors in rats "resulted in antitumor activity characterized by statistically significant inhibition of tumor growth as compared with vehicle controls." (Boulay 2004 at 254.)

114. Boulay 2004 describes that everolimus was "administered p.o. daily at 0.5 or 2.5 mg/kg (x6/week), twice weekly at 5 mg/kg, or weekly at 0.5, 1, 2, 3, or 5 mg/kg." (*Id.* at 253.) Boulay further indicates that the daily dosages were given "qd." (*Id.* at 254, Fig. 1, legend.) A person of ordinary skill would understand that everolimus was administered to the rats by mouth (*i.e.*, *per os* or p.o., Latin for by mouth) in a single administration (*i.e.*, *quaque die* or qd, Latin for daily) of the indicated dose for six days in a week. If the dosages had been administered in divided doses multiple times per day, the article would have indicated the timing

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differently, *e.g.*, bd (*bis in die*, twice per day), tid (*ter in die*, three times per day). Because Boulay 2004 describes the everolimus dose as administered "qd," a skilled artisan would understand that this was a single daily unit dose.

115. Boulay 2004 discloses that "for all treatment schedules, [everolimus] was well tolerated, with no significant body weight loss or mortalities observed." (*Id.*at 254.)

116. Boulay 2004 teaches that everolimus "was found to be well tolerated and to elicit antitumor potency equivalent to that of the cytotoxic agent 5-FU." (*Id.* at 258.)

117. Boulay 2004 further discloses that "the work presented here is the first full publication demonstrating significant antitumor efficacy of a rapamycin derivative in an animal model of pancreatic cancer," (*id.*), and a person of skill in the art would recognize, based on the use of the CA20948 tumor line, that this activity was specific to pNET, (Ex. 1010, De Jong at 357).

C. O'Donnell

118. O'Donnell (Ex. 1029) was published in June 2003 and is an abstract related to a poster presented at the ASCO Meeting May 31-June 3, 2003.

119. O'Donnell reports that human patients with solid tumors were administered everolimus in various dose levels. (*Id.*) O'Donnell describes everolimus was administered "orally, once weekly" at 5, 10, 20, and 30 mg. (*Id.*)

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If the dose had been administered in divided doses, a person of ordinary skill would have expected that the abstract would have included the timing of the divided doses to have been included, *e.g.*, administered twice or three times per day. Because O'Donnell describes these dosages were administered "once," a person of ordinary skill in the art would understand that everolimus was administered as single unit dose.

120. O'Donnell further reports that everolimus was "well tolerated with only mild degrees" of side effects. (*Id.*)

121. O'Donnell describes that "7/8 patients exhibits inhibition for at least 7 days." (*Id.*)

122. O'Donnell describes that a patient with non-small cell lung cancer (NSCLC) responded to everolimus treatment as measured by scanning and biomarker monitoring. (*Id.*)

123. O'Donnell further teaches that additional clinical studies have been initiated to explore the ability of everolimus, as an mTOR inhibitor, to treat human tumors. (*See id.*)

D. Tabernero

124. Tabernero J et al., "A phase 1 study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-Inhibitor 40-O-(2-hydroxyethyl)-rapamycin (RAD001) in patients (pts) with

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advanced solid tumors," *Proc Am Soc Clin Oncol*, 24:Abs 3007 (2005) (Ex. 1037, "Tabernero") published in June 2005. Tabernero is an abstract related to a presentation from the 2005 ASCO Annual Meeting, May 13-17, 2005.

125. Tabernero reports that everolimus effectively inhibits mTOR in the advanced solid tumors studied and reports the safety and recommended dose for further development of everolimus as an antitumor agent in human patients with advanced solid tumors. (*Id.*) A person of ordinary skill in the art would understand that "advanced solid tumors" are locally advanced or metastatic malignancies that are not "liquid tumors" (i.e. hematological malignancies) and that pNETs are solid tumors.

126. Tabernero discloses that human patients with advanced solid tumors were administered everolimus in doses of 20, 50, or 70 mg weekly or 5 or 10 mg daily. (*Id.*) If the dose had been administered in divided doses, a person of ordinary skill would have expected that the abstract would have included the frequency of the divided doses to have been included, *e.g.*, administered twice or three times per day. Because Tabernero describes the doses only as having been administered "weekly" or "daily," a person of ordinary skill in the art would understand that these doses were administered in a single unit dose.

127. Based on the study, Tabernero recommends a unit dose of 10 mg/day of everolimus for further phase II/phase III clinical trials. (*Id.*)

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E. Duran

128. Duran, I. et al., "A Phase II Trial of Temsirolimus in Metastatic Neuroendocrine Carcinomas (NECs)," *Suppl. J of Clin Oncol*, 23:3096 (2005) (Ex. 1011, "Duran") published in June 2005. Duran is an abstract submitted to the 2005 ASCO Annual Meeting, May 13-17, 2005.

129. Duran discloses that temsirolimus was administered to patients with metastatic neuroendocrine carcinomas, a malignant subset of advanced NETs. (*Id.*) Duran further discloses that NECs include "islet cell carcinomas," which are malignant islet cell tumors. (*Id.*) Thus, a person of ordinary skill in the art would understand Duran to reference islet cell tumors in discussing NECs.

130. Duran discloses that 11 of the 23 patients with neuroendocrine carcinomas who were administered temsirolimus had previously received chemotherapy. Duran reports that temsirolimus "appears to have antitumor activity in NECs." (*Id.*)

131. Duran does not specifically disclose the administration of everolimus to patients with advanced pNETs, but does reference islet cell carcinomas, a subset of pNETs. (*Id.*)

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IX. MOTIVATIONS TO COMBINE THE PRIOR ART

A. Motivation to Combine Oberg 2004 with Boulay 2004 and O'Donnell

132. As of the earliest claimed priority date, November 2005, a person of ordinary skill in the art seeking to treat pNETs would have known of Dr. Kjell Oberg, Professor of Endocrine Oncology at the Medical Faculty of Uppsala University, as one of the preeminent clinical researchers in the treatment of NETs. Dr. Oberg was one of the founders of the European Neuroendocrine Tumor Society (ENETS) and had published widely on the treatment of NETs. (Ex. 1058, Oberg Biography.) One primary aim of ENETS was "to establish guidelines for the diagnosis and therapy of gastroenteropancreatic neuroendocrine tumors (GEP NETs)." (Ex. 1059, ENETS Info.) These guidelines were published in *Neuroendocrinology* in 2004. (Ex. 1032, Plockinger et al., "Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours," *Neuroendocrinology* 80:394-424 (2004) ("NET Guidelines").) Therefore, Dr. Oberg's research would have been a primary starting point for a person of ordinary skill in the art seeking to treat pNETs in 2005.

133. Oberg 2004 explicitly teaches that advanced pNETs should be treated with "Rapamycin", as an inhibitor of "the m-TOR pathway", following the failure of cytotoxic chemotherapy. Oberg 2004 includes a figure outlining the suggested treatment options for all NETs, including pNETs (Ex. 1027, Oberg 2004 at Fig. 1):

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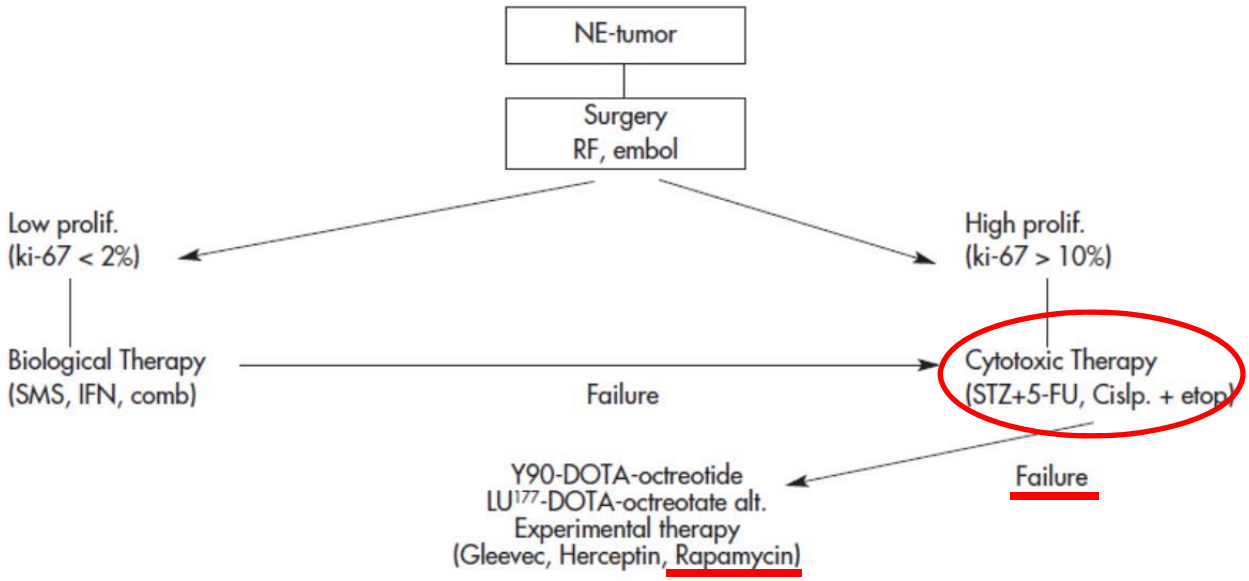

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

As can be seen in the Figure, Oberg 2004 teaches the then-advised treatment regimen for NETs, including pNETs. Specifically, Oberg 2004 teaches that high proliferative advanced NETs and low proliferative advanced NETs that failed to respond to biological therapy should be treated with cytotoxic therapy. Oberg 2004 further teaches that patients with advanced NETs, including advanced pNETs, that fail to respond to cytotoxic therapy should be administered "Rapamycin". (*Id.* at 60.)

134. The recommendation of Oberg 2004 is mirrored in Wiedenmann, which identified rapamycin as a "new hope" for improving the "limited treatment options" in NETs, including pancreatic NETS. (Ex. 1052, Wiedenmann at 97.)

135. By 2005, there was a significant body of published data regarding the administration of rapamycin derivatives, such as everolimus, to human patients as

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anticancer agents. (*E.g.*, Ex. 1054, Dukart; Ex. 1009, Dancey; Ex. 1037, Tabernero; Ex. 1011, Duran.) In contrast, there were no reported clinical data for the administration of rapamycin (i.e., the parent drug sirolimus) to human cancer patients at that time, and thus a skilled artisan would have had no data regarding dosing, safety, or efficacy for rapamycin for treating cancer patients. From this background, a person of ordinary skill in the art would be motivated to administer a rapamycin derivative, such as everolimus, with known similar biological activity to rapamycin (*i.e.*, an mTOR inhibitor) and reported successful and safe administration to human cancer patients, for the treatment of advanced pNETs as instructed by Oberg 2004. Further, everolimus was reported as having a potential "clinical advantage" over rapamycin because of its more favorable pharmacokinetic profile. (Ex. 1036, Schuler at 36-37.)

136. As of 2005, the predominant rapamycin derivatives reported in the oncology literature were everolimus (RAD001) and temsirolimus (CCI-779). A person of ordinary skill in the art looking for a rapamycin as an mTOR inhibitor to administer for the treatment of advanced pNETs as instructed by Oberg 2004 would have known from Boulay 2004 that everolimus was effective in a preclinical model of pNET.

137. Boulay 2004 describes the activity of everolimus in a pNET preclinical model, CA20948. (Ex. 1005, Boulay 2004 at 252.) Boulay describes

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administration of daily unit doses of 0.5 or 2.5 mg/kg of everolimus as a monotherapy to rats who had been injected with pNET tumor cells. (*Id.* at 253-54.) This daily dosage regimen resulted in statistically significant antitumor activity, and everolimus was "well tolerated, with no significant body weight loss or mortalities observed." (*Id.* at 254.) Thus, Boulay 2004 establishes that everolimus was known to be effective and safe in a rat model for pNET as a monotherapy.

138. Boulay 2004 specifically teaches that everolimus is an effective and safe therapy in a specific preclinical pNET model (in rats) but does not discuss the efficacy of everolimus in human cancer patients. A skilled artisan would have been motivated to identify information regarding the administration of everolimus to human cancer patients to determine whether everolimus would be a safe and effective therapy for humans. A person of ordinary skill in the art looking for information regarding everolimus as an anticancer agent in human cancer patients would have known from O'Donnell that everolimus is an effective and safe treatment for solid tumors in humans and would have been motivated to test everolimus in patients with pNETs. (Ex. 1029, O'Donnell at 808ab.)

B. Motivation to Combine Boulay 2004 with O'Donnell and Duran

139. Additionally, as of the earliest claimed priority date of the '224 patent in November 2005, a person of ordinary skill in the art would have been aware that

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the mTOR signaling pathway—the PI3K/Akt/PTEN signal transduction pathway—had been identified as a signaling network important for driving cell growth and proliferation in multiple tumor types, including specifically NETs. (*See* Ex. 1033, Rao; Ex. 1009, Dancey 2002; Ex. 1039, Vignot, and § VII.B, *supra*.) Thus, inhibitors of mTOR had been identified as a "promising class of novel therapeutics" that "may be useful in cancer therapy," and a person of ordinary skill in the art would have been motivated to look at known mTOR inhibitors as compounds of interest for anticancer therapeutics. (Ex. 1033, Rao at Abstract; *see also* Ex. 1039, Vignot.)

140. As of November 2005, the most well-studied mTOR inhibitors were rapamycin (i.e., sirolimus), everolimus, and temsirolimus, which had each been reported to have efficacy as antitumor agents. (*See* § VII.A, *supra*.)

141. Boulay 2004 discloses that everolimus was effective and well-tolerated in a preclinical model of pNET in rats. (Ex. 1005, Boulay 2004 at 252-254.) A person of ordinary skill in the art would have been motivated by the suggestion in the art to focus on mTOR inhibitors, such as everolimus, as cancer therapeutics to extend the work of Boulay 2004 to human cancer patients. A skilled artisan would have been motivated to identify information regarding the administration of everolimus to human cancer patients to determine whether everolimus would be a safe and effective therapy for humans. A person of

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ordinary skill in the art looking for information regarding everolimus as an anticancer agent in human cancer patients would have known from O'Donnell that everolimus is an effective and safe treatment for solid tumors in humans. (Ex. 1029, O'Donnell at 808ab.)

142. A person of skill in the art would have also looked to information regarding the use of rapamycins in humans with NETs to understand how NETs respond to treatment with rapamycin derivatives in humans. A skilled artisan would have known from Duran that temsirolimus showed efficacy in treating human cancer patients with advanced NETs. A person of ordinary skill in the art reviewing the animal model data in Boulay 2004 demonstrating the activity of everolimus against pNETs in rats would have had a reasonable expectation that everolimus would be effective in treating advanced pNETs in human cancer patients based on O'Donnell's teaching that everolimus was safe and effective in treating humans and Duran's teaching that the related rapamycin temsirolimus was safe and effective in treating humans with NETs.

C. Motivation to Combine Oberg 2004, Boulay 2004, O'Donnell, and Duran with Tabernero

143. Oberg 2004, Boulay 2004, O'Donnell, and Duran do not explicitly disclose a specific dose of everolimus to effectively treat advanced pNETs in human patients. Although dose titration to identify effective doses is a routine skill known to a person of ordinary skill in the art, a person of ordinary skill in the art

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would also search for any available information identifying a starting dose for the use of everolimus as an anticancer agent in order to treat advanced pNETs specifically. In the course of performing this search, a person of ordinary skill in the art would have known from Tabernero that patients in phase II and phase III clinical studies should be administered a unit dose of 10 mg/day of everolimus for the treatment of advanced solid tumors, which would include the advanced solid tumors of patients with advanced pNETs.

X. GROUNDS OF INVALIDITY

A. Ground 1: Claims 1-3 of the '224 Patent are invalid under 35 U.S.C. § 103 on the ground that they are rendered obvious by Oberg 2004 in view of Boulay 2004 and O'Donnell

1. Claim 1

144. Claim 1 of the '224 patent claims "[a] method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need thereof a therapeutically effective amount of everolimus as a monotherapy and wherein the tumors are advanced tumors after failure of cytotoxic chemotherapy."

145. Claim 1 is obvious in light of Oberg 2004 in view of Boulay 2004, and O'Donnell.

146. Oberg 2004 teaches that a rapamycin as a monotherapy after the failure of cytotoxic agents is an appropriate therapy for human patients with advanced NETs, including pNETs, as shown below. (Ex. 1027, Oberg 2004 at 60,

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Fig. 1.) Oberg 2004 identifies that a rapamycin "may block signal transduction through the m-TOR pathway." (*Id.* at 60.) Thus, Oberg 2004 identifies that "Rapamycin", as an mTOR inhibitor, is an "interesting new compound" for the treatment of advanced NETs, including pNETs. (*See id.*)

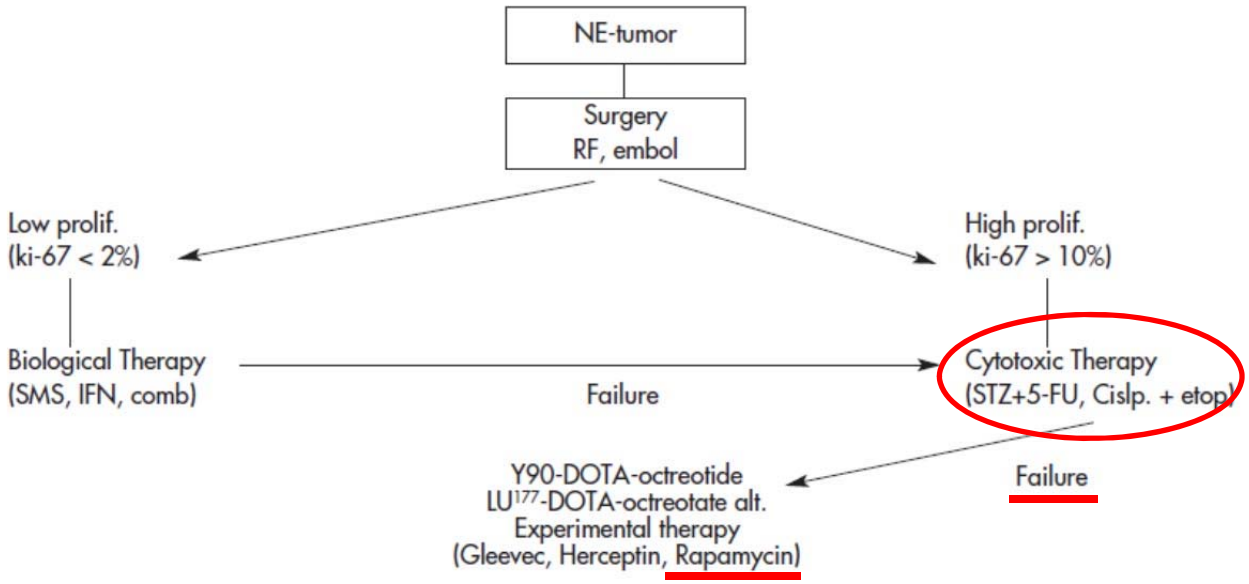

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

147. Boulay 2004 specifically teaches that everolimus "displays significant antitumor activity" in a preclinical pNET model in rats. (Ex. 1005, Boulay 2004 at 252-254.)

148. O'Donnell teaches that everolimus administered to human patients with solid tumors was well-tolerated and showed promising efficacy as an antitumor agent. (Ex. 1029, O'Donnell at 803ab.)

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149. Therefore, each limitation of claim 1 is taught in Oberg 2004, Boulay 2004, and/or O'Donnell. A person of ordinary skill in the art would be motivated to combine these teachings for the reasons discussed in § IX.A.

150. Oberg 2004 instructs the administration of a rapamycin for the treatment of advanced pNET in human cancer patients after failure of cytotoxic chemotherapy. A person of ordinary skill in the art would have a reasonable expectation of success in administering everolimus to human patients to treat advanced pNET in the manner instructed in Figure 1 of Oberg 2004 because the data in Boulay 2004 established that everolimus was effective as a monotherapy in treating rats with pNET and O'Donnell discloses that everolimus was safely and effectively administered to human cancer patients with solid tumors.

151. Thus, in my opinion, the method of treating advanced pNET in a human patient by administering everolimus as a monotherapy after the failure of cytotoxic chemotherapy would be obvious over Oberg 2004 in view of Boulay 2004 and O'Donnell.

2. Claim 2

152. Claim 2 depends from claim 1 and adds the further limitation that everolimus is administered as a unit dose of 10 mg/day. As described above, the disclosures of Oberg 2004, Boulay 2004, and O'Donnell teach everolimus as a treatment for advanced pNETs in human patients after the failure of cytotoxic

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chemotherapy. Finding an effective dosing regimen is routine experimentation for a person of ordinary skill in the art. Physicians routinely perform dose titration to ascertain a safe and effective dose to administer to their patients. In performing such dose titrations, a physician would identify information available in the literature regarding safe and effective doses. Boulay 2004 describes that daily unit doses of 0.5 and 2.5 mg/kg of everolimus were safe and effective in treating pNET in rats. O'Donnell describes that weekly unit doses of 5, 10, 20, and 30 mg of everolimus were safe and effective in treating solid tumors in humans. Other clinical reports indicated that everolimus was administered at 5-10 mg/day. Ex. 1039, Vignot at Table 1. A person of ordinary skill in the art would use this information to obtain a safe and effective unit dose of everolimus to treat humans with advanced pNET. Because O'Donnell describes that 30 mg of everolimus administered in a unit dose is safe in humans, a person of ordinary skill in the art would consider daily unit doses up to 30 mg in titrating doses to identify an effective daily unit dose of everolimus.

153. I am not aware of any information or data demonstrating that a unit dose of 10 mg/day is an optimal dose of everolimus for treating pNETs. Thus, in my opinion, a skilled artisan would have been able to identify a unit dose of everolimus that would safely and effectively treat human cancer patients with advanced pNET and that this unit dose would include 10 mg/day.

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154. Thus, in my opinion, claim 2 is obvious in view of the disclosures of Oberg 2004, Boulay 2004, and O'Donnell.

3. Claim 3

155. Claim 3 depends from claim 1 and adds the further limitation that the tumor is an islet cell tumor. Claim 3 is invalid as obvious in view of all the references discussed for claim 1.

156. As discussed above, a person of ordinary skill in the art would understand that "islet cell tumor" is another name for "pancreatic neuroendocrine tumors," as the '224 patent recognizes. (Ex. 1001, '224 patent at 2:49-54.) The instructions from Oberg 2004 apply equally to the "pancreatic neuroendocrine tumors" as well as "islet cell tumors." I am not aware of any data or evidence that islet cell tumors would have been understood or expected to behave differently than pNETs in responding to treatment. Therefore, in my opinion, a person of ordinary skill in the art would expect islet cell tumors to react identically to pNETs when treated with everolimus as suggested by Oberg 2004, Boulay 2004, and O'Donnell.

157. Accordingly, the method of treating advanced islet cell tumors in a human patient by administering everolimus as a monotherapy after the failure of cytotoxic chemotherapy would be obvious over Oberg 2004, Boulay 2004, and O'Donnell for the same reasons discussed for claim 1.

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B. Ground 2: Claim 2 of the '224 Patent is invalid under 35 U.S.C. § 103 on the ground that it is rendered obvious by Oberg 2004, Boulay 2004, and O'Donnell in view of Tabernero

158. Claim 2 depends from claim 1 and adds the further limitation that everolimus is administered as a unit dose of 10 mg/day. The elements of claim 1 are invalid as obvious in view of all the references and all the reasons discussed above in Ground 1.

159. Claim 2 is further obvious in view of Tabernero. Tabernero describes a phase I clinical study in patients with advanced solid tumors by administering various dosage regimens of everolimus. (Ex. 1037, Tabernero at 3007.) Tabernero concludes that "a dosage of 10 mg daily can be recommended for further phase II-III development with [everolimus] as a single agent." (*Id.*) Thus, Tabernero specifically directs a person of ordinary skill in the art to administer everolimus as a monotherapy to a patient with advanced solid tumors in a unit dose of 10 mg per day.

160. Accordingly, with the teaching from Tabernero, a person of ordinary skill in the art would have a reasonable expectation that administering a unit dose of 10 mg/day of everolimus as a monotherapy to a patient with advanced pNET in the manner described by Oberg 2004 would be successful in treating the advanced pNET. Thus, the combination of Oberg 2004, Boulay 2004, and O'Donnell in view of Tabernero renders claim 2 obvious.

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C. Ground 3: Claims 1-3 of the '224 Patent are invalid under 35 U.S.C. § 103 on the ground that they are rendered obvious by Boulay 2004 in view of O'Donnell and Duran

1. Claim 1

161. Claim 1 of the '224 patent claims "[a] method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need thereof a therapeutically effective amount of everolimus as a monotherapy and wherein the tumors are advanced tumors after failure of cytotoxic chemotherapy."

162. Claim 1 is obvious in light of Boulay 2004 in view of O'Donnell and Duran.

163. Boulay 2004 teaches that everolimus administered as a monotherapy was effective and well-tolerated in treating a rat model of pNET. (Ex. 1005, Boulay 2004 at 252-254.)

164. O'Donnell teaches that everolimus administered to human patients with solid tumors was well-tolerated and showed promising efficacy as an antitumor agent. (Ex. 1029, O'Donnell at 803ab.)

165. Duran reports that temsirolimus, another rapamycin , exhibited antitumor efficacy in human subjects with advanced NECs, a subset of advanced NETs. (Ex. 1011, Duran at 215s.) Duran further reports that temsirolimus was administered to patients with advanced NECs who had previously received cytotoxic chemotherapy. (*Id.*)

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166. In addition, a person of ordinary skill in the art would have understood that in treating human cancer patients with pNET, treatment with cytotoxic chemotherapy "has been associated with low success rates" even though it was considered the "gold standard" for NET treatment (*see, supra* ¶ 99; Oberg 2004 at 57) and upon progression of disease after cytotoxic chemotherapy, alternate treatments should be administered. (Ex. 1028, Oberg & Eriksson at 768 & Figure 2; Ex. 1025, Oberg, "Chemotherapy and biotherapy in the treatment of neuroendocrine tumours," *Ann. Oncol.* 12:S111-S114 (2001) at 112, Figure 1; Ex. 1063, O'Toole et al., "Chemotherapy for Gastro-Enteropancreatic Endocrine Tumours," *Neuroendocrinology* 80:79-84 (2004) at 79, 82, 83 (describing chemotherapy as a "reference" or "standard" treatment and stating that new targeted treatments were needed to advance treatment of these tumors).) As such, it would have been obvious to a person of ordinary skill in the art as of November 2005 that everolimus should be administered as a monotherapy to treat advanced pNETs after the tumor failed to respond to cytotoxic chemotherapy.

167. Boulay 2004 teaches that everolimus was safe and effective in treating pNETs in rats and states that everolimus is being "clinically developed" "as a novel therapeutic in the fight against human cancer." Boulay 2004 at 252. A person of ordinary skill would have a reasonable expectation that everolimus would be effective in treating humans with pNET because Boulay 2004 states that

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everolimus is being developed for treating human cancer patients, O'Donnell teaches that everolimus was safe and effective in treating solid tumors in humans, and Duran teaches that a closely related rapamycin, temsirolimus, was effective in treating advanced NETs in humans.

168. Therefore, each limitation of claim 1 is taught in Boulay 2004, O'Donnell, and Duran. A person of ordinary skill in the art would be motivated to combine these teachings for the reasons discussed in § IX.B.

2. Claim 2

169. Claim 2 depends from claim 1 and adds the further limitation that everolimus is administered as a unit dose of 10 mg/day. As described above, the disclosures of Boulay 2004, O'Donnell, and Duran teach everolimus as a treatment for advanced pNETs in human patients after the failure of cytotoxic chemotherapy. Finding an effective dosing regimen is routine experimentation for a person of ordinary skill in the art. Physicians routinely perform dose titration to ascertain a safe and effective dose to administer to their patients. In performing such dose titrations, a physician would identify information available in the literature regarding safe and effective doses. Boulay 2004 describes that daily unit doses of 0.5 and 2.5 mg/kg of everolimus were safe and effective in treating pNET in rats. O'Donnell describes that weekly unit doses of 5, 10, 20, and 30 mg of everolimus were safe and effective in treating solid tumors in humans. Other clinical reports

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indicated that everolimus was administered at 5-10 mg/day. Ex. 1039, Vignot at Table 1. A person of ordinary skill in the art would use this information to obtain a safe and effective unit dose of everolimus to treat humans with advanced pNET. Because O'Donnell describes that 30 mg of everolimus administered in a unit dose is safe in humans, a person of ordinary skill in the art would consider daily unit doses up to 30 mg in titrating doses to identify an effective daily unit dose of everolimus.

170. I am not aware of any information or data demonstrating that a unit dose of 10 mg/day is an optimal dose of everolimus for treating pNETs. Thus, in my opinion, a skilled artisan would have been able to identify a unit dose of everolimus that would safely and effectively treat human cancer patients with advanced pNET and that this unit dose would include 10 mg/day.

171. Thus, in my opinion, claim 2 is obvious in view of the disclosures of Boulay 2004, O'Donnell, and Duran.

3. Claim 3

172. Claim 3 depends from claim 1 and adds the further limitation that the tumor is an islet cell tumor. Claim 3 is invalid as obvious in view of all the references discussed for claim 1.

173. As discussed above, a person of ordinary skill in the art would understand that "islet cell tumor" is another name for "pancreatic neuroendocrine

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tumors," as the '224 patent recognizes. (Ex. 1001, '224 patent at 2:49-54.) The disclosure of Boulay 2004 applies equally to the "pancreatic neuroendocrine tumors" as well as "islet cell tumors." I am not aware of any data or evidence that islet cell tumors would have been understood or expected to behave differently than pNETs in responding to treatment. Therefore, in my opinion, a person of ordinary skill in the art would expect islet cell tumors to react identically to pNETs when treated with everolimus as suggested by Boulay 2004, O'Donnell, and Duran.

174. Accordingly, the method of treating islet cell tumors in a human patient by administering everolimus as a monotherapy after the failure of cytotoxic chemotherapy would be obvious over Boulay 2004, O'Donnell, and Duran.

D. Ground 4: Claim 2 of the '224 Patent is invalid under 35 U.S.C. § 103 on the ground that it is rendered obvious by Boulay 2004, O'Donnell, and Duran in view of Tabernero

175. Claim 2 depends from claim 1 and adds the further limitation that everolimus is administered as a unit dose of 10 mg/day. The elements of claim 1 are invalid as obvious in view of all the references and all the reasons discussed above in Ground 3.

176. Claim 2 is further obvious in view of Tabernero. Tabernero describes a phase I clinical study on patients with advanced solid tumors by administering various dosage regimens of everolimus. (Ex. 1037, Tabernero at 3007.) Tabernero

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concludes that "a dosage of 10 mg daily can be recommended for further phase II-III development with [everolimus] as a single agent." (*Id.*) Thus, Tabernero specifically directs a person of ordinary skill in the art to administer everolimus as a monotherapy to a patient with advanced solid tumors in a unit dose of 10 mg per day.

177. Accordingly, with the teaching from Tabernero, a person of ordinary skill in the art would have a reasonable expectation that administering a unit dose of 10 mg/day of everolimus as a monotherapy to a patient with advanced pNET in the manner described by Boulay 2004, O'Donnell, and Duran would be successful in treating the advanced pNET. Thus, the combination of Oberg 2004, Boulay 2004, and O'Donnell in view of Tabernero renders claim 2 obvious.

XI. SECONDARY CONSIDERATIONS

178. I am not aware of any secondary considerations that would make claims 1-3 of the '224 patent non-obvious over the prior art as described above. In my opinion, any possible secondary considerations would not overcome the compelling prior art that convincingly demonstrates that the subject matter of the claims of the '224 patent would have been obvious to a person of ordinary skill in the art as of November 2005.

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179. I reserve the right to supplement my opinions as appropriate if Novartis submits any allegations of such secondary considerations of non-obviousness.

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 statements 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.

Mark J. Ratain, M.D.

7/22/2016

Date

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