UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC., APOTEX CORP., APOTEX PHARMACEUTICALS HOLDINGS INC., and APOTEX HOLDINGS, INC.,
Petitioners,
v.

OSI PHARMACEUTICALS, INC.,
Patent Owner.

U.S. Patent No. 6,900,221
Issue Date: May 31, 2005
Title of Patent: Stable Polymorph on N-(3-ethylphenyl)-6,7-bis(2methoxyethoxy)-4-quinazolinamine hydrochloride, Methods of Production, and Pharmaceutical uses thereof

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Case No.: T.B.D.

DECLARATION OF GIUSEPPE GIACCONE, M.D., Ph.D.

I, Giuseppe Giaccone M.D. Ph.D, declare and state as follows:

1. I have been retained by counsel for Petitioners Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc. (collectively, "Petitioners") to review and analyze certain facts concerning U.S. Patent No. 6,900,221 ("the '221 patent"), and in particular, issued claims 44-47 and 53 of the '221 patent.

2. The opinions and conclusions I express in this declaration are based on my education, my extensive experience in the diagnosis and treatment of various lung cancers, and my review of materials related to this matter.

I. QUALIFICATIONS

3. I am currently the Associate Director for Clinical Research and Professor of Medical Oncology and Pharmacology at the Lombardi Comprehensive Cancer Center, Georgetown University. I oversee clinical research in oncology at Georgetown University Medical Center as well as in the Medstar Cancer Network (which comprises several hospitals in Maryland and the District of Columbia). In particular, I am responsible for research on the treatment and diagnosis of thoracic malignancies, which include lung cancer.

4. I earned my undergraduate degree in 1974 from Liceo Scientifico Galileo Ferrari, and my medical degree in 1980 from the University of Torino Medical School, both of which are located in Torino, Italy.

5. After earning my medical degree, I completed an internship, residency, and fellowships in medical oncology. In particular, from 1988 to 1990, I was a visiting fellow at the National Cancer Institute Navy Medical Oncology Branch in Rockville, Maryland. After completing my fellowship at the National Cancer Institute, I continued my studies and research in medical oncology at the Vrije University in Amsterdam, Netherlands, where, in 1995, I earned a doctorate from the Department of Medical Oncology. My thesis research concerned experimental and clinical research in lung cancer.

6. While working towards my doctorate degree, I held an appointment as an Assistant Professor at Vrije University in the Department of Medical Oncology. I was later promoted to Associate (1998) and then Full Professor (2000). I became the Head of the Department of Medical Oncology at Vrije University in 2003. During my 16 years at Vrije University, I cared for patients suffering from various lung cancers, and also oversaw research in diagnosis and treatment of lung cancer, including the development of new medicines for treating lung cancer.

7. In 2007, I returned to the National Cancer Institute in Bethesda, Maryland, as Chief of the Medical Oncology Branch.

8. In 2013, I joined the Lombardi Comprehensive Cancer Center at Georgetown University as the Associate Director for Clinical Research and Professor of Medical Oncology and Pharmacology.

9. During my 35-plus years in the field of medical oncology, I have authored over five hundred publications, many of which concern the diagnosis and treatment of various lung cancers. I have also authored many review articles concerning advances in the diagnosis and treatment of cancer, many of which dealt with advances in lung cancer therapy.

10. I have been, and am currently, on the editorial board for multiple scientific and medical journals, including Clinical Lung Cancer (1990 to present), Clinical Cancer Research (2002 to present), and Frontiers in Oncology (Editor in Chief, 2010 to present).

11. I have also presided over, been a board member, and been invited to speak at many symposia concerning lung cancer and oncology in general.

12. A more detailed account of my work experience, professional services, publications, and other qualifications is listed in my *Curriculum Vitae*, which is attached here to as **Appendix A**.

13. I have no financial interest in the outcome of this proceeding. I am being compensated at my standard hourly consulting rate for my time spent working on this matter, and my compensation is in no way contingent on the conclusions I reach herein, the specifics of my testimony, or the outcome of this proceeding.

II. MATERIALS REVIEWED

14. In forming my opinions, I have reviewed, among other things, the '221 patent and papers filed in the U.S. Patent and Trademark Office ("PTO") in connection with prosecution of the applications that led to the '221 patent, which I understand constitute the prosecution history of the '221 patent. A full list of materials I have considered can be found in **Appendix B**.

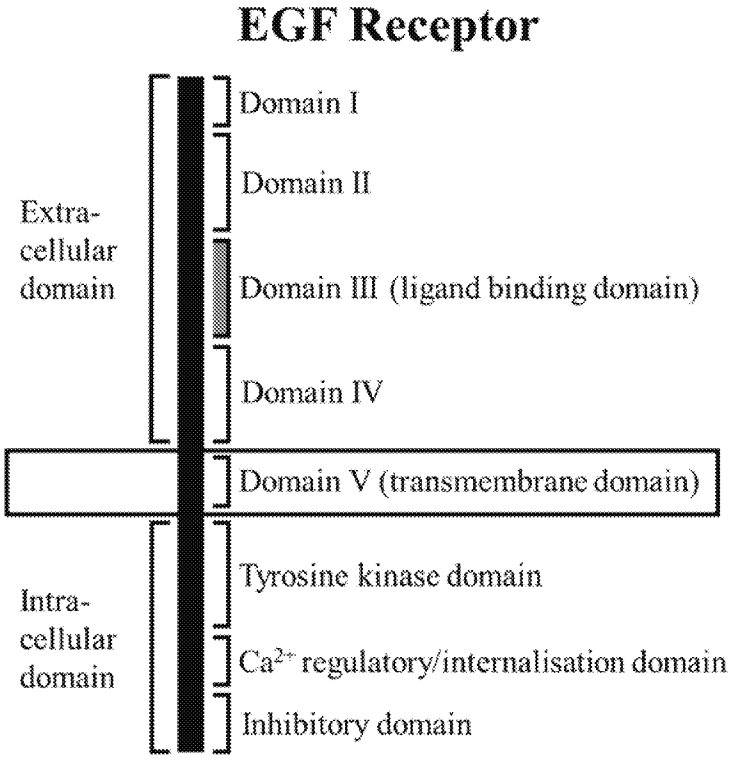
III. TECHNICAL BACKGROUND

A. Cancer and Epidermal Growth Factor Receptors

15. Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer cells oftentimes proliferate more quickly than other cells in the body in response to growth factors. One such growth factor is epidermal growth factor ("EGF"), which promotes cell proliferation and is found in almost all body fluids under normal physiological conditions. (*See, e.g.,* V. Rusch *et al.*, "The Epidermal Growth Factor Receptor and its Ligands as Therapeutic Targets in Human Tumors," *Cytokine & Growth Factor Reviews* 7(2):133-141 (1996) (**Ex. 1017**).)

16. Scientists have studied the role of EGF receptors in promoting tumor cell growth since at least the early 1980s. The receptor for EGF is a transmembrane glycoprotein found on the surface of many cells that includes: (1) an extracellular ligand-binding domain capable of binding a ligand such as EGF or

transforming growth factor-alpha ("TGF-α"); (2) a hydrophobic transmembrane region; and (3) an intracellular domain facing the cytoplasm. (*See* B.R. Voldborg *et al.*, "Epidermal growth factor receptor (EGFR) and EGFR mutations, function and possible role in clinical trials," *Ann. Oncol. 8*:1197-1206 (1997) (**Ex. 1019**) at 1197-98.) The structure of the EGF receptor is summarized in the following schematic diagram:



(*See id.* at 1198.)

17. Binding of a ligand (*e.g.*, EGF or TGF-α) at the extracellular ligand binding region transduces a signal across the cell membrane to the cytoplasm that results in intracellular phosphorylation of tyrosines, which subsequently leads to

downstream signaling that promotes the growth and survival of tumor cells. (*Id.* at 1197.)

B. EGF Receptors and Lung Cancer

18. Beginning in the early 1980s, extensive work began to examine the role of EGF receptors in promoting the growth of various lung cancers. It was recognized that lung cancers could be generally classified as either "small-cell" lung cancer (*i.e.*, "SCLC"), which accounted for about 20% of cases, or "non-small cell lung cancer" (*i.e.*, "NSCLC") which accounted for about 80% of cases. In 1999, and still today, the first step in the treatment of lung cancer by a person of ordinary skill in the art is a correct diagnosis of whether a patient suffers from NSCLC or SCLC.

19. Whereas the EGF receptor is largely absent from the surface of SCLC cells, it was found that well over 80% of NSCLC cell lines contained elevated levels of EGF receptors. (*See, e.g.*, Veale *et al.*, "The relationship of quantitative epidermal growth factor receptor expression in non-small cell cancer to long term survival," *Br. J. Cancer 68*:162-65 (1993) (**Ex. 1024**); Haeder *et al.*, "Epidermal Growth Factor Receptor Expression in Human Lung Cancer Cell Lines," *Cancer Res. 48*:1132-36 (1988) (**Ex. 1025**); Veale *et al.*, "Epidermal growth factor receptors in non-small cell lung cancer," *Br. J. Cancer 55*:513-16 (1987)

(**Ex. 1026**); T. Cerny, "Expression of epidermal growth factor receptor (EGF-R) in human lung tumours," *Br. J. Cancer 54*:265-69 (1986) (**Ex. 1018**).

20. Thus, by 1999, a person of ordinary skill in the art would have known that NSCLC is one of two types of lung cancer. Additionally, persons of ordinary skill in the art would have known that high levels of EGF receptors present on lung cancer tumor cells would more likely be NSCLC, and that strategies aimed at inhibiting EGF receptor phosphorylation were meant for treating NSCLC. (*See* **Ex. 1009**; **Ex. 1010**; **Ex. 1011**; **Ex. 1014**; **Ex. 1020**.)

C. EGF Receptor Variants

21. Characterization of EGF receptors elucidated mutations that modify the extracellular domain. (*See* **Ex. 1019** at 1198, col. 2.) By 1997, variant III (vIII or EGFRvIII), which included a deletion of a large portion of the EGFR gene, was the best understood of the variants (and was also the most often overexpressed in human cancer cells). (*See* **Ex. 1019** at 1198, col. 2.)

22. It had been shown that the deletions resulted in dimerization of the extracellular ligand binding site which caused self-activation of EGFR leading to downstream tumor cell growth. (*See* **Ex. 1019** at 1199, col. 1.) As a result, EGFRvIII was not affected by "indirect" inhibitors such as monoclonal antibodies, which acted on the ligand-binding domain. (*See* C.J. Wikstrand *et al.*, "Cell Surface Localization and Density of the Tumor-associated Variant of the

Epidermal Growth Factor Receptor, EGFRvIII," *Cancer Res. 57*:4130-40 (1997) (**Ex. 1023**).) Instead, inhibiting EGFRvIII at the intracellular tyrosine kinase domain demonstrated downstream antitumor effects. (D.K. Moscatello *et al.*, "Constitutive Activation of Phophatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor," *J. Biol. Chem. 273*(1):200-206 (1998) (**Ex. 1014**).)

23. By the late-1990s it was known that EGFRvIII was present in approximately 16% of NSCLC cells. (*See* I.E. Garcia de Palazzo *et al.*, "Expression of Mutated Epidermal Growth Factor Receptor by Non-Small Cell Lung Carcinomas," *Cancer Res. 53*:3217-20 (1993) (**Ex. 1022**).)

D. The Development of Therapeutics Targeting EGF Receptors

24. By the mid-1990's, extensive research was underway to develop cancer treatments that stopped tumor cell growth by "indirect" or "direct" inhibition of tyrosine phosphorylation by EGF receptors. Because the EGF receptor was known to be over-expressed in NSCLC cells, NSCLC was viewed as a prime candidate for treatment using drugs that indirectly and/or directly block the phosphorylation of tyrosine kinase at EGF receptors.

25. Monoclonal antibodies capable of blocking ligand-binding at the extracellular receptor domain were among the first therapies extensively studied in human NSCLC tumor cell lines. (*See, e.g.*, J.B. Gibbs, "Anticancer drug targets:

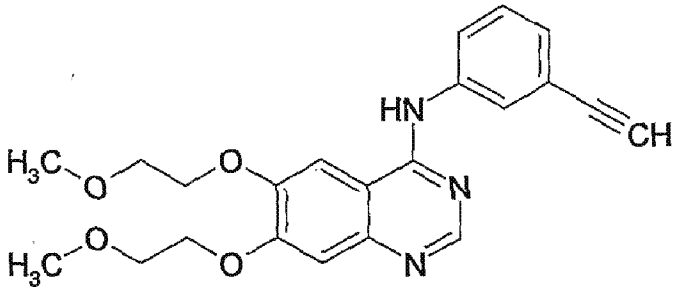
growth factors and growth factor signaling," *J. Clin. Invest. 105*(1):9-13 (Jan. 2000) ("*Gibbs*", **Ex. 1010**) at 10, col. 1; M. Lee *et al.*, "Epidermal Growth Factor Receptor Monoclonal Antibodies Inhibit the Growth of Lung Cancer Cell Lines," *J. Nat'l Cancer I. Monographs* (13):117-123 (1992) ("*Lee*", **Ex. 1020**); H. Masui *et al.*, "Growth Inhibition of Human Tumor Cells in Athymic Mice by Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies," *Cancer Res. 44*:1002-07 (1984) ("*Masui*", **Ex. 1021**).)

26. The "direct" blocking strategy sought to identify ligands that would directly inhibit tyrosine phosphorylation of the EGFR at the intracellular tyrosine kinase domain. (*See, e.g.*, **Ex. 1010** at 10, col. 1; U.S. Patent No. 5,747,498 ("*Schnur*", **Ex. 1009**) at col. 1, ll. 45-53; J.D. Moyer *et al.*, "Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase," *Cancer Res. 57*:4838-48 (1997) (**Ex. 1016**); A.E. Wakeling *et al.*, "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," *Breast Cancer Res. Tr. 38*:67-73 (1996) (**Ex. 1013**).) Of these early compounds, 4-anilinoquinazolines emerged as a leading class of compounds having potent antitumor properties. (**Ex. 1013**.)

E. Erlotinib

27. By 1999, erlotinib was developed as a leading 4-anilinoquinazoline compound that would directly inhibit phosphorylation at the intracellular tyrosine kinase domain. (**Ex. 1009**; **Ex. 1010**.)

28. The drug erlotinib is described chemically as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or [6,7-Bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine, and has the following chemical structure:



(*See, e.g.*, **Ex. 1016** at 4839, col. 1.)

29. During joint clinical development of erlotinib between OSI and Pfizer, and then subsequently, only OSI, the hydrochloride salt of erlotinib was commonly referred by the identifier CP-358,774, which was prepared as set forth in PCT Pub. No. WO 96/30347. (*See* **Ex. 1016** at 4839, col. 1; *See also* V.A. Pollack *et al.*, "Inhibition of Epidermal Growth Factor Receptor-Associated Tyrosine Phosphorylation in Human Carcinomas with CP-358,774: Dynamics of Receptor Inhibition In Situ and Antitumor Effects in Athymic Mice," *J. Pharmacol. Exp.*

Ther. 291(2):739-748 (Nov. 1999) ("*Pollack*," **Ex. 1015**) at 740 ("CP-358,774 . . . a colorless, crystalline, anhydrous compound, was synthesized in our laboratories (Arnold and Schnur, 1998)).)

30. As of 1999, Erlotinib was known to be a potent inhibitor of the EGF receptor tyrosine kinase domain. (*See* **Ex. 1015**; **Ex. 1009**; **Ex. 1010**; **Ex. 1011**.) In various cultured human tumor cell lines that expressed EGF receptors, this small molecule prevented cancer cell proliferation and induced apoptosis of tumor cells. (*See* **Ex. 1015**.)

IV. U.S. PATENT NO. 6,900,221

A. The '221 Patent

31. I have reviewed the '221 patent. In general, the '221 patent discloses pharmaceutical compositions that contain specific polymorphic compositions of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (*i.e.*, erlotinib), methods of preparing the compositions, and methods of administering the compositions to treat various types of cancer.

32. I have reviewed the claims of the '221 patent. The vast majority of the claims of the '221 patent require polymorph form B of erlotinib.[1] However,

[1] This is true of claims 1-41, 43, and 55-79. Claims 1 and 5 of the '221 patent, for example, require erlotinib hydrochloride to be present as "a homogeneous crystalline polymorph . . . designated the B polymorph," or "a crystalline

claims 44-47 and 53 include no such limitation requiring a specific polymorphic form of erlotinib. Instead, claims 44-47 and 53 are directed to methods of treating various types of cancer using any polymorphic form of erlotinib. For example, claims 44-47 and 53 of the '221 patent recite the following:

> 44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.
>
> 45. The method of claim 44, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
>
> 46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).
>
> 47. The method of claim 44, for use in treatment of tumors that express EGFRvIII.
>
> 53. The method of claim 44 for the treatment of non-small cell cancer (NSCLC).

(**Ex. 1001** at col. 35, ll. 26–65.)

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polymorph . . . designated the B polymorph . . . which is free of the A polymorph." (*See* Ex. 1001, col. 31, ll. 37-44; ll. 58-66.)

B. The PTO's Reasons Why Claims 44-47 and 53 of the '221 Patent Were Allowed to Issue

33. I have reviewed portions of the prosecution history of the '221 patent relevant to the entry, review, and allowance of the challenged claims. Issued claims 44-47 of the '221 patent correspond to claims 64-67 that were pending during prosecution, and which were entered by way of an amendment dated June 19, 2002. (*See* **Ex. 1003** (Amendment dated June 19, 2002) at 28-29.) Issued claim 53 of the '221 patent correspond to claims 88 of the '272 application, and was entered by way of a subsequent amendment. (*See* **Ex. 1005** (Amendment dated February 28, 2003) at 36-37.)

34. The PTO initially rejected claim 64 (and dependent claims 65, 66, and 67) as anticipated by U.S. Patent No. 5,747,498. (*See* **Ex. 1004** (Office Action dated August 30, 2002) at 10-11 (citing **Ex. 1009** at col. 14, ll. 6-16, 28; col. 16, ll. 46-51; claims 28 and 29).) In response, OSI amended claim 64 and argued that *Schnur* did not disclose the use of erlotinib to treat any of the conditions that were claimed. (*See* **Ex. 1005** at 23, 35.) Specifically, OSI argued that, whereas *Schnur* discloses the use of erlotinib to treat lung cancer, the use of erlotinib to treat non-small cell lung cancer (NSCLC) is not mentioned. (*See* **Ex. 1005** at 23.)

35. The PTO subsequently allowed pending claim 64 to issue as claim 44 of the '221 patent (and claims depending therefrom) based on a finding that this

claim "is drawn to treatment of specific cancers by any polymorph of the claimed compounds. These specific cancers are not found in *Schnur* ('498)." (*See* **Ex. 1006** (Notice of Allowance dated June 18, 2003) at 6.)

36. Thus, it is my understanding that the PTO's sole reason for allowing claims 44-47 and 53 of the '221 patent to issue was that *Schnur* did not disclose the use of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (*i.e.*, erlotinib) to treat, *inter alia*, NSCLC (which is a subset of lung cancer). Instead, the PTO found that *Schnur* merely taught the use of erlotinib to treat "lung cancer." (**Ex. 1006**.)

C. Disclosure of Claims 44-47 and 53 of the '221 Patent in U.S. Provisional Application No. 60/164,907 and U.S. Provisional Application No. 60/193,191

37. I have reviewed U.S. Provisional Application No. 60/164,907 and 60/193,191. In my opinion the first express disclosure concerning the use of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (*i.e.*, erlotinib) to treat the conditions recited in claim 44, and in particular NSCLC, is in Provisional Appl. No. 60/193,191, which was filed March 30, 2000. (*See* **Ex. 1008** (Provisional Appl. No. 60/193,191) at 1, ll. 20-26; 2, l. 21–3, l. 30; 4, ll. 10-13; and 7, l. 1)

38. In contrast, Provisional Appl. No. 60/194,907, which was filed November 11, 1999, lacks express disclosure for the use of erlotinib to treat any of

the conditions recited in claim 44, including non-small cell lung cancer (NSCLC), pediatric malignancies, any tumors caused or promoted by human papilloma virus (HPV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases. (*See* **Ex. 1007** (Provisional Appl. No. 60/194,907).) Instead, Provisional Appl. No. 60/194,907 discloses the use of erlotinib hydrochloride (*i.e.*, the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine) to treat conditions as described in *Schnur*. (*See* **Ex. 1007** at 6, l. 8 to 8, l. 8; and 10, l. 3 to 11, l. 24; *compare* **Ex. 1010** at col. 14, ll. 1-30.)

V. LEGAL STANDARDS

39. I am not an attorney, and counsel for Petitioners informed of the following legal standards that are relevant to my opinions.

40. I understand that an issued patent is presumed to be valid, and that the burden of establishing invalidity as to any claim of a patent rests upon the party asserting invalidity, here Petitioners.

A. Anticipation

41. I understand that a prior art reference "anticipates" a claim, and thus renders the claim unpatentable, if all elements of the claim are disclosed in that single prior art reference, either expressly or inherently.

42. Thus, I also understand that a prior art reference having an identical disclosure to that of the challenged claims would anticipate those claims to the extent that the claims are enabled and described.

B. Obviousness

43. I understand that an obviousness inquiry requires consideration of the following factors: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any objective indicia of non-obviousness, such as commercial success, long-felt but unresolved need, failure of others, industry recognition, copying, and unexpected results.

44. I further understand that a claim is invalid as obvious if the differences between the subject matter as claimed and the prior art would have been obvious to a person having ordinary skill in the art.

45. It is my understanding that the analysis of all prior art references are to be looked at from the viewpoint of a person of ordinary skill in the art at the time the invention was made. Thus, the use of hindsight is not permitted.

46. It is my understanding that differences between the claimed invention and the prior art can be deemed obviousness if the difference is simply within the common knowledge of a person of ordinary skill in the art.

47. I also understand that obviousness may be based on a combination of references according to known methods to yield predictable results. I further understand that obviousness based on a combination of references does not require an explicit suggestion in any of the references to combine them, if, as a matter of skill or practice in the field it would be known to do so.

48. I also understand that in other circumstances, a claimed invention simply substitutes one known element for another to obtain predictable results. .

C. The Field of the Invention and the Level of Ordinary Skill in the Art

49. I was asked to consider the technical field(s) relevant to the subject matter of the '221 patent, as well as the level of skill that an ordinary person working in that technical field would have had in 1999 to 2000 (the earliest priority date of the '221 patent). In my opinion, the technical field(s) relevant to the subject matter of the '221 patent concern the diagnosis and treatment of various cancers, among them, lung cancer.

50. I understand that factors such as the education level of those working in the field, the sophistication of the technology, the types of problems encountered in the art, the prior art solutions to those problems, and the speed at which innovations are made may help establish the level of ordinary skill in the art. I understand that a person of ordinary skill has the ability to understand the

technology and make modest adaptions or advances, and that a person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.

51. Further, I understand that a person of skill in the art is not necessarily an individual, but instead could be a team of individuals. Thus, a person of ordinary skill in the art could involve a collaboration between a medical doctor and, for example, others having relevant expertise in pharmaceutical formulation development and pharmaceutical drug development.

52. In my opinion, a person of ordinary skill in the art relevant to the '221 patent would have a medical degree and at least some specialized training in oncology. More specifically, a person of ordinary skill in the art relevant to the '221 patent would likely have at least some specialized training in thoracic oncology. Further, in my opinion a person of ordinary skill in the art would have several years of clinical experience, and a substantive understanding and experience using the medications and therapies effective for treating various lung cancers at the relevant time. A person of ordinary skill in the art would be aware of current advances at the time in the use of various medications and therapies to treat cancer.

53. As of the earliest priority date of the '221 patent, I was a person of at least ordinary skill in the medical arts relevant to the '221 patent. My opinions

provided herein are made through the lens of a person of ordinary skill in the art in the 1999 to 2000 time frame.

D. Claim Construction

54. I understand that in deciding whether to institute Petitioners' request for *Inter Partes* Review, the first step in the PTO's analysis will be to determine the scope of the claims of the '221 patent. I understand that the PTO presumes that the words of a patent claim have their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language.

55. In my opinion, a person of ordinary skill in the art having reviewed the claims, the specification, and the prosecution history of the '221 patent would understand the words used in claims 44-47 and 53 of the '221 patent to have their plain and ordinary meaning.

E. Priority Date of the '221 Patent

56. I have been advised by counsel that:

- A document that was made publicly available between March 30, 1999 and March 29, 2000 is prior art to claims 44-47 and 53 of the '221 patent under pre-AIA 35 U.S.C. § 102(a);
- A document that was made publicly available before March 30, 1999 is prior art to claims 44-47 and 53 of the '221 patent under pre-AIA 35 U.S.C. § 102(b); and

– A patent filing made in the United States before March 30, 2000, and which became publicly available after March 30, 2000, is prior art to claims 44-47 and 53 of the '221 patent under pre-AIA 35 U.S.C. § 102(e).

VI. DETAILED DESCRIPTION OF THE PRIOR ART

57. As discussed below, the prior art discloses, teaches, or suggests every limitation of claims 44-47 and 53, including the subject matter the PTO found missing from the prior art in the Reason For Allowance.

A. U.S. Patent No. 5,747,498 (Ex. 1009)

58. U.S. Patent No. 5,747,498 ("*Schnur*", **Ex. 1009**) was published on May 5, 1998, which is more than one year before the priority date of claims 44-47 and 53 of the '221 patent. As such, I understand that *Schnur* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA).

59. *Schnur* discloses a class of 4-anilinoquinazoline compounds that are "potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (*e.g.*, anticancer) in mammals, in particularly humans." (**Ex. 1009** at col. 14, ll. 1-6.) *Schnur* recognizes that inhibiting phosphorylation of EGF receptors at the intracellular tyrosine kinase domain is the underlying mechanism to prevent tumor growth. (**Ex. 1009** at col. 1, ll. 30-63; col. 14, ll. 35-41.) Further, *Schnur* discloses

that the compounds, including erlotinib, are suitable for use in the treatment of lung cancer. (*See* **Ex. 1009** at col. 5, ll. 56-60; col. 14, ll. 6-13.)

60. *Schnur* discloses that the effective dosages are dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician. (**Ex. 1009** at col. 15, ll. 55-58.) *Schnur* further teaches that in general, the effective dosages are disclosed to be in the range of approximately 0.001-100 mg/kg and preferably 1 to 35 mg/kg in single or divided doses. (**Ex. 1009** at col. 15, ll. 58-61.) For an Average 70 kg human, the taught amount would be from 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. (**Ex. 1009** at col. 15, ll. 61-62.)

61. *Schnur* also teaches that a specific amount of active compound, for instance a therapeutically-effective amount of erlotinib, can be administered as part of a pharmaceutical composition. (**Ex. 1009** at col. 15, l. 48 – col. 16, l. 19.) *Schnur* states that methods of preparing the various pharmaceutical compositions are taught to be routine to a person of ordinary skill in the art, and further cites a well-known reference titled *Remington's' Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

62. *Schnur* further discloses that the compounds can be used to treat cancer as a sole therapy "or may involve, in addition to the active compound, one or more other antitumor substances" that can be simultaneously, sequentially,

cyclically, or separately. (*See* **Ex. 1009** at col. 16, ll. 46-51.) Thus, *Schnur* discloses the use of the disclosed compounds (including erlotinib) along with a neo-adjuvant/adjuvant monotherapy—that is, an additional anti-tumor treatment given along with (before or after) treatment with erlotinib.

63. *Schnur* discloses that the compounds can be prepared as pharmaceutically acceptable salts, such as an acid-addition salt, and "can exist in solvated, as well as unsolvated forms, such as the hydrated forms." (**Ex. 1009** at col. 13, ll. 25-26; ll. 30-36.)

64. *Schnur* specifically discloses the synthesis of the freebase as well as the hydrochloride salt of erlotinib (*i.e.*, [6-,7-Bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride). (*See* **Ex. 1009** at col. 22, ll. 30-50 (Example 20).) In discussing *Schnur*, the '221 patent expressly admits that *Schnur* teaches an anhydrous form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride. (**Ex. 1001** at col. 8, ll. 43-45; col. 13, ll. 13-15.) Further, the '221 patent acknowledges that *Schnur* discloses a mixture of polymorphs A and B of erlotinib hydrochloride, and that the mixture is anhydrous. (*See* **Ex. 1001** at col. 8, ll. 43-45; col. 13, ll. 13-15.)

B. J.B. Gibbs, "Anticancer drug targets: growth factors and growth factor signaling," *J. Clin. Invest. 105*(1):9-13 (Jan. 2000) (Ex. 1010)

65. J.B. Gibbs, "Anticancer drug targets: growth factors and growth factor signaling," *J. Clin. Invest. 105*(1):9-13 (Jan. 2000) ("*Gibbs*", **Ex. 1010**) was published in January 2000, which is approximately two months before the priority date of claims 44-47 and 53 of the '221 patent. As such, I understand that *Gibbs* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(a) (pre-AIA).

66. *Gibbs* is a review article that provides an "overview of a growth factor signal transduction system, with a focus on those points that have been translated to drugs or clinical candidates." (**Ex. 1010** at 9, col. 1.) *Gibbs* discloses that CP-358,774 (*i.e.*, anhydrous erlotinib hydrochloride) is one of a well-known class of potent EGFR tyrosine kinase inhibitors that achieve anti-tumor activity, and that erlotinib had entered Phase II clinical trials which means the Phase I clinical trials demonstrated that erlotinib was administered to humans. (*See* **Ex. 1010** at 9, col. 1; 10, col. 1, Table 1.) Further, *Gibbs* discloses that erlotinib was shown to have good anti-cancer activity "with an acceptable therapeutic index, particularly in patients with NSCLC." (**Ex. 1010** at 10, col. 1.)

67. A person of ordinary skill in the art would have known that clinical trials involving a drug such as erlotinib necessarily involve administration to

mammals—*i.e.*, human subjects. Phase I clinical trials in cancer typically involve administration of a drug to a small group of healthy volunteers or, more often, advanced cancer patients with a variety of cancer types in order to evaluate, *inter alia*, its safety, determine a safe dosage range, and identify any side effects. Phase II clinical trials, as referred to in *Gibbs*, typically involve administration of the drug to a specific patient population.

68. As a person of ordinary skill in the art would have known at the time, "therapeutic index" refers to a comparison between the amounts of a drug, in this case erlotinib, which causes a therapeutic effect compared to that which causes toxicity. Therefore, a person of ordinary skill in the art reading *Gibbs* would have understood that studies conducted in patients suffering from NSCLC had established the amount of erlotinib necessary for therapeutic effects in those patients, as well as the amount that would cause toxicity. In my opinion, a person of ordinary skill in the art reading *Gibbs* would have understood that a therapeutically effective amount of erlotinib had been administered to human subjects suffering from NSCLC.

C. Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the Fiscal Year Ended September 30, 1998 Commission File Number 0-15190 OSI Pharmaceuticals, Inc. (Ex. 1011)

69. I have reviewed the declaration by Lawrence Lese, and understand that the "Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the Fiscal Year Ended September 30, 1998 Commission File Number 0-15190 OSI Pharmaceuticals, Inc." ("*OSI's 10-K*" **Ex. 1011**) was filed on December 23, 1998 and was published in the last week of December 1998. ("*Lawrence Lese Declaration*" **Ex. 1012**, ¶ 25.)

70. It is my opinion that *OSI's 10-K* discloses CP-358,774, the project name for erlotinib at that time, as a treatment for NSCLC. (**Ex. 1011** at 6.)

71. *OSI's 10-K* further describes that erlotinib is a potent, selective and orally active inhibitor of the epidermal growth factor receptor. (**Ex. 1011** at 6.)

72. *OSI's 10-K* also reports that erlotinib completed Phase I studies and is in Phase II clinical trials for cancers including NSCLC. A person of ordinary skill in the art would have understood this to mean that erlotinib was administered to a human for the treatment of NSCLC. (**Ex. 1011** at 6.)

D. A.E. Wakeling *et al.*, "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," *Breast Cancer Res. Tr. 38*:67-73 (1996) (Ex. 1013)

73. A.E. Wakeling *et al.*, "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," *Breast Cancer Res. Tr. 38*:67-73 (1996) ("*Wakeling*", **Ex. 1013**) was published in 1996, which is more than one year before the earliest priority date of claims 44-47 and 53 of the '221 patent. As such, I understand that *Wakeling* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA).

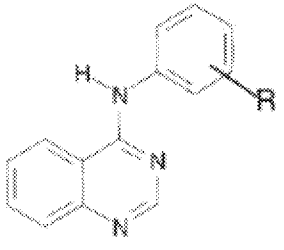
74. *Wakeling* first summarizes the state of the art in 1996 concerning the types of tumors that exhibit aberrant expression of epidermal growth factors (EGFR) and the role of EGFR in tumor proliferation. (**Ex. 1013** at 67-68.) Specifically, *Wakeling* teaches that aberrant expression of EGFR was known to occur in common solid tumors of epithelial origin. (**Ex. 1013** at 67.) Common solid tumors of epithelial origin known at that time concerned, *inter alia*, the breast, mouth, vulva, kidney, and lung. (**Ex. 1013** at 67-69.) *Wakeling* further discloses that the role of epidermal growth factors in the proliferation of various solid tumors of epithelial origin was well established over about a decade of research starting in the mid-1980s. (**Ex. 1013** at 67.)

75. By 1996, *Wakeling* establishes that a person of ordinary skill in the art understood that mitogenesis, or cell proliferation, was mediated by activation of intracellular signaling cascades. (**Ex. 1013** at 67-69.) A person of ordinary skill in the art would have further understood that *Wakeling* also establishes that this

EGFR mediated mechanism is ubiquitous among epithelial tumors that display aberrant EGFR expression.

76. To inhibit this known signaling pathway, *Wakeling* presents biologic activity data for a class of compounds that share the same basic 4-anilioquinazoline structure shown below:

Table 1. Biological activity of anilino-quinazoline derivatives



Compound	Substituent	Inhibition of EGF-RTK IC50 (μM)	Inhibition of EGF stimulated KB cells IC50 (μM)	Inhibition of basal KB cell growth IC50 (μM)
1	H	0.55	12.5	38
2	o-Cl	1	>12.5	25
3	m-Cl	0.04	1.2	15
4	p-Cl	0.5	3.6	6
5	m-F	0.12	4.7	25
6	m-Br	0.02	0.8	12.5
7	m-I	0.07	1.1	12.5
8	m-OMe	0.7	10–100	>10
9	m-Me	0.18	2.4	16.5
10	m-NMe_2	0.52	11	12.5
11	m-OH	0.65	7.3	28
12	m-NO_2	0.07	2.7	12.5
13	m-CF_3	0.16	3.9	12.5
14	m-CN	0.2	7.6	19
15	m-SMe	0.5	7.8	12.5

(**Ex. 1013** at 68, Table 1.)

77. *In vitro* testing showed that molecules having a particular substructure were the most potent inhibitors of EGFR. (**Ex. 1013** at 68, Table 1.) *Wakeling*

reported that substructures having the "R" group substituted at the meta position were the most potent. (**Ex. 1013** at Summary.)

78. *Wakeling* further reports that the most potent 4-anilinoquinazoline compounds have "R" groups that are small and non-polar. (**Ex. 1013** at Summary.)

79. *Wakeling* teaches that these 4-anilinoquinazoline-based structures inhibit tumor growth in vulval tumors (A431), oral squamous tumors (KB), kidney cells (NRK49F) and breast cancer cells (MCF-7). (**Ex. 1013** at Summary; 68-70.) A person of ordinary skill in the art would have understood that this class of compounds would likely inhibit epithelial lung tumors exhibiting aberrant expression of EGFR, particularly since *Schnur* confirms and extends the *Wakeling* study to lung tumors. (**Ex. 1009** at col. 14, l. 1 – col. 15, l. 47.)

80. *Wakeling* therefore discloses a class of compounds having the 4-anilinoquinazoline structure, which is "an important first stage in the search for novel antiproliferative, antitumour agents directed at signal transduction pathways." (**Ex. 1013** at 72, col.1.)

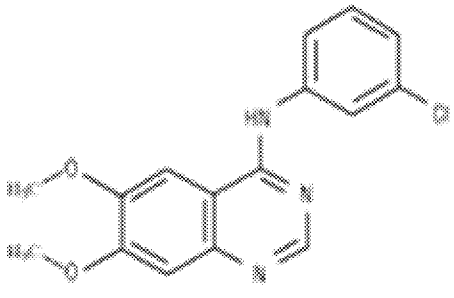
E. D.K. Moscatello *et al.*, "Constitutive Activation of Phosphatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor," *J. Biol. Chem. 273*(1):200-206 (Jan. 2, 1998) (Ex. 1014)

81. D.K. Moscatello *et al.*, "Constitutive Activation of Phosphatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor," *J. Biol. Chem. 273*(1):200-206 (Jan. 2, 1998) ("*Moscatello*", **Ex. 1014**) was published on January 2, 1998, which is more than one year before the priority date of claims 44-47 and 53 of the '221 patent. As such, I understand that *Moscatello* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA).

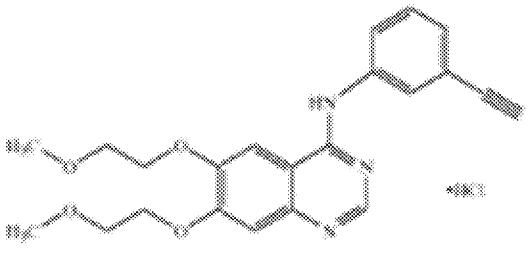
82. *Moscatello* discloses a study that compares normal EGFR with EGFRvIII. *Moscatello* specifically investigates the effects of a known tyrosine kinase domain inhibitor, tyrphostin AG1478, on normal EGFR and EGFRvIII. (**Ex. 1014** at 202, 205-206.) *Moscatello* reports previous studies that identified that normal EGFR and the mutant EGFRvIII are in NSCLC tumor cells lines, and further presents empirical proof that both are subject to the same type of inhibiting effects at the intracellular tyrosine kinase domain which prevents phosphorylation and downstream cell signaling events that regulate tumorigenesis and tumor growth. (**Ex. 1014** at 202, 205-206.)

83. According to *Moscatello*, the cell signaling events impeded by tyrphostin AG1478 show that targeting the tyrosine kinase domain to prevent phosphorylation plays a central role in regulating tumor growth, morphological transformation, and cell death by both the normal EGFR and mutant EGFRvIII. (**Ex. 1014** at 206.)

84. A person of ordinary skill in the art would have known that the structure of tyrphostin AG1478 is in the same class of tyrosine kinase domain inhibitor as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride. The compounds discussed by *Schnur* and *Moscatello* are members of the same class of drugs and their biological activity were well known in the art. Further a person of ordinary skill in the art would have known the structures of the two compounds were:



Tyrphostin AG1478



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride

85. It is my opinion that the experimental and analytical techniques used in *Moscatello* were well known to a person of ordinary skill in the art.

86. It is also my opinion that a person of ordinary skill in the art would have known that the two compounds shown above both inhibit the intracellular tyrosine kinase domain of EGFR by the same mechanism, with the only difference stemming from the amount administered to elicit an observable effect.

87. *Moscatello* teaches that EGFRvIII is overexpressed in various tumors, and specifically NSCLC tumors. (**Ex. 1014** at 200, col. 2.) *Moscatello* further presents empirical proof that the same type of inhibition at the intracellular tyrosine kinase domain of normal EGF receptors occurs in variant type EGFRvIII, and similarly inhibits phosphorylation thereby preventing cell signaling activation that is important to tumorigenesis. (**Ex. 1014** at 202.) Specifically, *Moscatello* subjected normal EGFR and the mutant EGFRvIII to tyrphostin AG1478, a highly specific EGFR tyrosine kinase inhibitor. (**Ex. 1014** at 202.)

88. The subsequent reduction in cell signaling in both receptors, suggested that the intracellular tyrosine kinase domain of both the normal EGFR and mutant EGFRvIII are similarly inhibited by tyrphostin AG1478 and directly involved in blocking tumorigenesis and tumor cell growth. (**Ex. 1014** at 202, 205-206.) Further, EGFRvIII was known to respond poorly to extracellular ligand domain-mediated treatments. As such, a person of skill in the art would be actively researching studies such as the one reported in *Moscatello* or would have

performed similar research to determine if NSCLC tumors expressing EGFRvIII are receptive to similar tyrosine kinase domain-mediated therapies.

VII. CLAIM CONSTRUCTION

89. I understand that claim language is read in light of the whole patent, including the other claims, the specification, and the prosecution history as it would be interpreted by a person of ordinary skill in the art. The meaning of a claim term is the ordinary and customary meaning of the term to a person of ordinary skill in the art at the time of the invention unless the patentee provides a special definition of that term. Further, as discussed herein *supra*, I am informed that the claim terms in the '221 patent are to be given their broadest reasonable construction or interpretation in light of the specification of the patent as understood by a person of ordinary skill in the art.

90. After reviewing claims 44-47 and 53, as well as the specification and prosecution history of the '221 patent, it does not appear that the OSI in any way defined the terms used in these claims to have meanings other than their plain and ordinary meanings, as would have been understood by a person of ordinary skill in the art in the 1999 to 2000 timeframe.

VIII. CLAIMS 44-47 and 53 ARE UNPATENTABLE OVER THE PRIOR ART

Claim 44 and 53

91. Independent claim 44 requires the following:

> 44. A method for the treatment of NSCLC (non-small cell lung cancer) . . . in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms and a carrier.

(**Ex. 1001** at col. 35, ll. 26-36.)

92. It is my understanding that claim 53 is dependent from claim 44 and narrows the list of hyperproliferative disorders to solely NSCLC.

93. *Schnur* discloses a genus of compounds that includes erlotinib. (*See* **Ex. 1009** at, *e.g.*, col. 38, l. 13 – col. 39, l. 12.) *Schnur* expressly discloses erlotinib (*i.e.*, "[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine") as a preferred compound, and in fact erlotinib is one of the preferred compounds, as specifically identified in claim 8 of *Schnur*. (*See* **Ex. 1009** at col. 39, l. 33 – col. 40, l. 65)

94. *Schnur* discloses that the compounds can be administered to a mammal for the treatment of a hyperproliferative disorder. (**Ex. 1009** at col. 3, l. 48; col. 4, ll. 8-9; col. 5, ll. 49-52 ("[t]he invention further relates to a method of

treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.").) *Schnur* also claims "[a] method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1"; "wherein said hyperproliferative disorder is cancer"; and "wherein said cancer is brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, gynecological or thyroid cancer." (*See* **Ex. 1009** at col. 41, ll. 55-63.)

95. The therapeutically effective amount can depend on the subject being treated, on the severity of the affliction, on the manner of administration, and on the judgment of a prescribing physician. (*See* Ex. **1009** at col. 15, ll. 55-58.) Generally, a therapeutically effective dosage is in the range of approximately 0.001-100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses. (**Ex. 1009** at col. 15, ll. 58-61.) For an Average 70 kg human, a therapeutically effective amount is from 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. (**Ex. 1009** at col. 15, ll. 61-62.) In my opinion, a person of ordinary skill in the art would have understood *Schnur* to disclose a therapeutically effective amount of erlotinib userful to treat lung cancer. My understanding is confirmed at least in part by the fact that *Schnur*'s disclosure of the therapeutically effective dose is identical to that

disclosed by the '221 patent. (*Compare* **Ex. 1009** at col. 15, ll. 55-62, *with* **Ex. 1001** at col. 24, ll. 19-27, *and* **Ex. 1001** at col. 24, ll. 33-43; col. 30, ll. 29-35.)

96. *Schnur* further discloses that a specific amount of an active compound, such as the therapeutically-effective amount of erlotinib, are prepared as various pharmaceutical compositions by methods known to those of skill in the art and cites *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pas., 15th Edition (1975), which is a reference guide well known to a person of ordinary skill in the art. (**Ex. 1009** at col. 16, ll. 41-45.) *Schnur* provides that the composition may be a tablet, capsule, pill, powder, a solution, parenteral injection, an emulsion, cream, ointment, or suppository. (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 1.)

97. *Schnur* also teaches that the pharmaceutical composition for administration may also include a carrier, and identifies suitable carriers to "include inert diluents or fillers, water and various organic solvents." (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 7; col. 16, ll. 21-22.)

98. In my opinion, *Schnur* teaches all elements of claim 44, but does not expressly identify "NSCLC" as a hyperproliferative disorder. (*See* **Ex. 1005** at 23; *see also* **Ex. 1006** at 2.) Instead, *Schnur* only discloses that erlotinib is useful to treat, *inter alia*, "lung cancer." (**Ex. 1009** at col. 14, ll. 1-6.)

99. It is my understanding that the PTO allowed claim 44 to issue on the basis that it was "drawn to treatment of specific cancers by any polymorph of the claimed compounds. These specific cancers are not found in *Schnur* ('498)." (**Ex. 1006** at 2.) Accordingly, it is my opinion that the only reason claim 44 (and claims 45-47 and 53 that depend therefrom) was allowed to issue was because *Schnur* does not include a verbatim disclosure of NSCLC.

100. Although NSCLC was not expressly disclosed in *Schnur*, it is my opinion that claims 44 and 53 would have been obvious in view of what was common knowledge to a person of ordinary skill in the art before the earliest priority date of the claims. Indeed, a person of ordinary skill in the art would have recognized *Schnur* as disclosing compounds that inhibit EGF receptor phosphorylation, which were known to be meant for treating NSCLC.

101. The fact that a person of ordinary skill in the art would have recognized erlotinib as an obvious choice to treat NSCLC is confirmed by *Gibbs* and *OSI's 10-K*. A person of ordinary skill in the art would have been aware of *Gibbs* and *OSI's 10-K* which document what was known in the field of lung cancer contemporaneous with *Schnur*.

102. *Gibbs* teaches that CP-358,774 (*i.e.*, anhydrous erlotinib hydrochloride) was a kinase inhibitor "with an acceptable therapeutic index,

particularly in patients with non-small cell lung cancer," and had entered Phase-II clinical trials. (*See* **Ex. 1010** at 9, col. 1; 10, col. 1, Table 1.)

103. *OSI's 10-K* discloses that CP-358,774 (*i.e.*, anhydrous erlotinib hydrochloride) was a clinical candidate that had "achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients." (**Ex. 1011** at 6.) *OSI's 10-K* further discloses that CP-358,774 is a potent, selective and orally active inhibitor of the EGFR and being used to target ovarian, pancreatic, non-small cell lung, and head and neck cancers. (**Ex. 1011** at 6.)

104. A person of ordinary skill in the art viewing *Gibbs* or *OSI-s 10-K* would have understood that of all the specific compounds disclosed by *Schnur*, erlotinib was the most preferred, and in fact had entered Phase II clinical trials.

105. It is my opinion, that *Gibbs* or *OSI's 10-K* would have guided a person of ordinary skill in the art to single out erlotinib as the most preferred compound disclosed in *Schnur*.

106. Moreover, whereas *Schnur* in view of *Gibbs* or *OSI's 10-K* teaches and suggests the preferred use of erlotinib to treat lung cancer, *Gibbs* or *OSI's 10-K* would have further instructed a person of ordinary skill in the art that erlotinib is also the preferred compound to treat NSCLC in humans. (**Ex. 1010** at 10, col. 1; **Ex. 1011** at 6.)

107. Therefore, notwithstanding the fact that a person of ordinary skill in the art would have equated *Schnur*'s disclosure of the treatment of lung cancer as synonymous with the treatment of NSCLC, the preferred use of erlotinib to treat NSCLC is made explicit when *Schnur* is viewed through the lens of *Gibbs* or *OSI's 10-K*.

108. In my opinion, *Schnur* in view of *Gibbs* or *OSI's 10-K* would have directed a person of ordinary skill in the art to a method of treating NSCLC in a human by administering a therapeutically effective amount of a pharmaceutical composition comprising anhydrous N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride and a carrier.

109. In view of my statements above, it is my opinion that combining the teachings of *Schnur* with *Gibbs* or *OSI's 10-K* would have predictably resulted in a method of treating NSCLC with erlotinib. It is my understanding that a person of ordinary skill in the art would have relied on the teachings in *Schnur* regarding the use of 4-anilinoquinazoline derivatives, including erlotinib, to treat lung cancer in mammals, including implementation of the effective dose ranges, routes of administration, pharmaceutical compositions, and carriers. (**Ex. 1009** at col. 14, l. 1 – col. 16, l. 52.) *Gibbs* or *OSI's 10-K* instructs a person of ordinary skill in the art to specifically select erlotinib from the disclosed 4-anilinoquinazolines and further that erlotinib is used to treat NSCLC. (**Ex. 1010** at 9, col. 1; **Ex. 1011** at 6.)

To then apply the teachings of *Schnur* for the treatment of NSCLC would have been routine to a person of ordinary skill in the art, and the outcome would have been predictable, particularly since *Gibbs* and *OSI's 10-K* represented that erlotinib had already been administered to humans for the treatment of NSCLC. (**Ex. 1010** at 9, col. 1; **Ex. 1011** at 6.)

110. Further, in my opinion there would have been motivation for a person of ordinary skill in the art to combine the teachings of *Schnur* with *Gibbs* or *OSI's 10-K*. On the one hand, *Schnur* discloses a genus of preferred compounds (that includes anhydrous N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride) that are useful for treating cancer in humans through EGFR inhibition. On the other hand, *Gibbs* and *OSI's 10-K* are contemporaneous prior art references published soon after *Schnur* that specify precisely which compound disclosed in *Schnur* had in fact been tested in a clinical setting. Moreover, both *Gibbs* and *OSI's 10-K* disclose that erlotinib had entered clinical testing to treat NSCLC.

111. The teachings of these prior art references differ only in that *Schnur* teaches a genus of compounds that includes erlotinib for use to treat lung cancer whereas *OSI's 10-K* and *Gibbs* specify that the compound anhydrous erlotinib hydrochloride treats a type of lung cancer called NSCLC. Therefore, a person of ordinary skill in the art would have found it obvious to view *Schnur* through the

further disclosure of *Gibbs* or *OSI's 10-K* because each of these references expressly disclose the same molecule, for blocking the same therapeutic target, in the same field of treatment.

112. Further, *Gibbs* and *OSI's 10-K* both report that erlotinib had completed Phase I studies and initiated Phase II studies. (**Ex. 1010** at 10, Table 1; **Ex. 1011** at 6.) A person of ordinary skill in the art would have understood that this meant erlotinib was administered to humans, thereby providing further confirmation that erlotinib would have been reasonably expected to treat NSCLC in mammals.

113. Accordingly, it is my opinion that if *Gibbs* and/or *OSI's 10-K* were before the PTO during prosecution of the '221 patent, claims 44 and 53 would have been rejected because each of these prior art references specifically directs a person of ordinary skill in the art to the single preferred compound disclosed in *Schnur*, erlotinib, and its use to treat NSCLC. This evidence would have negated the only reason for allowance given by the PTO as to claim 44 and dependents thereof. (*See* **Ex. 1005** at 23; *see also* **Ex. 1006** at 2.)

Claim 45

114. It is my understanding that claim 45 further limits the method recited in claim 44 such that "the treatment further comprises a palliative or neoadjuvant/adjuvant monotherapy." (**Ex. 1001**, col. 35, ll. 37-39.)

115. *Schnur* teaches that the disclosed compounds, among them erlotinib, can be administered with "one or more other antitumor substances," and that "[s]uch conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment." (**Ex. 1009** at col. 16, ll. 46-51.) Thus, a person of ordinary skill in the art would have recognized that *Schnur* discloses the use of the disclosed compounds (including erlotinib) along with a neo-adjuvant/adjuvant monotherapy—that is, an additional anti-tumor treatment given before or after treatment with erlotinib—to treat, *inter alia*, lung cancer.

116. Further, a person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *OSI's 10-K* would have recognized that erlotinib, in particular, was the preferred compound disclosed by *Schnur*, that erlotinib was particularly useful to treat NSCLC (the most prevalent of the two main forms of lung cancer), and that such treatment of NSCLC could be achieved by administering a therapeutically effective dose of erlotinib along with a neo-adjuvant/adjuvant monotherapy.

117. It is my opinion, that the further limitation recited in claim 45 is expressly taught by *Schnur*, and thus in view of *Gibbs* or *OSI's 10-K* claim 45 would have been obvious to a person of ordinary skill in the art.

118. As stated before, there would have been motivation for a person of ordinary skill in the art to combine the teachings of *Schnur* with *Gibbs* or *OSI's*

10-K. On the one hand, *Schnur* discloses a genus of preferred compounds (that includes anhydrous N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride) that are useful for treating cancer in humans through EGFR inhibition. On the other hand, *Gibbs* and *OSI's 10-K* are contemporaneous prior art references published soon after *Schnur* that specify precisely which compound disclosed in *Schnur* had in fact been tested in a clinical setting. Moreover, both *Gibbs* and *OSI's 10-K* disclose that erlotinib had entered clinical testing to treat NSCLC.

119. The teachings of these prior art references differ only in that *Schnur* teaches a genus of compounds that includes erlotinib for use to treat lung cancer whereas *OSI's 10-K* and *Gibbs* specify that the compound anhydrous erlotinib hydrochloride treats a type of lung cancer called NSCLC. Therefore, a person of ordinary skill in the art would have found it obvious to view *Schnur* through the further disclosure of *Gibbs* or *OSI's 10-K* because each of these references expressly disclose the same molecule, for blocking the same therapeutic target, in the same field of treatment.

120. Further, *Gibbs* and *OSI's 10-K* both report that erlotinib had completed Phase I studies and initiated Phase II studies. (**Ex. 1010** at 10, Table 1; **Ex. 1011** at 6.) A person of ordinary skill in the art would have understood that this meant erlotinib was administered to humans, thereby providing further

confirmation that erlotinib would have been reasonably expected to treat NSCLC in mammals.

Claim 46

121. It is my understanding that claim 46 depends from claim 44 and adds a further limitation that the treatment comprises blocking epidermal growth factor (EGF) receptors. (**Ex. 1001** at col. 35, ll. 40-42.)

122. *Schnur* discloses that "[t]he active compounds of this invention [which includes erlotinib] are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (*e.g.*, anticancer) in mammals." (**Ex. 1009** at col. 14, ll. 1-6.) Thus, *Schnur* specifically teaches that the compounds disclosed (including erlotinib) block EGFR as the underlying treatment for lung cancer. (**Ex. 1009** at col. 14, l. 1 – col. 15 l. 47.)

123. *Gibbs* also discloses that erlotinib is part of a well-known class of compounds which have anti-cancer properties by inhibiting ATP from binding to intracellular tyrosine kinase domains on EGFR. (**Ex. 1010**, col. 1.)

124. Similarly, *OSI's 10-K* discloses that erlotinib is a potent inhibitor of EGFR, which is key to the treatment of NSCLC. (**Ex. 1011** at 6). *Gibbs* likewise discloses that CP-358,774 (*i.e.*, anhydrous erlotinib hydrochloride) achieves its

anti-tumor activity by targeting the EGFR and further specifies that this is the mechanism exploited to treat NSCLC. (*See* **Ex. 1010** at 9, col. 1; 10, col. 1, Table 1.)

125. All three references—*Schnur*, *Gibbs*, and *OSI's 10-K*—teach a person of ordinary skill in the art that erlotinib treats cancer by inhibiting EGFR. (*See* **Ex. 1009**; *see also* **Ex. 1010**, **Ex. 1011**.)

126. As discussed above, a person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *OSI's 10-K* would have been directed to a method of treating NSCLC in a human by administering a therapeutically effective amount of a pharmaceutical composition comprising erlotinib with a carrier. Moreover, a person of ordinary skill in the art would have known that whereas NSCLC tumors responded to EGFR inhibition, small cell lung cancer tumors did not. Therefore, *Schnur* in view of *Gibbs* or *OSI's 10-K* would have provided a reasonable expectation that the therapeutically effective amount of erlotinib would treat NSCLC by blocking EGFR.

127. Accordingly, in my opinion a person of ordinary skill in the art would have found that each and every limitation of claim 46 was obvious in view of *Schnur*, *Gibbs*, and *OSI's 10-K*.

128. Again, it is my opinion that there would have been motivation for a person of ordinary skill in the art to combine the teachings of *Schnur* with *Gibbs* or

OSI's 10-K. On the one hand, *Schnur* discloses a genus of preferred compounds (that includes anhydrous N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride) that are useful for treating cancer in humans through EGFR inhibition. On the other hand, *Gibbs* and *OSI's 10-K* are contemporaneous prior art references published soon after *Schnur* that specify precisely which compound disclosed in *Schnur* had in fact been tested in a clinical setting. Moreover, both *Gibbs* and *OSI's 10-K* disclose that erlotinib had entered clinical testing to treat NSCLC.

129. The teachings of these prior art references differ only in that *Schnur* teaches a genus of compounds that includes erlotinib for use to treat lung cancer while *OSI's 10-K* and *Gibbs* specify that the compound anhydrous erlotinib hydrochloride to treat a type of lung cancer called NSCLC. Therefore, a person of ordinary skill in the art would have found it obvious to view *Schnur* through the further disclosure of *Gibbs* or *OSI's 10-K* because each of these references expressly disclose the same molecule, for blocking the same therapeutic target, in the same field of treatment.

130. Further, *Gibbs* and *OSI's 10-K* both report that erlotinib had completed Phase I studies and initiated Phase II studies. (**Ex. 1010** at 10, Table 1; **Ex. 1011** at 6.) A person of ordinary skill in the art would have understood that this meant erlotinib was administered to humans, thereby providing further

confirmation that erlotinib would have been reasonably expected to treat NSCLC in mammals.

131. In view of the foregoing, a person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* with *Gibbs* or *OSI's 10-K* to arrive at claim 46 of the '221 patent.

Claim 47

132. It is my understanding that claim 47 depends from claim 44 and further specifies that the method of treatment is used in "tumors that express EGFRvIII." (**Ex. 1001**, col. 35, ll. 43-44.)

133. The title of *Schnur* is "Alkynyl and Azido-Substituted 4-anilinoquinazolines," and a person of ordinary skill in the art would have known from the chemical name for erlotinib that erlotinib is a alkynyl substituted 4-anilinoquinazoline.

134. *Schnur* teaches that the anti-tumor properties of erlotinib for treating, *inter alia*, lung cancer, is based on inhibiting phosphorylation at the intracellular EGFR tyrosine kinase domain. (**Ex. 1009** at col. 14, l. 1 – col. 15, l. 47.)

135. *Gibbs* teaches that erlotinib is one of several leading compounds in clinical trials for cancer treatment that function by inhibiting intracellular ATP binding sites on EGFR. (**Ex. 1010** 10, col. 1.)

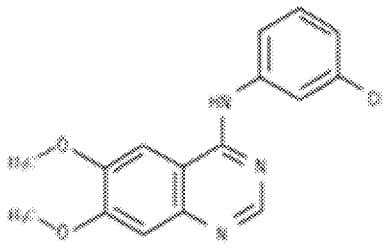
136. *Wakeling* teaches that aberrant expression of EGFR is common in solid tumors of epithelial origin, which include tumors of the lungs, mouth, kidneys, breasts, and vulva. (**Ex. 1013** at 67-68.) *Wakeling* also establishes that erlotinib, as taught in *Schnur*, is part of a well-known class of 4-anilinoquinazoline compounds that share a basic chemical structure and function to treat cancer by inhibiting intracellular ATP binding sites on the EGFR in tumor cells. (**Ex. 1013** at summary, 67-68, Table 1.)

137. In my opinion, a person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *Wakeling* would have recognized erlotinib as a 4-anilinoquinazoline compound that had entered use in the clinic to treat NSCLC, and therefore reasonably expected that erlotinib's anti-tumor effects operated by a similar mechanism to that of other 4-anilinoquinazoline compounds—through the inhibition of EGFR.

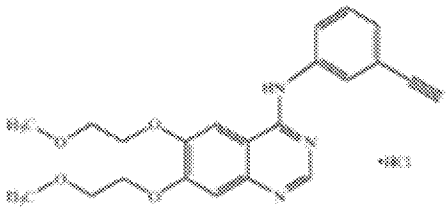
138. *Moscatello* teaches that overexpression of EGFR is implicated in the abnormal growth of many tumors, including tumors of the lung, and that a common genetic variant—"EGFRvIII"—had been identified in a number of cancers, including NSCLC tumors. (**Ex. 1014** at 200, col. 2.) *Moscatello* further teaches that EGFRvIII, like normal EGFR, can be inhibited at the intracellular tyrosine kinase domain by a 4-anilinoquinazoline to prevent cell signaling activation that is important to tumorigenesis. (**Ex. 1014** at 202.) Specifically,

Moscatello exposed normal EGFR and the variant EGFRvIII to tyrphostin AG1478, a 4-anilinoquinazoline compound, and observed that cell signaling in both EGFR and EGFRvIII and tumor growth was inhibited. (**Ex. 1014** at 202.) Thus, *Moscatello* teaches that the intracellular tyrosine kinase domains in both normal EGFR and the variant EGFRvIII are involved in tumorigenesis and tumor cell growth, and that these processes can be inhibited by a 4-anilinoquinazoline (tyrphostin AG1478) that directly blocks the receptors. (*See* **Ex. 1014** at 202, 205-206.)

139. Since *Moscatello* teaches that the 4-anilinoquinazoline compound, tyrphostin AG1478, prevents EGFRvIII phosphorylation at the intracellular tyrosine kinase domain, it is my opinion that a person of ordinary skill in the art would reasonably expect based on *Schnur* in combination with *Gibbs* or *Wakeling* that other 4-anilinoquinazoline compounds would function similarly. This is particularly true given the structural similarity between AG1478 and erlotinib (shown below), and the fact that erlotinib had already entered the clinic for the treatment of NSCLC and other cancers.



Tyrphostin AG1478



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride

140. It is my opinion that the teachings of *Schnur* in view of *Gibbs* or *Wakeling* in combination with *Moscatello* would have led a person of ordinary skill in the art to reasonably conclude that tyrphostin AG1478 and erlotinib would affect tumors of epithelial origin expressing the mutant EGFRvIII in the same way. Therefore, a person of ordinary skill in the art reviewing *Schnur* and *Gibbs* or *Wakefield* in view of *Moscatello* would have recognized that because erlotinib was an EGFR inhibitor of phosphorylation at the intracellular tyrosine kinase domain, like AG1478, erlotinib would inhibit EGFRvIII.

141. For these reasons, it is my opinion that each and every limitation of claim 47 would have been obvious to a person of ordinary skill in the art.

142. It is my opinion that a person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* and *Gibbs* or *Wakeling* with *Moscatello* because each of these publications concerns 4-anilinoazoquinoline compounds for treating cancer, that includes erlotinib, and characterize the mechanism by which these compounds (including erlotinib) interact with tumors, which includes inhibiting EGFR tyrosine kinase in tumors of epithelial origin.

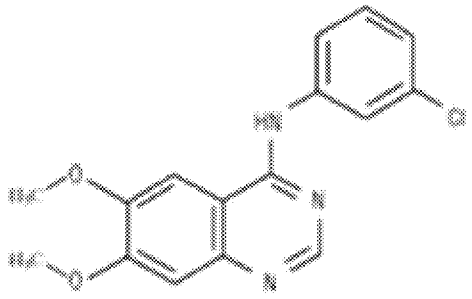
143. Where their teachings differ, they offer complementary approaches for addressing their common problem of combating hyperproliferation of tumor cells by inhibiting EGFR. Because these references address the same field and the same issues, a person of ordinary skill in the art would have looked to their complementary disclosures.

144. *Schnur*, *Gibbs*, *Wakeling*, and *Moscatello* are generally directed to the treatment of cancer, and in particular, the use of drugs that treat certain types of cancer by inhibiting the intracellular tyrosine kinase domain of EGFR.

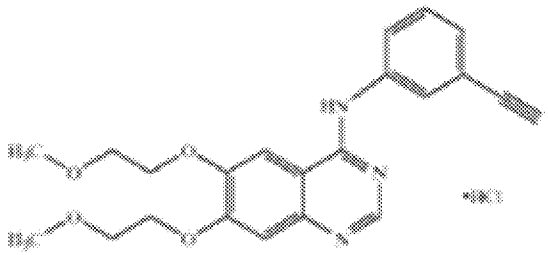
145. *Schnur* teaches that molecules such as erlotinib treat tumor growth in lung cancer by inhibiting EGFR phosphorylation at the intracellular tyrosine kinase domain. (**Ex. 1009** at col. 1, ll. 30-63; col. 14, ll. 1-34.) Impeding phosphorylation prohibits activation of a downstream signaling network involving cell proliferation, cell cycle progression, and survival.

146. *Moscatello* teaches tyrosine kinase domain inhibition of normal EGFR and the mutant EGFRvIII with tyrphostin AG1478. The compounds discussed by *Schnur* and *Moscatello* are members of the same class of drugs and their biological activity were well known in the art as shown in *Gibbs*. (**Ex. 1010** 10, col. 1.) Therefore, *Schnur* and *Moscatello* utilize structurally similar molecules to inhibit the tyrosine kinase domain of EGFR, but *Moscatello* shows additionally that such

molecules are also effective inhibitors of EGFRvIII. The molecules are shown below.



Tyrphostin AG1478



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride

147. Based on the structural and functional similarity between the compound used in *Moscatello* and the anhydrous erlotinib hydrochloride disclosed in *Schnur* and *Gibbs* or *Wakeling*, a person of ordinary skill in the art would have been motivated to utilize *Moscatello* in order to build on the teachings of *Schnur* and *Gibbs* or *Schnur* and *Wakeling*. Further, a person of ordinary skill in the art would have reasonably expected that, like the compound studied in *Moscatello*, anhydrous erlotinib hydrochloride would similarly function to inhibit EGFRvIII.

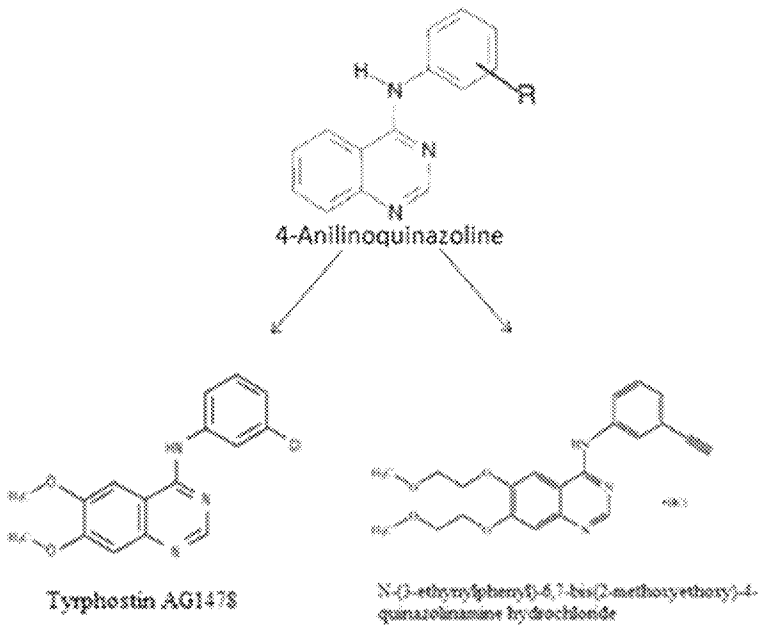
148. Additionally, *Schnur* and *Gibbs* teach that erlotinib hydrochloride is a potent tyrosine kinase domain inhibitor that has anticancer properties for a variety of cancers, including NSCLC. *Moscatello* complements these teachings by empirically proving that EGFRvIII, which was known to be prevalent in NSCLC, is subject to the same inhibition by compounds such as erlotinib that target the intracellular tyrosine kinase domain. (**Ex. 1014** at 202, 205-206.) Accordingly, a

person of ordinary skill in the art would have understood *Moscatello* to be applicable to erlotinib hydrochloride for treating NSCLC tumors that express EGFRvIII. As such, a person of ordinary skill in the art would have known that simply substituting tyrphostin AG1478 with erlotinib hydrochloride would have predictably resulted in the subject matter of claim 47.

149. A person of ordinary skill in the art would have relied on prior art such *Moscatello* in order to better understand the mechanism by which erlotinib acts in the body. This is common practice for persons of ordinary skill in the art because of the similarity between tyrphostin AG1478 and erlotinib hydrochloride would avoid "re-inventing the wheel." After initial comparison studies, it would have been very surprising if the mechanisms underlying the activity of these two compounds were somehow different. Additionally, studies had already established that EGFRvIII was known to respond poorly to extracellular ligand domain-mediated treatments. (*See* **Ex. 1014**, 200.) As such, a person of skill in the art would be actively researching studies such as the one reported in *Moscatello* or would perform similar research to determine if NSCLC tumors expressing EGFRvIII are receptive to similar intracellular tyrosine kinase domain-mediated therapies.

150. *Wakeling* teaches that both AG1478 and erlotinib are in a commonly known class of compounds that share the same basic structure and functions called

4-anilinoquinazolines which have anti-cancer effects in a variety of solid tumor cells of epithelial origin such as NSCLC. Further, *Wakeling* reports that 4-anilinoquinazolines substituted at the meta position exhibited the most potent inhibitory effects on the intracellular EGFR tyrosine kinase domain, a structural property that is shared with erlotinib (as shown below).



151. Given the same base structure and function of a well-known class of molecules, it is my opinion that a person of ordinary skill in the art would have reasonably expected that the compound used in *Moscatello* and the anhydrous erlotinib hydrochloride disclosed in *Schnur* would function similarly to inhibit EGFRvIII.

152. It was also known that cancer cells that express EGFRvIII respond poorly to treatments that bind at the extracellular ligand domain. (*See* **Ex. 1014**,

200.) As such, a person of ordinary skill in the art would have been motivated to combine the teachings of *Moscatello* with prior art related to compounds such as erlotinib, which was a known inhibitor of normal EGFR and functioned by competitive binding at the intracellular tyrosine kinase domain.

153. In view of the foregoing, it is my opinion that a person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* with *Gibbs* or *Wakeling*, and look to *Moscatello* for further insight into the mechanism underlying erlotinib's efficacy as a tyrosine kinase receptor inhibitor for the treatment of NSCLC. Doing so would have provided the predictable result that is recited in claim 47 of the '221 patent.

IX. CONCLUSION

154. In view of the foregoing, I must conclude that claims 44-47 and 53 of the '221 patent are directed to subject matter that was already well-known to a person of ordinary skill in the art. Accordingly, it is my opinion that claims 44-47 and 53 of the '221 patent are unpatentable for the reasons discussed above.

I declare under penalty of perjury that, to the extent of my knowledge and belief, the foregoing is true and correct. I further 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 understanding that knowing and 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.

Date: June 17, 2016

Giuseppe Giaccone, M.D., Ph.D.

Appendix A

Giuseppe Giaccone, M.D., Ph.D. — *Curriculum Vitae*

June 3, 2016

CURRICULUM VITAE
GIUSEPPE GIACCONE, MD PhD

PERSONAL INFORMATION:

Home Address: 7515 Marbury Road
Bethesda, MD 20817
301 3203482

Office Address: Lombardi Comprehensive Cancer Center
Georgetown University
5700 Reservoir Road
Washington DC,
Tel 202 6877072
Fax 202 6876471

LICENSURE:

State: Maryland
License No: D-48393
Issue Date: 09/27/2007
Renewal/Expiration Date: 09/30/2016
State: Washington DC
License No: MD041113
Issue Date: 01/30/2013
Renewal/Expiration Date: 12/31/2016

CERTIFICATION:

Board Certification: Internal Medicine (Italy)
Date of Certification: 1988

Sub-Specialty Board: Clinical Oncology (Italy)
Date of Certification: 1983

EDUCATION:

Undergraduate:
Institution: Liceo Scientifico Galileo Ferraris
Address: Torino, Italy
Dates of Attendance: 1969 - 1974
Degree, Major: High School Diploma

Medical Education:
Institution: University Torino Medical School
Address: Torino, Italy
Dates of Attendance: 1974 - 1980
Degree: Medical Doctor (MD)

Graduate Education:
Institution: National Cancer Institute, NIH
Department: Navy Medical Oncology Branch (Dr. Minna and Dr. Gazdar)
Address: Rockville Pike, Bethesda
Dates of Attendance: 1988 - 1990
Degree, Major: Visiting Fellow

Graduate Education:
Institution: Vrije Universiteit
Department: Department of Medical Oncology
Address: Amsterdam, The Netherlands
Dates of Attendance: 1990 - 1995
Degree, Major: PhD

Internship:
Institution: Institute of Oncology
Department: Medical Oncology
Address: Torino, Italy
Dates of Attendance: 1980 - 1981
Department Chief of Service: A. Calciati

Residency:
Institution: University Medical School
Department/Type: Internal Medicine rotation
Address: Torino
Dates of Attendance: 1983 - 1988
Department Chair/Chief of Service

Fellowship:
Institution: Institute of Oncology
Department/Type: Medical Oncology
Address: Torino
Dates of Attendance: 1981 - 1983
Department Chief of Service: A.Calciati

PROFESSIONAL EXPERIENCE:

Title: Associate Director for Clinical Research, Professor of Medical Oncology and Pharmacology
Co-Leader of the Experimental Therapeutic Program
Director of research for the Medstar Georgetown Cancer Network
Institution: Lombardi Comprehensive Cancer Center, Georgetown University
Address: 5700 Reservoir Road, Washington DC
Date(s) of Service: Janaury 2013 to date

Title: Chief, Medical Oncology Branch
Institution: National Cancer Institute
Address: 10 Center Drive, Bethesda MD
Date(s) of Service: April 2007 to December 2012

Title: Senior medical oncologist (1990), then Deputy Head (1998), then Head (2003), Department of Medical Oncology
Institution: Vrije Universiteit Medical Center
Address: Amsterdam, The Netherlands
Date(s) of Service: October 1990 – March 2007

Title: Assistant Professor (1990), then Associate Professor (1998), then full Professor (2000)

Institution: Vrije Universiteit
Address: Amsterdam, The Netherlands
Date(s) of Service: October 1990 – March 2007

Title: Consultant Medical Oncologist (bi-weekly)
Institutions: Waterland Ziekenhuis (Purmerend) and Gemini Ziekenhuis (Den Helder), The Netherlands
Date(s) of Service: October 1991 – March 2003

Title: Full time Medical Assistant
Institution: Institute of Oncology
Address: Torino, Italy
Date(s) of Service: December 1981 – September 1990

HONORS and AWARDS:

Appointed Adjunct Professor at the Tianjin University Cancer Center and Hospital, Tianjin China, October 29, 2015.

Honorary Member of the Hellenic and International Society of Molecular-Genomic Medicine and Research.
Institute/Organization: Hellenic and International Society of Molecular-Genomic Medicine and Research
Date October 2012

Award: NDDO Honorary Award during the 9th International Symposium on Targeted Anticancer Therapies (TAT2011), Paris 7-9 March 2011.
Institution/Organization: New Drug Development Office (NDDO) Foundation
Date: March 2011

Award: NCI Director's Award, as part of the Physician Data Query Adult Treatment Editorial Board.
Institution/Organization: National Cancer Institute
Date: November 2010

Award: Daniel C. Ihde Memorial Lecture Award.
Institution/Organization: National Cancer Institute
Date: June 2009

Award: Federal Technology Transfer Award.
Institution/Organization: National Cancer Institute
Date: September 2009

Award: Certificate of Merit at the ESMO 27th Presidential Symposium.
Institution/Organization: European Society of Medical Oncology
Date: October 2002

Award: Award of the Istituto Oncologico Romagnolo for the best

poster presented at the 'Second International Conference on Small Cell Lung Cancer', Milano Marittima May 11-12, 1990.
Institution/Organization: Istituto Oncologico Romagnolo (Italy)
Date: May 1990

Award: Fellowship of the NCI-EORTC Research Training Program and awards from Italian Association for Research on Cancer (AIRC) and Italian National Research Council (CNR) for a two year research at the National Cancer Institute, Bethesda, USA.
Institution/Organization: NCI-EORTC, AIRC (Italy), CNR (Italy)
Date: 1988

Award: Award of the Italian Association for Research on Cancer for a 2 months of clinical training at the New York University and Memorial Sloan Kettering, New York, USA.
Institution/Organization: AIRC (Italy)
Date: 1984

PROFESSIONAL SOCIETY MEMBERSHIP:

Society Name: American Association for Cancer Research (AACR), member
Leadership Role (if appropriate):
Date(s) of Membership: 1990 - present

Society Name: American Society of Clinical Oncology (ASCO), member
Leadership Role (if appropriate):
Dates of Membership: 1990 - present

Society Name: European Society of Medical Oncology (ESMO), member
Leadership Role (if appropriate):
Dates of Membership: 1995 - present

Society Name: International Association for the Study of Lung Cancer (IASLC), member
Leadership Role (if appropriate):
Dates of Membership: 2000 – present

PUBLIC SERVICE:

Editorial Board of Scientific Journals

Name of Editorial Board: Cell Death and Disease
Role/Status: Section Editor
Date(s) of Service: January 2010 - present

Name of Editorial Board: Frontiers in Oncology
Role/Status: Editor in Chief
Date(s) of Service: August 2010 - present

Name of Editorial Board: Clinical Cancer Research
Role/Status: Editorial Board member
Date(s) of Service: 2002 - present

Name of Editorial Board: Journal of Clinical Oncology
Role/Status: Editorial Board member
Date(s) of Service: 2005 - 2007

Name of Editorial Board: Cancer Chemotherapy and Pharmacology
Role/Status: Editorial Board member
Date(s) of Service: 2005 - present

Name of Editorial Board/Study Section: European Journal of Cancer
Role/Status: Editorial Board member
Date(s) of Service: 2002 - 2008

Name of Editorial Board: Clinical Lung Cancer
Role/Status: Editorial Board Member
Date(s) of Service: 1990 - present

Name of Editorial Board: Annals of Oncology
Role/Status: Editorial Board member
Date(s) of Service: January 2012 - 2015

Name of Editorial Board: Tumori
Role/Status: International Advisory Board member
Date(s) of Service: 1998 - 2013

Name of Editorial Board: Current Oncology Reports
Role/Status: Editorial Board member
Date(s) of Service: 1999 - 2013

Name of Editorial Board: Oncologie Actueel (The Netherlands)
Role/Status: Editorial Board member
Date(s) of Service: 2003 - 2007

Name of Editorial Board: The Oncologist
Role/Status: Editorial Board member
Date(s) of Service: 1998 - 2015

Name of Editorial Board: Journal of Experimental Therapeutics & Oncology
Role/Status: Associate Editor
Date(s) of Service: 2004 - present

Name of Editorial Board: Nederlands Tijdschrift voor Oncologie
Role/Status: Editorial Board member

Date(s) of Service: 2002 – 2007

Name of Editorial Board: Framingham on lung cancer
Role/Status: Consulting Editor
Date(s) of Service: 2002 - present

Name of Editorial Board: Targeted Oncology
Role/Status: Editorial Board member
Date(s) of Service: 2006 - present

Name of Editorial Board: Investigational New Drugs
Role/Status: Editorial Board member
Date(s) of Service: 2011 – present

Name of Editorial Board: Scientific Reports
Role/Status: Editorial Board member
Date(s) of Service: 2015 – present

Name of Editorial Board: Cancer Biology & Medicine
Role/Status: Editorial Board member
Date(s) of Service: 2016 – present

Ad hoc reviewer for:
Journal of Clinical Oncology, Cancer Research, Clinical Cancer Research, European Journal of Cancer, British Journal of Cancer, Annals of Oncology, Oncology, Biochemical Pharmacology, American Journal of Pathology, Lung Cancer, Cancer, Gene Therapy, Cancer Chemotherapy and Pharmacology, Hepatology, Journal of the National Cancer Institute, The Lancet, Life Sciences, Nature Reviews Cancer, Nature Clinical Practice Oncology, Molecular Canter Therapeutics, Molecular Cancer Research, Genes Chromosomes and Cancer, Human Mutation, Journal of Thoracic Oncology, New England Journal of Medicine, FASEB Journal, PLOS Medicine, PLOS One, Cancer Cell, Lancet Oncology, Proceedings of the National Academy of Science USA.

Study Section and Grant reviewer

Study Section: Cancer Research Campain (UK)
Role/Status: Reviewer for site visit University of Glasgow
Date(s) of Service: March 1991

Study Section: Ministere delegue a la Recerche at aux Nouvelles Technologies (France)
Role/Status: Reviewer
Date(s) of Service: 1995

Study Section: Swiss Cancer Society

Role/Status: Reviewer
Date(s) of Service: 1995- 1997

Study Section: Human Frontiers (France)
Role/Status: Reviewer
Date(s) of Service: 1998

Study Section: Medical Research Council (UK)
Role/Status: Reviewer
Date(s) of Service: 1999

Study Section: Dutch Cancer Society (KWF)
Role/Status: member of the Scientific Council
Date(s) of Service: 2000 – 2005

Study Section: Framework 6 of the European Commission
Role/Status: Reviewer
Date(s) of Service: 2002

Study Section: Cancer Research UK
Role/Status: Reviewer for site visit University of Oxford
Date(s) of Service: October 2004

Name of Community Organization: Fondazione Italiana per la Ricerca sul Cancro (FIRC)
Role/Status: Member of the scientific committee for the Guido Venosta Price
Date(s) of Service: 2004

Study Section: The European Agency for the Evaluation of Medicinal Products (EMEA)
Role/Status: Expert consultant
Date(s) of Service: 2004

Study Section: International Union against Cancer (UICC)
Role/Status: Reviewer
Date(s) of Service: 2005

Study Section: The Netherlands Organization for Health Research and Development (ZonMW)
Role/Status: Reviewer
Date(s) of Service: 2005 - 2008

Study Section: Island Cancer Society
Role/Status: Reviewer
Date(s) of Service: 2006

Study Section: Framework 7 of the European Commission
Role/Status: reviewer
Date(s) of Service: 2007

Study Section: Austrian Science Fund
Role/Status: Reviewer
Date(s) of Service: 2007

Study Section: NIH ARRA RC3 and R43
Role/Status: Reviewer
Date(s) of Service: 2007

Study Section: National Medical Research Council (Singapore)
Role/Status: Reviewer
Date(s) of Service: 2008

Study Section: Associazione Italiana per la Ricerca sul Cancro (AIRC)
Role/Status: International Reviewer
Date(s) of Service: 2007 - present

Study Section: French National Cancer Institute
Role/Status: Reviewer
Date(s) of Service: 2009

Study Section: American Association for Cancer Research (AACR) sub Committee for HER Family Pathway Scientific Review Committee
Role/Status: Member of Scientific Review Committee
Date(s) of Service: 2010

Study Section: American Association for Cancer Research (AACR) Clinical and Translational Research Grants
Role/Status: Member of Scientific Review Committee
Date(s) of Service: 2011

Study Section: Department of Defense (DOD) – Lung Cancer Research
Role/Status: reviewer
Date(s) of Service: January 2012

Study Section: Health and Medical Research Fund – Hong Kong
Role/Status: reviewer
Date(s) of Service: January 2013

Study Section: International Association for the Study of Lung Cancer – Chinese translational fellowships
Role/Status: reviewer
Date(s) of Service: November 2013

Study Section: NCI P01 Program Project Meeting II
Role/Status: reviewer
Date(s) of Service: December 2013

Study Section: NCI SPORE (P50) Program
Role/Status: reviewer
Date(s) of Service: February 2014

Study Section: International Association for the Study of Lung Cancer – Lung Cancer Fellowships and Young Investigator Awards
Role/Status: reviewer
Date(s) of Service: February 2014

Study Section: NCI SPORE (P50) Program
Role/Status: reviewer
Date(s) of Service: February 2015

Study Section: International Association for the Study of Lung Cancer – Lung Cancer Fellowships and Young Investigator Awards
Role/Status: reviewer
Date(s) of Service: February 2015

Study Section: 2015 AACR Clinical and Translational Cancer Research Grants Scientific Review Committee
Role/Status: reviewer
Date(s) of Service: September 2015

Study Section: 2016 AACR Clinical and Translational Cancer Research Grants Scientific Review Committee
Role/Status: reviewer
Date(s) of Service: February 2016

Other functions

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group
Role/Status, Dates of service: member 1982 – 1987; vice-chairman 1987 – 1990; chairman 1993 – 2000

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Protocol Review Committee (PRC)
Role/Status: member
Dates of service: 1987 – 2000

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Board
Role/Status: member
Dates of service: 2000 – 2003

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) New Treatment Committee (NTC)
Role/Status: member
Dates of service: 2000 – 2003

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Biological Therapeutics Development Group
Role/Status: member
Dates of service: 1998 - 2004

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group Role/Status: member
Dates of service: 1997- 2004

Name of Community Organization: European Organization for Research and Treatment of Cancer (EORTC) Early Clinical Studies Group Role/Status: Associate Clinical Consultant to the NDDO (New Drug Development Office)
Dates of service: 1992 - 1994/

Name of Community Organization: National Cancer Institute Physician Data Query (PDQ) program
Role/Status, Date(s) of Service: Reviewer for the European submissions 1992 – 2007; Member of the PDQ Adult Treatment Editorial Board 2008 - present
:
Name of Editorial Board/Study Section/Community Organization: Thoracic Malignancy Steering Committee's Clinical Trials Planning Meeting (CTEP)
Role/Status: Member
Date(s) of Service: 2009 – present

Name of Editorial Board/Study Section/Community Organization: NeXT (NCI Experimental Therapeutic Program).
Role/Status: Member
Date(s) of Service: 2009 - present

Name of Editorial Board/Study Section/Community Organization:Safety and Monitoring Committee (NCI)
Role/Status: Member
Date(s) of Service: 2008/7 – present

Name of Editorial Board/Study Section/Community Organization: Lung Cancer intramural program (NCI)
Role/Status: Chair
Date(s) of Service: 2007/10 - present

Name of Editorial Board/Study Section/Community Organization: Center of Excellence in Molecular Oncology (NCI)
Role/Status: Chair
Date(s) of Service: 2008– 2010

Name of Editorial Board/Study Section/Community Organization:Intramural Lung Cancer Stem Cell project (NCI)
Role/Status: Chair
Date(s) of Service: 2008 – present

Name of Editorial Board/Study Section/Community Organization: tenior track selecting committee for the Laboratory of Immunology Branch (NCI) Surgery Branch (NCI) and Neurooncology Branch (NCI)
Role/Status: Member
Date(s) of Service: 2008

Name of Editorial Board/Study Section/Community Organization: PRMC (Protocol Review and Monitoring Committee) of the National Cancer Institute.
Role/Status: Member
Date(s) of Service: 2007 – 2008

Presidency, Board member of International Symposia, Workshops, Conferences and Data and Safety Monitoring Committees, presentations at FDA meetings

2015	Member of the Organizing Committee, chair at the 13th International Symposium on Targeted Anticancer Therapies (TAT2015), Paris 2-4 March 2015.
2014	President of the 12th International Congress on Targeted Anticancer Therapies (TAT 2014), Washington DC 5-7 March 2014.
2013	Member of the Scientific Committe of the 15th World Conference on Lung Cancer, Sydney 27-31 October 2013.
2013	Chair of the Scientific advisory board of the 11th International Congress of "Targeted Anticancer Therapies", Paris March 4-6, 2013.
2012	Chair of the Scientific advisory board of the 10th International Congress of "Targeted

	Anticancer Therapies", Amsterdam March 8-10, 2012.
2011	Member of the Scientific Committe of the 14th World Conference on Lung Cancer, Amsterdam 3-7 July 2011.
2011	Chairman of the Scientific Advisory Board for the 9th International Symposium on Targeted Anticancer Therapies (TAT2011), Paris 7-9 March 2011.
2010 - 2013	Chair of the Data Monitoring and Safety Committee for TAILOR (Tarceva Italian Lung Optimization Study).
2010	Member of the Lung Cancer Biomarker Project, sponsored by the College of American Pathologists, International Association for the Study of Lung cancer and Association for Molecular Pathology.
2010	Member of the National Cancer Institute Special Emphasis Panel "Early therapeutics development with phase II emphasis", Rockville 1-2 December, 2010.
2010	Member of the Scientific Committee of the AACR-NCI-EORTC International Conference 'Molecular Targets and Cancer Therapeutics', Berlin 16-19 November 2010.
2010	President of the 8th International symposium on Targeted Anticancer Therapies (TAT2010), Bethesda 4-6 March 2010.
2009	Member of the Scientific Committee of the AACR-NCI-EORTC International Conference 'Molecular Targets and Cancer Therapeutics', Boston 15-19 November 2009.
2009	Organizer of the '1st International Conference on Thymic Malignancies', Bethesda 20-21 August 2009.
2009	International Scientific Committee member of the 13th World Conference on Lung Cancer, San Francisco 31 July– 4 August, 2009.
2009	Chair of the Scientific Committee of the 7th

	International symposium on Targeted Anticancer Therapies (TAT2009), Amsterdam 23-25 March 2009.
2008 – present	Co-chair of ASCO committee to develop new guidelines for advanced non-small cell lung cancer
2008	President of the 6th International symposium on Targeted Anticancer Therapies (TAT2008), Bethesda 20-22 March 2008.
2007 – 2012	Chair of the Data Safety Monitoring Committee of the phase III studies M-Fortis and C-Fortis: "A randomized double-blind placebo controlled study of oral talactoferrin in addition to best supportive care in patients with NSCLC who have failed two or more prior regimens", "A randomized placebo controlled study of oral talactoferrin in combination with carboplatin and paclitaxel as first line therapy in patients with locally advanced or metastatic NSCLC".
2007	International Scientific Committee member of the '12th World Conference on Lung Cancer', Seoul 2-6 September 2007.
2007 – 2014	Chair of the Data Safety Monitoring Committee of the phase III study "Erlotinib or placebo in the adjuvant treatment of resectable non-small cell lung cancer – RADIANT study".
2007	Subcommittee Chairperson of AACR Annual Meeting.
2007	Chair of the scientific committee of the ESMO International Symposium on Chest Tumors, Geneva 30 March 1 April 2007.
2007	President of the 5th International symposium on Targeted Anticancer Therapies (TAT2007), Amsterdam 8-10 March 2007.
2006 - 2011	Faculty coordinator for ESMO.
2006 – 2010	Member of the Data Safety Monitoring Committee of the phase III study "Vorinostat or placebo in pretreated patients with

	malignant pleural mesothelioma".
2006 – 2011	Chair of the Data Safety Monitoring Committee of the phase III study "Bayer 12006. Phase III of cisplatin, gemcitabine and sorafenib or placebo in advanced non-small cell lung cancer".
2006	Member of the Scientific committee of the 7th European conference Perspectives in lung cancer, Athens 8-9 September 2006.
2006	Member of the Scientific committee of AACR Annual Meeting, Washington April 2006.
2006	President of the 4th International symposium on Targeted Anticancer Therapies (TAT2006), Amsterdam 16-18 March 2006.
2005	Member of the scientific committee of the 11th World Conference on Lung Cancer Barcelona 3-6 July 2005.
2005	President of the 3rd International symposium on Targeted Anticancer Therapies (TAT2005), Amsterdam 3-5 March 2005.
2005	Chair of the Scientific Program Committee of the ASCO Annual conference, Developmental Therapeutics: Molecular Therapeutics.
2004	Member of the Scientific Program Committee of the ASCO Annual conference, Developmental Therapeutics: Molecular Therapeutics.
2004 – 2007	Member of the Corresponding Committee of the International Affairs Committee of ASCO.
2003	President of the '2nd International symposium on signal transduction modulators in cancer therapy', Amsterdam 23-25 October 2003.
2003	Member of the Scientific committee of the 'International Conference on Applied Genomics: 9th ESACP/16th ISDQP meeting', Amsterdam 1-4 October 2003.
2002	Member of the Scientific committee of the conference 'Cancer of the esophagus and

	gastric cardia: from gene to cure', Amsterdam 13-15 December 2002.
2002	Chair of the scientific committee of the 1st international symposium on signal transduction modulators in cancer therapy, Amsterdam 23-25 September 2002.
2001	Member of the Scientific Committee and International Advisory Board of the "Eleventh Conference on DNA topoisomerases in therapy", New York 8-10 October 2001.
1999	Member of the Program Commitee of the AACR-NCI-EORTC International Conference "Molecular targets and cancer therapeutics", Washington 16-19 November 1999.
1999	Conference Director of 'The Tenth Conference on DNA Topoisomerases in Therapy', Amsterdam 6-8 October 1999.
1999	Member of the local organizing committee of 'Chemotherapeutic strategies for treatment of colorectal cancer - present and future developments', Amsterdam 10-12 February 1999.
1999	Member of the Scientific Committee and International Advisory Board of the 'Ninth International Congress on anti-cancer treatment', Paris 2-5 February, 1999.
1998	Member of the Scientific Board of The Ninth Conference on DNA topoisomerases in Therapy, New York 5-8 October 1998.
1998	Scientific Advisory Board member of the 10th NCI-EORTC Symposium, Amsterdam 16-19 June, 1998.
1998	Presenter to the ODAC (Oncologic Drug Advisory Committee) of the FDA of the application for registration of Taxol in first line treatment of non-small cell lung cancer, Bethesda 20 March 1998.
1998	Presenter of the IND of the Bec2/BCG vaccine study in small cell lung cancer (EORTC 08971) to the FDA, Rockville 28 February

1998.

1997	Conference Director of 'The Eighth Conference on DNA topoisomerases in Therapy', Amsterdam 15-17 October, 1997.
1996	Member of the Scientific Committee of the '2nd International Congress on lung cancer', Crete 9-13 November 1996.
1996	Member of the Scientific Board of 'The Seventh Conference on DNA topoisomerases in Therapy', New York 21-24 October 1996.
1996	Member of the Scientific Committee of the IASLC Workshop 'Biological basis of lung cancer prevention', Nancy 20-22 October 1996.
1996	Member of the Scientific Advisory Board of the '9th NCI-EORTC Symposium', Amsterdam March 12-15 1996.
1995	Conference Director of 'The Sixth Conference on DNA topoisomerases in Therapy', Amsterdam September 6-8 1995.
1994	Member of the Scientific Advisory Board of the '8th NCI-EORTC Symposium', Amsterdam March 15-18 1994.
1992	Member of the Scientific Advisory Board of the '7th NCI-EORTC Symposium', Amsterdam 17-20 March 1992.

INVITED LECTURES: **Presentations and chairmanship at conferences**

Invited speaker at 'The 4th Annual International Conference of Societas Europeana Pneumologica (SEP)', Basle September 1985: "Thymomas".

Invited speaker at 'The IST International Conference on multimodality treatment of ovary cancer', Genova September 24-26, 1987: "Cisplatin and carboplatin in combination chemotherapy for advanced ovary cancer".

Invited speaker at 'The First Perugia International Cancer Conference', Perugia June 17-18, 1988: "The European Organization for Research and Treatment of Cancer (EORTC) trials of new agents for advanced non-small cell lung cancer".

Invited speaker at 'IASLC workshop on small cell lung cancer', Elsinore July 1989: "Second line chemotherapy in small cell lung cancer".

Invited speaker at 'International Symposium on Teniposide' organized by Bristol Myers, London September 1989: "Teniposide combination chemotherapy in small cell lung cancer"; "The EORTC experience with teniposide".

Invited speaker at 'Joint Meeting of the 3rd IASLC tumor biology workshop and Europe Against Cancer programme', Cambridge August 6-9, 1990: "Role of DNA-topoisomerases in multidrug resistance of lung cancer".

Invited speaker at 'The ECCO6 Conference', Florence October 27-31, 1991: "Clinical trial of new drugs for small cell lung cancer"; co-chairman and rapporteur at the "Leukemia/Myeloma" section.

Invited speaker at 'The 12th Asia Pacific Congress on Diseases of the Chest', Seoul October 4-7, 1992: "EORTC Lung Cancer Cooperative Group experience"; "Development of new agents for the treatment of lung cancer"; chairman of the sections "Treatment of lung cancer" and "Oncology 2".

Invited speaker at 'The International Congress Biological response modifiers. Present use and future prospects', Naples February 23-25, 1993: "Mechanisms of resistance of cancer cells to anticancer agents".

Invited speaker at '4th IASLC lung tumor biology workshop', Airlie Virginia April 13-16, 1993: "Topoisomerase IIα and ß gene expression in non-small cell lung cancer".

Invited speaker at 'The Third International Conference on Small Cell Lung Cancer,' Ravenna May 6-7, 1993: "Small cell lung cancer and topoisomerases".

Invited speaker at 'The XVII World Congress on Disease of the Chest', Amsterdam June 13-18, 1993: "Pathology and biology of non-small cell lung cancer"; "Treatment of extensive disease small cell lung cancer".

Invited speaker at 'Conference Growth Factors and Medical Oncology', Rimini June 14-16, 1993; Session co-chairman "Small cell lung carcinoma".

Invited speaker at 'The Perugia International Cancer Conference IV Chemotherapy of non-small cell lung cancer: five years later',

Perugia June 18-19, 1993: "Overview of new drugs: an introduction"; co-chairman of the session "New drugs and future directions".

Invited speaker at the 'Eighth Brasilian Congress of Clinical Oncology', Sao Paulo, October 9-12, 1993: "New promising drugs for clinical application"; "Treatment of soft tissue sarcomas"; "New treatments in the therapy of colon cancer".

Invited speaker at the 'XI National meeting of Italian basic and clinical research associations' Bari, October 20, 1993: "Treatment of non-small cell lung cancer".

Invited speaker at the Conference 'Advances and Prospects in Clinical Experimental Oncology', Amsterdam January ,7 1994: "Reversal of multidrug resistance in the clinic".

Invited speaker at 'The First International Conference on Germ Cell Tumors', Ravenna April 16-17, 1994: "Extragonadal germ cell tumors: another disease ?".

Invited speaker at the Symposium 'Quality Assurance and GCP in Cancer Drug Development', Freiburg June 10, 1994: "Implementation of GCP within EORTC trials".

Invited speaker at 'The International Congress for Lung Cancer', Athens June 22-26, 1994: "Camptothecins in the treatment of lung cancer".

Invited speaker at the Symposium 'Current Perspectives in the treatment of non-small cell lung cancer', organized by Bristol-Myers, Colorado Springs June 28, 1994: "Dose finding and sequencing study of paclitaxel and carboplatin in advanced non-small cell lung cancer".

Invited speaker at the ESO Task Force meeting: 'Breast Cancer - management of the resistant patient', Amsterdam September 6, 1994: "Multidrug resistance".

Invited speaker at the '13th European Society for Therapeutic Radiology and Oncology', Granada September 26-29, 1994: "The role of chemotherapy in the treatment of NSCLC".

Invited speaker at the 'Fifth Conference on DNA topoisomerases in therapy', New York October 3-6, 1994: "Overexpression of DNA topoisomerase I and II: its consequence for drug cytotoxicity".

Invited speaker at the EORTC-Rhone-Poulenc Rorer symposium 'Cutting Edges in Oncology - NSCLC: planning the future'. Saint

Paul de Vence (Nice), October 20-22, 1994: "Brainstorming on experimental data. Cancer genetics, cell and molecular biology. Is this the way forward?".

Invited speaker at the Conference 'Trattamento del carcinoma della mammella: alla ricerca del consenso', San Giovanni Rotondo December 2-3, 1994: "New drugs".

Invited speaker at 'The 2nd International Symposium Drug resistance in leukemia and lymphoma', Amsterdam March 6-8 1995: "Topoisomerase IIa gene expression in childhood acute lymphoblastic leukemia".

Invited speaker at 'The 3rd Central European Lung Cancer Conference', Prague May 28-31, 1995: "New drugs in lung cancer"; "EORTC Lung Cancer Cooperative Group experience".

Invited speaker at the '49e Oncologiedag - Therapie resistentie', Rotterdam June 16, 1995: "Klinische aspecten en mogelijkheden tot modulatie van MDR: een overzicht".

Invited speaker at the Symposium 'New approaches in NSCLC management', Madrid June 26-27, 1995: "EORTC Lung Cancer Group".

Conference Director and Chairman of proferred paper session at 'The Sixth Conference on DNA topoisomerases in Therapy', Amsterdam September 6-8, 1995, and speaker: "Present and future of topoisomerase I inhibitors".

Invited speaker at the 'International meeting on drug resistance in cancer', Dublin September 20-23, 1995: "Clinical trials of reversal of multidrug resistance. An overview".

Invited speaker at the 'The 13th Congress of the European Association of Internal Medicine', Athens October 4-7, 1995: "Neo-adjuvant chemotherapy of non-small cell lung cancer".

Invited speaker at the 'ECCO 8 conference', Paris October 29 - November 2, 1995: Rapporteur of "Small cell lung cancer".

Invited speaker at the 'VI Congresso Nazionale - il tumore del polmone', Pisa November 24-25, 1995: "New drugs".

Invited speaker at 'The First meeting of the Indonesian Society of Oncology', Bandung December 7-9, 1995: "Good clinical practice in clinical trials"; Bristol-Myers Squibb satellite symposium: "Current practice and future directions for paclitaxel (Taxol) chemotherapy in cancer patients".

Invited speaker at the 'Bristol-Myers Squibb Cancer Research Symposium', Lawrenceville US January 12, 1996: "Topoisomerase and other resistance genes in lung cancer".

Invited speaker at The Fox Chase and Free University Hospital Investigators' Workshop and Consensus Conference', organized by Bristol-Myers Squibb, Marrakesh January 18-20, 1996: "Teniposide/Cisplatin versus Paclitaxel/Cisplatin in advanced non-small cell lung cancer: interim results of a randomized phase III study of the EORTC-LCCG".

Invited speaker at the Symposium 'Chemotherapy for NSCLC: best supportive care?', within the 'VI International Congress on treatment against cancer', Paris February 6, 1996: "Background".

Invited speaker at 'The First Pan Arab Cancer Conference', Cairo March 20-22, 1996: "Drug resistance in lung cancer"; "Chemotherapy of NSCLC".

Invited speaker at 'The Fourth International Conference on small cell lung cancer', Ravenna April 25-26, 1996: Chairman and speaker of the session "Forum on experiences and perspectives of major cooperative groups"; "The experience of the EORTC Lung Cancer Cooperative Group".

Invited speaker at 'The 5th I.A.S.L.C. Lung Tumor Biology Workshop', Ermatingen August 13-17, 1996: "New agents which circumvent drug resistance in lung cancer".

Invited speaker at the'European Respiratory Society, Annual Congress', Stockholm September 7-11, 1996: "Sanctuaries of lung cancer after chemotherapy".

Invited speaker at the '4th Central European Lung Cancer Conference', Gdansk September 26-29, 1996: "SCLC: is more better ?"; Co-chairman of the session "Treatment of advanced NSCLC".

Invited speaker at the 'XIV National Conference of experimental and clinical oncology', Milano October 13-16, 1996: Chairman of the session "Neoadjuvant chemotherapy".

Invited speaker at the 'Seventh Conference on DNA topoisomerases in Therapy', New York October 21-24, 1996: co-chairman of the poster session on October 23; "Expression of topoisomerase IIa in advanced non-small cell lung cancer in relation to sensitivity to chemotherapy".

Invited speaker at the Symposium 'Emerging strategies in medical oncology', organized by Bristol-Myers-Squibb, Vienna

November 2, 1996: "EORTC data: paclitaxel plus cisplatin versus teniposide plus cisplatin in the treatment of lung cancer".

Invited speaker at the '21st Congress of the European Society of Medical Oncology', Vienna November 1-5, 1996: Reviewer of the lung: "SCLC session".

Invited speaker at the '2nd International Congress on Lung Cancer', Crete 9-13, November 1996: Oral presentations: "Chemotherapy for stage IV NSCLC versus best supportive care"; "Radioenhancement by cisplatin, from preclinical investigation to phase II trials in NSCLC"; Chairman of the main symposium "New drugs developed for lung cancer"; Chairman of the Chemotherapy session III.

Invited speaker at the Symposium 'Lung cancer. What's new ? International meeting', Ravenna November 22, 1996: "Biological prognostic factors".

Invited speaker at the Symposium 'Biomedicina '96', Montecatini Terme November 29-30, 1996: "Nuove strategie terapeutiche antitumorali".

Invited speaker at the Symposium ''Chemioterapia Antitumorale', Firenze December 6-7, 1996: "Lung cancer, the basic knowledge".

Invited speaker during a tour of four cancer centers in Canada (Calgary, Winnipeg, Toronto, Ottawa), February 10-14, 1997; "Chemotherapy in non-small cell lung cancer"

Invited speaker at the 'Symposium on Paclitaxel' organized by Bristol-Myers Squibb, Naples February 28 - March 1, 1997: "Paclitaxel in lung cancer. Review".

Invited speaker at the 'Fourth International Symposium on the treatment of cancer', Buenos Aires May 7-9, 1997: "Clinical relevance of resistance to topoisomerase inhibitors"; "Strategies in the treatment of advanced non-small cell lung cancer. The experience of the EORTC"; "High-dose chemotherapy in lung cancer".

Chairman at the Conference 'Lung cancer in the elderly', Naples June 6, 1997.

Invited speaker at the 'Post-ASCO evaluation meeting', Zeist June 26, 1997: "Long kanker".

Invited speaker at the Conference 'New trends in the treatment of lung cancer', Naples June 26-27, 1997: chairman of the session

"New drugs in the treatment of metastatic NSCLC".

Invited speaker at the 'UICC Cancer management meeting; First international meeting on advances in the knowledge of cancer management', Vienna June 28 - July 1, 1997: "Reversal of multidrug resistance".

Invited speaker at the 'Eighth World Conference on Lung Cancer', Dublin 10-14, August 1997: SKB Symposium, August 10 – "New perspectives on small cell lung cancer chemotherapy; The clinical significance of drug resistance in lung cancer"; August 12 - Chairman of session "Chemotherapy"; BMS Symposium, August 12 "Current perspectives in the treatment of non-small cell lung cancer; A randomized trial of cisplatin plus paclitaxel versus cisplatin plus teniposide in advanced non-small cell lung cancer"; August 13 – "Grand-round for journalists: Recent developments with topotecan in the treatment of small cell lung cancer - Topotecan as second-line therapy for small cell lung cancer"; August 14 - TeleReview-live Video-Conference with WTC Amsterdam.

Invited speaker at the 'ECCO 9', BMS Satellite Symposium Emerging concepts in clinical oncology, Hamburg September 15, 1997: "Paclitaxel/gemcitabine in NSCLC and future directions in lung cancer"; September 16, 1997 - 'M'power: empowering the media to empower women - to fight cancer: "Lung cancer - an emerging women's cancer"; "What's so important about clinical trials ?"

Invited speaker at the 'European Respiratory Society, Annual conference', Berlin September 20-24, 1997: Meet the Professor: "New combination chemotherapy in lung cancer".

Conference Director, and chairman of 'The Eighth Conference on DNA topoisomerases in Therapy', Amsterdam October 15-17, 1997.

Invited speaker at the 'Gemzar Lung Cancer Consultants' Meeting', organized by Eli-Lilly, Stresa October 16-19, 1997: "Review of competitive cooperative group randomized trials for stage III/IV NSCLC - European experience - EORTC"; Chairman of the "Breakout session for advice on Gemzar NSCLC strategies: Spain, Italy, France, Belgium, Brasil".

Invited speaker at the Symposium 'Non-small cell lung cancer symposium', Barcelona November 6, 1997: "EORTC trials in lung cancer".

Invited speaker at the '3rd Annual scientific meeting Connective Tissue Oncology Society', Milan November 6-8, 1997: "The use

of chemosensitizers".

Invited speaker at the 'Workshop Il trattamento dei tumori primitivi e secondari del polmone', Aviano January 24,1998: "Nuovi protocolli chemioterapici nel NSCLC".

Invited speaker at 'The Fox Chase Cancer Center and Free University Hospital Paclitaxel Investigators' Work and Consensus Conference', St. Thomas (Virgin Islands) March 26-28, 1998: "Paclitaxel/cisplatin vs. Teniposide/cisplatin in non-small cell lung cancer: pharmacoeconomic analysis".

Co-chairman of the Minisymposium "Pharmacology and experimental therapeutics 13; downstream effects of cytotoxic drugs and reversal of checkpoint abrogations", American Association for Cancer Research, New Orleans March 28 - April 1, 1998.

Invited speaker at the 'International conference - Il trattamento del cancro del polmone non microcitoma localmente avanzato e metastatico', Napoli 17, April 1998, "I nuovi farmaci".

Invited speaker at the 'Health Care Course: An introduction to oncology & cancer chemotherapy', Amsterdam April 21-22, 1998, "Lung cancer".

Invited speaker at the 'Lung Intergroup meeting LUNG IWC' organized by the US National Cancer Institute, Bethesda April 28, 1998, "EORTC directions".

Invited speaker at the 'Oncology Global Medical Conference' at Eli Lilly and Company, Indianapolis May 12-15, 1998, "EORTC studies in non-small cell lung cancer".

Invited speaker at the Symposium 'Progress in the treatment of lung cancer', Madrid June 5, 1998, "Biological approaches to the treatment of lung cancer", "EORTC trials in lung cancer".

Invited speaker at the 'Post ASCO Evaluatie Meeting', Zeist June 10, 1998, "Lung cancer".

Invited speaker at the 'Satellite symposium Topotecan nuovi sviluppi nel trattamento del cancro del polmone', Bari June 11, 1998, "Topotecan nel trattamento del microcitoma del polmone, una overview".

Invited speaker at the '10th NCI-EORTC symposium on new drugs in cancer therapy', June 16-19, 1998, member of the Scientific Advisory Board and Chairman of the session: "Tubuline inhibitors: mechanisms and combinations".

Invited speaker at the Round Table "Cancer Genetics" organized by the Foundation Pezcoller, Trento July 9, 1998.

Invited speaker at the meeting of the British Thoracic Society, Edinburgh July 11, 1998, "Lung cancer: quality of life and epidemiological differences in Europe".

Invited speaker at the 3rd Nordic Symposium on Lung Cancer, Lofoten Norway August 15-19, 1998, "Preclinical drug testing".

Invited speaker at the International Symposium 'Thoraxmalignome: state of the art and outlook', St. Gallen August 28, 1998, "Vaccination against lung cancer?"

Breakout session leader at the "Eli Lilly and Company Lung Cancer Consultants' Meeting", Montreal September 11-12, 1998.

Invited speaker at the '5th Central European Lung Cancer Conference', Prague September 13-16, 1998, "New drugs in the treatment of NSCLC", and chairman of the session "New drugs part II".

Invited speaker at the 'Ninth Conference on DNA topoisomerases in therapy', New York October 5-7, 1998, "Randomized studies of CPT-11 and topotecan in Europe", and co-chairman of the Poster session on October 6.

Invited speaker at the conference 'Chemotherapy of non-small cell lung cancer: ten years later', Perugia October 11-13, 1998, "The experience of major cooperative groups: EORTC", co-chairman of session V, "Perspectives in chemotherapy of NSCLC" on October 13.

Invited speaker and 'Meet the Professor Session' at the Oncology Symposium, Istanbul October 24-25,1998, "Chemotherapy in lung cancer".

Invited speaker at the '3rd International Congress on lung cancer', Rhodos October 31 - November 4,1998, "The prognostic value of biologic parameters in radically resected NSCLC", and chairman of the session "Management of treatment and disease related morbidity in lung cancer".

Invited speaker at the symposium 'Hycamptin (topotecan Hcl), new advances in chemotherapy', Athens November 6, 1998, "Role of Hycamptin in small cell lung cancer".

Invited Poster Reviewer at the '23rd Congress of the ESMO', Athens November 6-10, 1998, "Non-small cell lung cancer",

"Small cell lung cancer".

Invited speaker and Chairman at the '55de Oncologiedag', Amsterdam 18, December 1998, "Prognostic factors in lung cancer".

Invited speaker at the '6th European Winter Oncology Conference', Meribel France January 24-29, 1999. "Small cell lung cancer".

Invited speaker at the conference 'Biliopancreatic malignancy: from gene to cure', Amsterdam 4-5, February 1999. "Current chemotherapeutic possibilities".

Invited speaker at the conference 'Current approaches in the treatment of solid tumors', Milan February 8-9, 1999. "Phase II of gem+cis as induction regimen for patients with stage IIIA NSCLC (EORTC)"; "MTA-multitargeted antifolate".

Local organizing committee member of 'Chemotherapeutic strategies for treatment of colorectal cancer - present and future developments', Amsterdam February 10-12, 1999. Speaker: "Topoisomerase I inhibitors - preclinical"; Chairman of the session 'New drugs and combinations, clinical part 2'.

Invited speaker at the 'Cooperative Refresher Day in Lung Cancer', organized by ESO, February 17-19, 1999, Budapest/Krakow/Prague; "Medical Oncology".

Invited speaker at the 'First World Conference on Clinical Cooperative Research for Lung Cancer', Brussels March 4-6, 1999; "Trials with lung cancer surgery - the EORTC experience", "Small cell lung cancer - the EORTC programme".

Invited speaker at the '2de consensusdag, Behandeling van het stadium IV niet kleincellig longcarcinoom', Amsterdam March 19, 1999; "Keuze van cytostatica".

Member of the 1999 AACR program Committee and Co-chairman of the Poster Discussion session "ABC transporters in multidrug resistance", AACR Annual conference, Philadelphia 10-14, April 1999.

Invited speaker at the 'V Congresso AIOM Oncologia High-Tech', Asti April 23-24,1999; "Acquisizioni recenti e direzioni future nella diagnosi e nella terapia delle neoplasie polmonari: quali indicazioni per la pratica clinica oncologica ?"

Invited speaker at the 'IV Middle East Oncology Congress', Beirut April 28- May 1,1999; "Chemotherapy for advanced

NSCLC. Have we reached a plateau ?"

Invited speaker at the '1999 Oncology Global Medical Conference', Indianapolis May 12-14, 1999, "Preliminary analysis of EORTC 3 arm trial in NSCLC", "MTA in NSCLC: single agent and second-line".

Faculty at the 1999 ASCO program and discussant at the oral presentation "Enhancing chemotherapy through modulation of systemic exposure", ASCO Annual Conference, Atlanta 15-18, May 1999.

Invited speaker at the 'Post-ASCO evaluatie meeting', Zeist June 9, 1999, "Lung cancer".

Invited speaker at the 'IASLC International workshop in lung cancer, Prognostic and predictive factors', Athens June 17-19, 1999, "Prognostic and predictive factors: present status".

Invited speaker at the 'Nascholingscursus Oncologie', Amsterdam June 24-26, 1999: "New developments in the treatment of lung cancer", "Running phase I trials".

Member of the International Organizing Committee of the "6th Central European Lung Cancer Conference", Budapest September 1-4, 1999.

Invited speaker at the International Conference "Controversies in the management of lung cancer", Athos Greece September 2-5, 1999: "Topotecan in the treatment of lung cancer", "New approaches to the treatment of small cell lung cancer".

Invited speaker at the ECCO 10, Vienna September 12-16, 1999, "Early non-small cell lung cancer: the need for combined treatments".

Invited speaker at the Eli Lilly Satellite Symposium 'Novel agents for the treatment of thoracic, GI and GU cancers' during ECCO 10, Vienna September 12, 1999, "Gemzar + cisplatin in early stage NSCLC".

Invited speaker at the Astra Zeneca Satellite Symposium 'Tomudex (raltitrexed) in combination – emerging evidence of broad anti-tumor activity' during ECCO 10, Vienna September 14, 1999, "Tomudex and platinum agents – a potential treatment standard for mesothelioma".

Invited speaker at the Update meeting of the Division of Oncology of Padova, September 22, 1999 Padova: "New perspectives in the medical treatment of lung cancer".

President of 'The Tenth Conference on DNA Topoisomerases in Therapy', Amsterdam October 6-8, 1999.

Chairman and speaker at the 'Eli Lilly and Company Lung Cancer Consultants' Meeting', Malta October 14-15, 1999, "New approaches to the treatment of NSCLC".

Invited speaker at the 'International conference New perspectives in the management of small cell lung cancer', Lausanne October 28-30, 1999: "Adjuvant therapy with metalloproteinase inhibitors or vaccination".

Invited discussant at the 'Lung cancer – a global view', organized by Network for Medical Communication & Research, New York November 5-6, 1999.

Program Committee member of the AACR-NCI-EORTC International Conference "Molecular targets and cancer therapeutics", Washington 16-19, 1999.

Scientific Committee member of the 10th International Congress on anti-cancer treatment, Paris January 31-February 3, 2000.

Invited speaker at the Annual meeting of the Taiwan Lung Cancer Society, "Clinical trials for lung cancer – European experience", Taipei March 4, 2000.

Invited speaker at the 4th Pan-European Cancer Symposium: a new era in the management of lung cancer, organized by Bristol-Myers Squibb, "The taxol experience in locally advanced NSCLC", Cannes March 17, 2000.

Invited Expert at the "Ask the Expert" Forum at the AACR, San Francisco April 1-5, 2000.

Invited speaker at the Academic Investigators' Meeting organized by Pharmacia Oncology: "Semoxid (SU5416) + gemcitabine/cisplatin", and "Ellence in SCLC", Miami April 28-29, 2000.

Invited speaker at the 1st Heidelberg Thoracic Oncology Symposium "Diagnosis and treatment of stage I/II NSCLC: current strategies and future concepts", Heidelberg May 12-13, 2000, "Clinical studies for lung cancer – EORTC studies", and chairman of the session "New Treatment approaches".

Invited speaker in the Panel discussion for the Press "Emotie en Chemotherapie", Den Haag May 25, 2000.

Invited speaker at the 36th Annual Meeting of the American Society of Clinical Oncology, New Orleans May 22, 2000, "SCLC: have we made progress?"

Invited speaker at the Post-ASCO Evaluatie Meeting, Zeist June 8, 2000, "Long tumoren".

Invited participant in the "Lung cancer state of science – Integration of new therapeutic agents in the multimodality treatment of locally advanced non-small cell lung cancer", organized by the US National Cancer Institute, Bethesda June 14-15, 2000.

Invited speaker at the Taxol ASCO 2000 Review Symposium, Munich July 1, 2000, "New developments in the treatment of advanced NSCLC with taxol".

Invited speaker at the First International Lung Cancer Congress, Maui Hawaii July 12-15, 2000: "EORTC efforts in NSCLC: trial design and results of randomized studies".

Invited speaker at the 9th World Conference on Lung Cancer, Tokyo September 11-15, 2000, "Strategy of combined modality treatment in unresectable stage III NSCLC: European randomized trials". Chairman of the "Chemotherapy 12" session; speaker at the Satellite Symposium organized by BMS Current perspectives in the treatment of non-small cell lung cancer "Neoadjuvant taxol plus carboplatin for early-stage non-small cell lung cancer"; speaker at the Satellite Symposium organized by Astra-Zeneca 'The role of platinum therapy in the treatment of lung cancer' "Platinum therapy and lung cancer – still room for improvement ?"; chairman and speaker at the Satellite Symposium organized by Astra-Zeneca 'Targeting the Epidermal Growth Factor Receptor (EGFR) in non-small cell lung cancer: a role for a selective EGFR tyrosine kinase inhibitor'? "Introduction: the need for new approaches in treating non-small cell lung cancer".

Invited speaker at the Gordon Research Conference Chemotherapy of experimental/clinical cancer, Oxford September 17-22, 2000: "New topoisomerase inhibitors in clinical development".

Invited speaker at the WCLC Post Tokyo evaluatiemeeting, Rotterdam September 28, 2000: "New drugs for lung cancer".

Invited speaker at a tour of Oncology Institutes in Switzerland, October 5-6, 2000, Inselspital Bern, CHUV Lousanne, OSI Lugano: "State of the art in the treatment of NSCLC".

Invited speaker at the ESMO Satellite Symposium 'New Agents

and combinations in the treatment of solid malignancies: AstraZeneca's portfolio approach', Hamburg October 13, 2000: "ZD0473: increasing the potential of platinum-based chemotherapy by combating drug resistance".

Invited speaker at the 25th ESMO Congress, Hamburg October 13-17, 2000: "Challenge your expert: Treatment of thymoma and thymic carcinoma".

Invited speaker at the First European Conference Perspectives in lung cancer, Lisbon November 3-4, 2000: "New developments and management of minimal residual disease", and speaker at the Satellite Symposium 'Innovative agents for the treatment of lung cancer': "Novel Multitargeted Antifolate – Preclinical and clinical overview".

Invited speaker at the 11th NCI-EORTC-AACR symposium on new drugs in cancer therapy, Amsterdam November 7-10, 2000: "EGFR inhibitors: a general overview".

Invited speaker at the Symposium in occasion of 5 years of Gemzar – Chemotherapy in the 21st century, Utrecht November 23, 2000: "US phase III studies in NSCLC" and "Concluding remarks, future developments".

Invited speaker at the 5th Lung Cancer Advisory Panel (LCAP), Tokyo November 25, 2000: "EORTC lung cancer group experience with gemcitabine".

Invited speaker at the AstraZeneca's Oncology Meeting, Copenhagen November 28, 2000: "Summary of platinum based chemotherapy focusing on resistance and Iressa phase II results on combination therapy".

Invited speaker at the '3^{e} Nationale Longkanker Symposium', Amsterdam January 12, 2001: "Very new drugs".

Invited speaker at the Satellite Symposium 'Novel approaches in the treatment of NSCLC', Helsinki February 7, 2001: "New directions in the treatment of advanced NSCLC".

Invited speaker at the 'First International North Adriatic Sea Symposium on novel targets for cancer therapy', Trieste March 8-9, 2001, "Drug induced apoptosis in epithelial cancer cells".

Invited speaker at the 'European Conference on Cancer Strategies & Outcomes', Edinburgh March 11-14, 2001, "Lung cancer – medical oncology".

Invited speaker at the 'International Symposium Respiratory

Oncology An Update', Leuven March 31, 2001, "Glaxo-Welcome Chair Lecture: Prospects for biologic therapy in lung cancer: a clinical view".

Invited speaker at the 4th International congress on lung cancer, Halkidiki April 26-30, 2001, "Targeted therapies in lung cancer".

Invited speaker at the 7th Central European Lung Cancer Conference, Prague June 3-6, 2001, "Clinical value of biological prognostic factors in routine practice – against", and chairman of the session Biological prognostic factors.

Invited speaker at the Eli Lilly Satellite Symposium New Standards in the treatment of advanced/metastatic NSCLC, Prague June 4, 2001, "Treatment of advanced/metastatic NSCLC – state of the art".

Invited speaker at the Post ASCO Evaluation Meeting, Zeist June 7, 2001, "Longkanker".

Invited speaker at the Lilly Thoracic Advisory Board, Venice June 19-21, 2001, "Current status of major new principles in NSCLC: anti-VEGF, EGFR-TKI, Antisense and others".

Invited speaker at the 2nd European Interuniversity AIMO Workshop, Maastricht June 22-23, 2001, "State of the art lecture. Towards a molecular classification of tumors".

Invited speaker at the Second International Lung Cancer Congress, Kauai Hawaii July 18-21, 2001, "EORTC trials in lung cancer".

Invited speaker at the SASMO/SASCRO 2001 Congress, Johannesburg September 21-23, 2001, "The management of non-small cell lung cancer", "Recent advances in the treatment of lung cancer", co-chair in the poster discussion.

Chairman at the "Second International Chicago Symposium on Malignancies of the Chest and Head & Neck", Chicago October 4-6, 2001, "Symposium I Stage IV NSCLC", selected oral presentation: "ZD1839 ("Iressa") an orally, active, selective epidermal growth factor receptor tyrosine kinase inhibitor, as combination therapy with gemcitabine and cisplatin in patients with advanced solid tumors: Preliminary tolerability, efficacy and pharmacokinetic results".

Member of the Organizing Committee, Invited speaker and chairman of the "Eleventh conference on DNA topoisomerases in therapy", New York October 8-10, 2001, "Preclinical studies and clinical application of camptothecins in Europe", chairman of

"Novel topoisomerase I and II inhibitors in clinical and preclinical research".

Invited speaker at the satellite symposium "Gemzar and Pemetrexed in thoracic cancers: present and future perspectives", Lisbon October 21, 2001. "EORTC phase III randomized trial in advanced NSCLC: platinum containing doublets vs. a non-platinum doublet".

Invited speaker at ECCO11, Lisbon October 21-25, 2001: "Educational session Lung Cancer: State of the art in systemic treatment of lung cancer".

Invited speaker at "Fourth congress on lung cancer", Barcelona November 8-9, 2001: "Novel approaches in NSCLC: new targets".

Invited speaker at "60e Oncologiedag – Receptors and signals: new therapies for cancer", Amsterdam November 30, 2001: "Inhibition of the epidermal growth factor receptor".

Invited speaker at the "Second European conference Perspectives in lung cancer", London December 7-8 2001: "Tyrosine kinase inhibitors for lung cancer", and invited speaker at the Lilly satellite symposium: "Targeted therapies in development in the treatment of NSCLC".

Invited speaker at the 4e Nationale Longkanker Symposium, Amsterdam January 18, 2002: "Targeted agents: new opportunities for NSCLC patients? "

Invited speaker at the symposium "Cancer trials in Asia, Hong Kong March 5-6, 2002: "Development of biological therapies for lung cancer".

Invited speaker and chairman at the "Oncology Regional Medical Conference" organized by Eli-Lilly in Hong-Kong March 8-10, 2002: "Advances in non-small cell lung cancer treatment".

Chairman and International scientific committee member of the IASLC International Workshop "Early invasive lung cancer: new diagnostic tools and treatment strategies" Turin March 14-15, 2002.

Invited speaker at the symposium "Oncologische interventies op maat", Cambridge April 5-6, 2002: "Groeifactorremming in solide tumoren".

Invited speaker at the "14e Internistendagen", Veldhoven April 24-26, 2002: "EGFR blockers, meer speciaal bij het niet-

kleincellig bronchuscarcinoom".

Invited speaker and co-chairman at the 2002 Lilly Oncology Global Medical Conference, Indianapolis, May 15-17, 2002: "Introduction and overview of ALIMTA".

Invited speaker at the "26th International Congress of Internal Medicine", Kyoto May 26-30, 2002: "Molecular target based drugs for epidermal growth factor".

Invited speaker and co-chairman of the "Post ASCO evaluation meeting", Zeist June 6, 2002: "Long kanker".

Invited speaker at the "French – Dutch exchange. Thoracic oncology: strategies and perspectives", Noordwijk June 13-15, 2002: "Pharmacogenomics and new biological correlates in NSCLC".

Invited speaker and chairman of the Cambridge Oncology Workshop organized by Astra-Zeneca, Cambridge July 23-25, 2002, "Results with Iressa to date".

Invited speaker at the 8th Central European Lung Cancer Conference, Vienna September 1-4, 2002: "Cisplatin versus carboplatin in non-small cell lung cancer".

Chair of the scientific committee of the 1st international symposium on signal transduction modulators in cancer therapy, Amsterdam September 23-25, 2002, chair of session 3, and invited speaker: "EGFR and EGFR inhibitors".

Invited speaker at the '4o congresso nazionale di oncologia medica', Turin September 28 –October 1, 2002, "Terapie oncologiche personalizzate".

Co-chair of the conference 'Oncology Update –1', Wassenaar October 11, 2002, and speaker: "EGFR and EGFR inhibitors".

Invited speaker at the Challenge your expert, 27th ESMO, Nice October 18-22, 2002: "Mesothelioma: combined modality treatments"; invited speaker at AstraZeneca satellite symposium "Combination of a new agents (ZD1839) with chemotherapy: emerging data"; invited speaker at Roche satellite symposium "Tarceva™ - new opportunities for the management of NSCLC".

Invited speaker at the 'Workshop on the management of locally advanced non-small cell lung cancer', Taipei October 24-25, 2002: "New drugs and approaches to the treatment of non-small cell lung cancer", "Neoadjuvant chemotherapy in non-small cell lung cancer".

Invited speaker at the '7th Congress of Asian Pacific Society of Respirology', Taipei October 25-28, 2002: "Tyrosine kinase inhibitors for lung cancer", and co-chair of the session "Lung cancer: from basic to clinical".

Invited speaker at the European Institute of Healthcare Oncology Symposium New Approaches in Cancer Research, Barcelona November 9, 2002: "EGFR and EGFR inhibitors".

Invited speaker at the 43rd annual meeting of the Japan Lung Cancer Society, Fukuoka November 21-22, 2002: "EGFR inhibition, an effective treatment modality for non-small cell lung cancer", "Targeted therapies in lung cancer".

Invited speaker at the "Gastro-intestinale tumoren: de zin en onzin van diagnostiek, therapie en follow-up" Ede November 28-29, 2002: "Van neoadjuvante behandeling naar nieuwe perspectieven: chirurgie nog alleen biopsie?"

Invited speaker at the "Cancer of the esophagus and gastric cardia: from gene to cure", Amsterdam December 13-15, 2002: "Targeted therapies in esophageal cancer", "Immunochemotherapy, clinical aspects", and chair of the Epidemiology and oncogenesis session.

Member of organizing committee, chairman, invited speaker at First IASCL/ASCO International Conference on 'Molecular targeted therapies inlung cancer', Marbella January 15-19, 2003. "Phase III studies with Iressa"; "Apoptosis overview".

Invited speaker at the Satellite Symposium "Targeting EGFR signalling in non-small cell lung cancer and other tumours", ICAT 2003, Paris February 3, 2003: "Gefitinib ('Iressa', ZD1839) as a new therapeutic option for advanced non-small cell lung cancer".

Invited speaker at the symposium "Iressa EGFR inhibitor: clinical outcome and perspectives", Vienna February 28, 2003: "Clinical monotherapy and combination trials in NSCLC".

Invited speaker at the VI Conferenza Nazionale AIOM, Alghero March 30 –April 1, 2003: "Dal bersaglio molecolare singolo alla strategia di inibizione multipla".

Invited speaker at the 2003 Lilly Oncology Global Medical Conference, Indianapolis May 29-30, 2003: "Gemcitabine".

Invited speaker at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago May 31- June 3, 2003:

"The role of chemotherapy in stage IIIA N2 non-small cell lung cancer", "The best of Oncology: INTACT1 study in advanced NSCLC".

Invited speaker at the Symposium Targeted therapies, Born, June 10, 2003: "The Iressa and EGFR stories".

Invited speaker at the CLDO day, Amsterdam June 12, 2003: "Target of cancer therapy".

Invited speaker at the Post ASCO evaluation meeting, Zeist June 19, 2003: "Translational research".

Invited speaker and member of the scientific committee of the 10th World Conference on Lung Cancer, Vancouver August 10-14, 2003: "Epidermal growth factor tyrosine kinase inhibitors in combination with chemotherapy"; ASCO Satellite Broadcast Symposium :'Multidisciplinary approach to treating lung cancer'; chair of the symposium 'Novel HER1/EGFR-targeted agents for NSCLC: current state of the art'; speaker at the symposium 'The evolving role of platinum-based therapy and integration of new agents in lung cancer treatment': "Phase I experience with a new oral taxane"; speaker at the symposium 'EGFR inhibition in the treatment of NSCLC and head & neck cancer: promise or reality?': "Inhibition of EGF receptor in lung cancer, is it working?".

Invited speaker at the Satellite symposium of the Finnish Oncology meeting, Turku August 29, 2003: "EGFR tyrosine kinase inhibitors in lung cancer".

Invited speaker at the Post Vancouver meeting, Zeist September 11, 2003: "New drugs".

Invited speaker at ECCO12, Copenhagen September 21-25, 2003: chairman and speaker at the European Press Conference "10 years of Taxol – history in the making and new horizons in cancer therapy" 'Taxol a remarkable discovery and its role in hard to treat tumor types'; satellite symposium "Taxanes in the management of solid tumors: status and perspectives", 'Paclitaxel combinations in the first-line treatment of NSCLC'; satellite symposium "Major advances in oncology: the clinical potential of proteasome inhibition", 'Clinical potential of proteasome inhibition in solid tumors'; 'EGFR inhibitors in the treatment of lung cancer"; debate "This house believes that concurrent targeted and chemotherapy treatments is the best way to go"-Contra.

Chair and invited speaker at the 'International Conference on Applied Genomics: 9th ESACP/16th ISDQP Meeting',

Amsterdam October 1-4, 2003; chair of the session 'Molecular diagnosis and therapy of cancer: EGFR and its inhibitors', talk "EGFR inhibitors, therapeutic aspects"; chair of the session 'Functional Genomics and Pharmacogenomics'.

Invited speaker at the symposium 'Novel agents in the treatment of lung cancer', Cambridge, MA, October 17-18, 2003 "Role of gefitinib (Iressa) in lung cancer".

President, chair and speaker at the '2nd international symposium on signal transduction modulators in cancer therapy', Amsterdam October 23-25, 2003. Chair of plenary session 1 and 6; speaker "EGFR inhibitors, small molecules".

Co-chair and speaker at the AstraZeneca Opinion leader Summit meeting, Boston November 14-16, 2003: "Combination therapy with gefitinib and cytotoxic therapy".

Invited speaker at the Astra-Zeneca (Iressa) satellite symposium: "Basic research in EGFR inhibition and future development in lung cancer", Taipei December 14, 2003.

Invited speaker at the British Thoracic Oncology Group Annual National Meeting 2004, Dublin January 21-24, 2004: "Non-small cell lung cancer tumor biology – other targets for therapy", and chairman of the symposium "EGFR as a target for therapy".

Invited speaker at the conference "Targeted cancer therapies, one year of progress", Nice February 13-14, 2004: "Gefitinib (Iressa) in solid tumors".

Invited speaker at the conference "Targeted therapies for the treatment of lung cancer", San Diego February 19-21, 2004: "Pan erbB targeted therapies", and chairman of session VI – Other targeted therapies.

Invited speaker and cochairman at the conference "Diagnostik und therapie von mediastinal-tumoren im kindes und erwachsenenalter", Hannover March 6, 2004.

Invited speaker at the Ninth International Symposium on Oncology Pharmacy Practice, Turin April 14-17, 2004: "Recent advances in NSCLC".

Invited speaker at the pre-ASCO industry-sponsored satellite symposium 'EGFR-targeted antibodies vs small molecule TKIs: facts, fallacies, and misconceptions', New Orleans June 4, 2004: "Clinical trials, where do we go from here?".

Invited speaker at the 40th Annual Meeting of the American

Society of Clinical Oncology, New Orleans June 5-8, 2004, Discussant "Developmental therapeutics: Molecular Therapeutics"; discussant "Lung cancer II".

Invited speaker at the ICE II (Iressa Clinical Experience II) meeting, organized by Astra-Zeneca. Athens June 25-27, 2004: Chair of the breakout session on "sequencing, maintenance and first-line therapy", and "Gastrointestinal tumors, including oesophageal and colorectal".

Invited speaker at the 1st EGFR symposium, Utrecht July 1, 2004: "Resultaten van de belangrijkste klinische EGFR studies (alle maligniteiten behalve colorectal).

Invited speaker at the "Second IASLC/ASCO/ESMO International Conference: Molecular targeted therapies in lung cancer", Algarve Portugal September 1-5, 2004.

Invited speaker at the "Third annual symposium on anti-signaling strategies in human neoplasia": "State of the art and future directions on clinical trials using EGFR inhibitors", Barcelona September 16-18, 2004.

Invited speaker at the 29th ESMO Congress, Vienna October 29 – November 2, 2004: "twenty-five years of treating advanced NSCLC: what have we achieved?", and moderator of the Controversy session "Lung cancer: Adjuvant therapy".

Invited speaker at "Het eerste Roche Oncologie Lagerhuisdebat", Vienna October 31, 2004: "Niet chemotherapie, maar targeted therapieën zullen het probleem kanker oplossen".

Invited speaker at the 29th ESMO Congress, Vienna October 29 – November 2, 2004, at the Industry Satellite Symposium "The appliance of science: from anemia management to proteasome inhibition – 10 years of innovation in cancer": "Clinical potential of proteasome inhibition with bortezomib in solid tumors".

Invited speaker and cochair at the Bronchioloalveolar Consensus Conference, New York November 4-6, 2004: "Systemic therapies".

Invited speaker at the Dedicated Training Course "Oncology Drug Development in Practice, organized by NDDO in Noordwijk, November 16-19, 2004: "Major tumor types and their treatment".

Invited chairman and speaker at the Regional Thoracic Cancer Symposium "Alimta EU", organized by Eli-Lilly, Berlin November 18, 2004: "Historical review of 2nd line NSCLC".

Invited speaker at the 'Tarceva 1-day scientific meeting' organized by Roche, Berlin November 21, 2004: "Predictive markers for response and/or survival in NSCLC".

Invited speaker at the symposium "La terapia medica del tumore del polmone, recenti acquisizioni e prospettive future", Reggio Emilia November 26, 2004: "Targeted therapy".

Chairman and invited speaker at the symposium "Oncology Update-2", Zeist December 1, 2004, "From signal transduction to drug development".

Chairman and speaker a the Lilly Oncology Innovation Workshop, Barcelona January 12-14, 2005: "Development of targeted agents – what have we learnt ?".

Chairman and speaker at the conference "Phase III clinical trials in oncology – accelerating late-phase development for targeted therapies", Amsterdam February 28 –March 2, 2005: "Assessing the future impact of translational research analysis on phase III clinical trials".

President and organizer of the TAT 2005 symposium "3rd International Symposium on Targeted Anticancer Therapies" Amsterdam March 3-5, 2005; also speaker "Small molecule inhibitors of the HER family of receptors".

Invited speaker at the "Longartsen dagen", Papendal April 4, 2005: "Biologicals en longkanker".

Invited speaker at the AACR 96th Annual Meeting, Anaheim April 16-20, 2005: Meet the Expert Sunrise Session "Targeted therapy in lung cancer".

Chair and invited speaker at the 41st ASCO Annual Meeting, Orlando May 13-17, 2005: Chair and speaker at the Scientific Symposium "Apoptosis: targeting death for life"; Chair and speaker at the Scientific Symposium "EGFR mutations, a year later"; chair of the poster discussion session "Developmental therapeutics: molecular therapeutics".

Invited speaker at the "Tarceva investigators Meeting", Orlando May 15, 2005: "Predictive markers for response and survival in NSCLC".

Cochair in the workshop "DNA topology in the global regulation of genome functions: basic studies and clinical applications", Bertinoro June 1-4, 2005.

Invited speaker at the Post ASCO 2005, Oosterbeek June 16, 2005: "New drugs".

Invited speaker at Euro cancer 2005, Paris June 22, 2005: "EGFR TK inhibitors: where to use them ?".

Invited speaker at the 'Oncology Highlights post-ASCO 2005', Amsterdam June 25, 2005: "Lung cancer".

Invited co-chair and speaker at the '11th World Conference on Lung Cancer', Barcelona July 3-6, 2005: Hot topic 14 – targeted therapy for lung cancer: "The future of targeted therapy trials"; proffered paper "Targeted therapies".

Invited speaker at the symposium 'Le nuove conoscenze sulla famiglia dei recettori EGF: come introdurle nella pratica clinica', Torino September 15, 2005: "Il network post-recettoriale; significato biologico e clinico della terapia HER targeted".

Invited speaker at the Amsterdam Symposium Algemene Interne Geneeskunde', Amsterdam September 16, 2005: "Angiogenese remmers".

Invited speaker at the EORTC Head & Neck group scientific meeting, Amsterdam September 17, 2005: "Targeted therapy".

Invited speaker at the 'Third International Conference on Thrombosis and Hemostasis issues in cancer', Bergamo October 14-16, 2005: "Clinical trials with angiogenesis inhibitors".

Invited speaker and chairman at the ECCO13, Paris October 30–November 3, 2005: "Advanced lung cancer: case study and discussion"; discussant of Plenary Symposium "The STELLAR 2 study"; chair and discussant of the Lung cancer NSCLC oral session; speaker at the scientific symposium 'The modern management of early stage NSCLC' "Targeted therapies in NSCLC".

Invited speaker at the workshop 'Onafhankelijkheid van onderzoek en wetenschappelijke integriteit', Amsterdam November 8, 2005; "Doctors and money: where the conflict of interest begins".

Invited speaker and chair of the conference "Controversie nel trattamento del tumore del polmone", Florence November 18-19, 2005: "Stato dell'arte nel microcitoma polmonare".

Chair and speaker at the Tarceva Scientific Symposium for the Launch of Tarceva in Europe, 'Future directions and closing remarks', Amsterdam November 10, 2005.

Invited speaker at the 'Sixth Annual Targeted therapies of the treatment of lung cancer', Santa Monica January 26-28, 2006: " Combining targeted agents".

Invited speaker and co-chairman of the 21st Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, Nagoya February 24-25, 2006: 'EGFR and EGFR inhibition in NSCLC'.

President, chair and speaker at the 4th International symposium on Targeted Anticancer Therapies, Amsterdam March 16-18, 2006. Chair and speaker of the taskforce MDICT (Methodologies for the Development of Innovative Anticancer Therapies).

Invited chair at the 97th AACR conference, Washington DC April 1-5, 2006; mentor in the roundtable 'Careers in clinical and translational cancer research', chair of the session 'Experimental and molecular therapeutics 34 – receptor tyrosine kinase inhibitors'.

Chair and speaker at the symposium "Targeted therapy – toepassing in de klinische praktijk", Utrecht April 13, 2006. 'Targeted therapy voor de behandeling van het nietkleincellig longcarcinoom'.

Invited speaker at the '2nd International Symposium of Translational Oncology', Barcelona May 11-12, 2006: "Lung cancer: translational research".

Invited speaker at the 'Post-ASCO 2006 conference', Oosterbeek June 23, 2006: 'Lung cancer'.

Invited speaker at the '7th European conference Perspectives in lung cancer', Athens September 8-9, 2006: "Apoptotic agents".

Invited speaker at the 7th International conference of the Asian Clinical Oncology Society and the 9th annual meeting of Chinese Society of Clinical Oncology, in collaboration with ASCO and ESMO, Peking September 14-18, 2006: "Molecular predictors of treatment outcome in lung cancer".

Invited chair and speaker at the 31st ESMO congress, Istanbul September 29 –October 3, 2006: speaker "Next generation oncology drug development: opportunities and challenges"; "ESMO minimum clinical recommendations – NSCLC"; Chair and discussant of "Proffered Papers session Lung cancer II"; discussant at the Presidential symposium, for the paper "Customizing cisplatin based on quantitative ERCC1 mRNA expression: a phase III randomized trial in non-small cell lung

cancer".

Invited speaker at the Joint Meeting of the 3rd ISC International Conference on Cancer Therapeutics and the 11th International Symposium on Cancer Chemotherapy "Target to Cure", Tokyo December 6-8 2006: "EGFR inhibitors in first-line treatment of advanced NSCLC" and "Advanced in the treatement of non-small cell lung cancer".

President, chair and speaker at the 5th International Symposium on Targeted Anticancer Therapies, Amsterdam 8-10 March 2007: "Angiogenesis inhibitors in lung cancer"; "Apo2-L".

Chair and speaker at the 'ESMO International Symposium on Chest Tumors', Geneva 30 March – 1 April 2007: "Selecting targeted therapies".

Invited speaker at the '1st Annual John R. Murren Memorial Symposium' 'Advances in Thoracic Oncology', Las Vegas April 11-13 2007: "EGFR inhibitors in lung cancer – defining those who benefit and those who do not".

Chair and speaker at the AACR Annual Meeting 2007, Los Angeles April 14-18 2007: "Pathways to apoptosis, introduction".

Chair and speaker at the "International Workshop Clinical Oncology in Croatia – strategic planning and beyond" Zagreb May 11-13 2007: "Lung Cancer".

Invited speaker at the 2007 ASCO Annual Meeting, Chicago June 1-5 2007: Discussant at the Clinical Science Symposium "Individualized therapy in non-small cell lung cancer".

Chair and speaker at the ASCO Independent Satellite Symposium 'Targeted Therapies and evolving treatment paradigms' Chicago June 1 2007: "Emerging targeted agents for NSCLC: future horizons".

Discussant at the ASCO Independent Satellite Symposium 'Charting rough waters' June 2 2007: "Signal transduction inhibitors: identifying the magic bullets from the broken arrows".

Invited speaker at the 4th IRCC International Cancer Conference 'Invasive growth: a genetic program for stem cells and cancer': "Targeted therapies in solid tumors – is the cancer stem cell being spared ?".

Invited speaker at the 2007 Workshop 'Accelerating anticancer agent development and validation', Bethesda June 20-22 2007: "Global issues in oncology drug development".

Invited speaker at the 'ESMO Conference Lugano', Lugano 5-8 July 2007: "Highlights in lung cancer", chair and poster discussant.

Invited speaker at the conference 'Percorso terapeutico nel carcinoma polmonare', Bari 9-10 July 2007: "Novel targets in lung cancer".

Invited speaker at the 'Sixth International Congerss on Targeted Therapies in cancer', Washington DC 24-26 August 2007: "Overview on Apoptosis".

Invited speaker at the '12th World Conference on Lung Cancer', Seoul 2-6 September 2007: "Advances in moleculr targeted therapy" and chair of the session 'Molecular predictors of EGFR TKIs'.

Invited speaker at the symposium 'Establishing a new treatment standard: the evolution of anti-angiogenic agents' during the '12th World Conference on Lung Cancer', Seoul 4 September 2007: "Lessons from the past: a historic review of NSCLC therapy".

Invited speaker at the Course Translational Research in Clinical Oncology (TRACO) organized by NCI CCR, Bethesda September 10 2007: "Small cell lung cancer".

Invited speaker at the 11th annual Fall Oncology Conference 'Clinical challenges in cancer medicine', Hilton Head Island 28-30 September 2007: "Tranlational medicine: an overview"; "Lung cancer"; "Metastatic lung cancer".

Invited speaker at the Fourth Annual Oncology Conference, Birmingham AL, 20-21 October 2007: "Future directions of lung cancer".

Invited speaker at the "Third Annual New York Lung Cancer symposium", New York 6 November 2007: "Update on key data on anti-VEGF antibodies", "Targeting the IGF axis".

Invited speaker and chair at the 4th ISC International Conference on cancer therapeutics and the 7th Princess Maraget Hospital conference New developments in cancer management, Toronto 15-17 November 2007: "Surgical debate: is there a role for surgery in stage IIIA NSCLC ?".

Invited speaker at the 10th International Symposium on Platinum Coordination Compounds in Cancer Chemotherapy (ISPCC 2007), Verona Italy 30 November – 3 December 2007:

"Combining platinums – lung cancer".

Invited speaker and chair at the Winter SPORE meeting and the 8th Annual Targeted Therapies on the treatment of lung cancer meeting, Santa Monica 20-23 February 2008: "NCI initiative in lung cancer"; "Clinical trials of epothilones"; "Talactoferrin-update".

Invited speaker at the 2nd Annual John R. Murren Oncology Symposium: Advances in Thoracic Oncology, Las Vegas 7-8 March 2008: "Keynote Address" Targeted therapies in lung cancer".

President, chair and speaker at the 6th International Symposium on Targeted Anticancer Therapies (TAT2008), Bethesda 20-22 March 2008: "Report MDICT Task Force: phase 0 studies".

Invited speaker at the Grand Rounds of the Center for Cancer Research of the National Cancer Institute, Bethesda 8 April 2008: "Targets and targeted therapies for lung cancer".

Invited speaker at the 4th Annual Staff Scientist and Staff Clinical Retreat of the Center for Cancer Research of the National Cancer Institute, Rockville 18 April 2008: "Targets and targeted therapies for lung cancer".

Invited speaker at the 1st European Lung Cancer Conference, Geneva 23-26 April 2008: "Is the a rational development of targeted treatment ?", and chair of the session "Metastatic NSCLC, state of the art".

Invited speaker at the ASCO 2008 meeting, Chicago May 30 – June 3 2008: discussant "Biomarkers: predictive or prognostic ?"

Planning Committee Chair and speaker at the 'Lung cancer in Croatia – Workshop', Zagreb 19-20 June 2008; "Genetic changes in lung cancers arising in smokers and never smokers", "Treatment at relapse and targeted therapies".

Invited speaker at the Rosewell Park Lung Cancer Symposium, Niagara-on-the lake 5-7 September 2008: "Novel targets for lung cancer therapy".

Scientific Committee member, chair and speaker at the 33rd ESMO Congress, Stockholm 12-16 September 2008. Speaker at Satellite Symposium organized by Amgen 'Meeting current and future chalenges in oncology': "The value of individualised cancer treatment"; chair and spaker at the educational symposium 'Lung cancer: new opportuninties' : "New opportunities in systemic therapy".

Invited speaker at the Thoracic Oncology Seminar series at the Dana Farber Cancer Institute, Boston 6 October 2008: "Targets and targeted therapies in lung cancer".

Invited speaker at the sixth Cambridge Conference 'Novel agnents in the treatment of lung cancer. Advanced in EGFR inhibitors', Cambridge MA 24 October 2008: "Erlotinib (Tarceva) 2008: role in lung cancer therapy".

Invited speaker at the XXVI Chemotherapy Foundation Symposium, New York 4-7 November 2008: "Talactoferrin in refractory NSCLC".

Invited speaker at the '9th Annual Targeted Therapies of the Treatment of Lung Cancer meeting', Santa Monica 18-21 February 2009: "Talactoferrin"; "PF-00299804".

Chair of the Scientific Committee, chair and speaker at the 7th International Symposium on Targeted Anticancer Therapies (TAT2009), Amsterdam 23-25 March 2009: "Bcl-2 inhibition".

Scientific committee member of the AAA Workshop (Accelerating Anticancer Agent Development and Validation Workshop), Bethesda 18-20 June 2009.

Invited speaker at the FDA Grand Rounds, White Oak MD, April 3, 2009: "Chemotherapy in combination with targeted agents in advanced NSCLC"

Scientific committee member of the 13th world conference on lung cancer, San Francisco, July 31-August 4, 2009.

Speaker at the 150th Meeting of the National Cancer Advisory Board, Bethesda June 11 2009: "Lung Cancer Program at NCI".

Scientific committee member of the "Accelerating Anticancer Agent Development and Validation Workshop", Bethesda June 17-19 2009.

Cochair, speaker and member of scientific committee of the '13th World Conference on Lung Cancer', San Francisco July 31 – August 4 2009. Chair of "Novel targets beyond EGFR and VEGFR"; discussant of "Novel combination regimens and unique pathways"; speaker at the meet the professor session "Novel signal transduction pathways"; cochair and speaker at the symposium 'Individualizing treatments fro thoracic malignancies'.

Cochair and speaker at the '1st International 1st International

Conference on Thymic Malignancies', Bethesda 20-21 August 2009: "Targeted therapy in Thymic Neoplasms".

Moderator and speaker at the 'Eighth International Congress on Targeted Therapies in Cancer', Washington DC August 21-23 2009: "Novel inhibitors of Bcl-2 function".

Cochair and invited speaker at the ECCO15/34thESMO joint conference, Berlin 20-24 September 2009: "The role of biomarkers in selecting the right targeted agent to combine with chemotherapy"; "Debate: this house believeds that targeted treatment should be used in all cases with lung cancer: In favor".

Invited speaker at the conference 'Le nuove frontiere nle management del NSCLC; l'importanza della diagnosi nella pianificazione del trattamento', Turin 9 October 2009; "Lettura Magistrale".

Invited speaker and co-chair at the 'XI Congresso Nazionale di Oncologia Medica, AIOM' Milano 10-13 October 2009 "Migrazione dei cervelli – chi e' rimasto", cochair of 'carcinoma del polmone'.

Invited speaker at the symposium 'New directions in cancer treatment: targeted therapies', Ft. Lauderdale 17 October 2009: "Use of kinase inhibitors in NSCLC".

Invited speaker at the symposium 'Emerging frontiers in thoracic oncology', Reston VA 24 October 2009: "Latest advances in lung cancer clinical trial research".

President, chair and speaker at the 8th International Symposium on Targeted Anticancer Therapies (TAT2010), Bethesda 4-6 March 2010: "A phase I study of PF-04929113 (SNX5422), an orally bioavailable heat shock protein 90 (HSP90) inhibitor after twice weekly administration in patients with refractory solid tumor malignancies and lymphoma.".

Invited speaker and Chair at the "AACR Conference on Translational Cancer Medicine 2010 (Europe)", Amsterdam March 21-24, 2010: "Small cell lung cancer: a forgotten disease ?".

Invited speaker at the 'NCI-PCF Metastatic Prostate Cancer Treatment Sciences Meeting', Bethesda April 6 2010: "Lung cancer: using molecular tools to choose therapy".

Invited speaker at the NCI Grand Rounds, Bethesda April 21 2010: "From genes to targets in thoracic malignancies".
Invited speaker at the Instituto Nacional de Cancerologia, Mexico

City May 14 2010: "Advances made by NIH in lung cancer".

Invited speaker at the '2nd worldwide innovative networking in personalized cancer medicine', Paris 7-9 July 2010: "Phase II and III clinical trial design and endpoints in the targeted therapy era-future goals and challenges".

Invited speaker and chair at the "Ninth International Congress on Targeted Therapies in Cancer", Washington DC 20-22 August 2010: "Clinical development of Apoptosis-Targeted agents".

Invited speaker at the '2nd Niagara Lung Cancer Symposium 2010', Niagara-on-the-Lake, 10-12 September 2010: "Novel targets fro lung cancer therapy".

Invited speaker at the '2nd International Thoracic Oncology Congress Dresden', 16-18 September 2010: "Novel agents – discussant".

Invited speaker at the 35th ESMO Congress, Milan 8-12 October 2010: "Chest tumors 2, discussant".

Invited speaker at the SPORE Lung Cancer Comprehensive Research Center Seminar, Tampa, 25 October 2010: "Targets and targeted therapies in lung cancer".

Invited speaker at the AACR-NCI-EORTC International Conference 'Molecular Targets and Cancer Therapeutics', Berlin 16-19 November 2010: "Biology and treatment of thymoma".

Invited speaker at the 2010 Chicago Multidisciplinary Symposium in Thoracic Oncology, Chicago 9-11 December 2010: "Thymoma".

Invited speaker at the '2011 Canadian Lung Cancer Conference', Vancouver 27-28 January 2011: "Lung cancer today and tomorrow".

Invited speaker at the '8th Annual Winter Lung Cancer Conference', Miami 11-13 February 2011: "Leveraging the EML4-ALK fusion gene in NSCLC", "Key questions being answered in ongoing clinical trials in NSCLC".

Invited speaker at the '11th Annual Targeted Therapies of the Treatment of Lung Cancer', Santa Monica 23-25 February 2011: "Talactoferrin", "EGFR mutations".

Invited speaker and NDDO Honorary Award Lecture 2011 at the 9th International Symposium on Targeted Anticancer Therapies (TAT2011), Paris 7-9 March 2011: "The changing landscape of

lung cancer and its treatment".

Invited speaker at the '41st Annual Spring Meeting of the Society of Nuclear Medicine', Ocean City 8-10 April 2011: "FDG-PET in solid tumors".

Invited speaker at the Grand Rounds of the VA Hospital, Washington DC, 11 May 2011: "Molecular profiling of thoracic malignancies".

Invited speaker at the Grand Rounds of the Roswell Park Cancer Institute, Buffalo 13 May 2011: "Molecular profiling of thoracic malignancies".

Invited speaker at the 14th World Conference on Lung Cancer, Amsterdam 3-7 July 2011:"Biology of thymoma", chair of educational session "Advanced thymomas", chair of the oral session "Cancer Biology", chair of the oral session "Preclinical models-1".

Invited speaker at the "NCI Translational science meeting 2011, Washington DC July 28-29, 2011: "Molecular profiling of thoracic malignancies".

Invited speaker at the Grand Rounds of the University of Texas Southwestern, Dallas 15 September 2011: "Profiling thoracic malignancies".

Invited speaker at the 58th Meeting of the National Cancer Institute Director's Consumer Liaison Group (DCLG). Washington DC 21 September 2011: "Molecular profiling of thoracic malignancies".

Invited speaker at Grand Rounds of the Princess Margaret Cancer Center, Toronto Canada, December 15 2011: "Profiling thoracic malignancies".

Invited speaker and chair to the "Clinical Trials Planning meeting: strategies for integrating biomarkers into clinical development of new therapies for lung cancer, a joint NCI Thoracic Malignancies Steering Committee – FDA Workshop", Bethesda February 2-3 2012: "Molecular profiling in thoracic malignancies".

Invited speaker at the 12th Annual Targeted Therapies of the treatment of lung cancer conference, Santa Monica February 22-25, 2012: "AZD 2281", "Talactoferrin".

Chair at the 10th International Congress of "Targeted Anticancer Therapies", Amsterdam March 8-10, 2012. "Opening ceremony",

"Combining targeted agents".

Invited speaker at the Spring 2012 CTEP Early drug development meeting, March 12-13 2012 Rockville MD: "Initiatives to optimize characterization of SCLC at the molecular level".

Invited speaker at the 3rd European Lung Cancer Conference, Geneva April 18-21 2012: "Lessons learned from negative phase III lung cancer trials of targeted agents", "Developments in small cell lung cancer".

Invited speaker at the 2012 ASCO Annual Meeting, Chicago June 1-5 2012: Discussant for the presentation "Clinical activity and safety of anti-PD1 in patients with advanced NSCLC".

Invited speaker at the "Tenth International Congress on Targeted Therapies in Cancer" Washington DC 17-18 August 2012: "Bcl-2 inhibitors".

Invited speaker at the "First Congress of the Hellenic and International Society of Molecular Genomic Medicine and Research", Volos Greece 12-13 October 2012: "Personalized individual molecular profile of the cancer patient, where are we now ? where can we go ?".

Invited speaker at Grand Rounds of the Weill Cornell Dean's Lecture at the Cornell University, New York City 14 June 2013: "Targets in thoracic malignancies".

Invited speaker at Grand Rounds at the Medical University of South Carolina, Charleston July 17 2013: "Targets in thoracic malignancies".

Invited speaker at the Medical Grand Rounds of Georgetown University, Washington DC July 18 2013: "Targets in thoracic malignancies".

Invited speaker at the "11th Annual International Congress on Targeted Therapies in Cancer", Washington DC August 17 2013: "SMAC mimetics".

Invited speaker at the "ITMIG 2013, 4th International Thymic Malignancy Interest Group Annual Meeting" Bethesda September 7, 2013: "Emerging drug targets and the role of targeted therapy".

Invited speaker at the "Fall 2013 NCI-CTEP Early Drug Development Meeting", Bethesda September 9, 2013: "Pilot trial of molecular profiling and targeted therapy for advanced non-small cell lung cancer, small cell lung cancer, and thymic

malignancies".

Invited speaker at the European Cancer Congress, Presidential Session, Amsterdam, September 28, 2013: "A phase III study of belagenpumatucel-L therapeutic tumor cell vaccine for non-small cell lung cancer".

Invited chair of the '2nd Annual Biomedical Informatics Symposium at Georgetown University', Washington DC October 11, 2013 "Genomics and Translational Medicine".

Member of the Scientific Committee of the '15th World Conference on Lung Cancer' Sydney October 27-30, 2013, invited speaker "Maximizing the benefit of chemotherapy for advanced NSCLC", invited discussant "Preclinical Therapeutic models I", selected presentations "Clinical ativity of sunitinib in patients with thymic carcinoma" and "Combined pan-Erbb and AL/ROS1/MET inhibition with dacomitinib and crizotinib in advanced non-small cell lung cancer: update of a phase I trial".

Invited speaker at "Practical and emerging approaches for lung cancer", Dallas December 14-15, 2013: "Dacomitinib: a pan-her family inhibitor".

Invited speaker and co-chair at the 12th International Congress on Targeted Anticancer Therapies (TAT 2014), Washington DC 5-7 March 2014 : "Verbal Report of the Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT) Meeting: Genomics-based early-phase clinical trials in oncology".

Invited speaker and co-chair at the 4th European Lung Cancer Conference Geneva 26-29 March 2014 : "Thymoma – systemic therapy".

Invited speaker at the 2014 AACR Annual Meeting, San Diego 5-9 April 2014, in the Educational Session 'Immune modulation for the treatment of lung cancer' : "Why has immunotherapy not worked in lung cancer?".

Invited speaker at the 1st meeting of the Hellenic and International Society of Molecular Targeted-personalized treatments, Volos May 2-3, 2014: "Resistance to TKIs in lung cancer: the way forward".

Invited speaker at the MidAtlantic Lung Consortium, Washington DC 16 July 2014. "Post-ASCO review".

Moderator at the Lung cancer breakout session at the 2nd NCI-SNMMI Workshop on targeted radionuclide therapy, Bethesda

24-25 2014.

Invited speaker at the 2nd annual Summit on practical and emerging approaches for lung cancer, Dallas 13-14 December 2014, "Third generation EGFR inhibitors".

Invited speaker at Department of Medicine Grand Rounds, Georgetown University, 15 January 2015, "Thymic malignancies; from genetics to treatment".

Invited speaker at the "15th Annual Targeted Therapies of the Treatment of Lung Cancer", Santa Monica 18-21 February 2015: "Ganetespib plus doxorubicin".

Invited speaker at the Grand Rounds of the Sylvester Cancer Center, Miami 15 April 2015: "Targets and Targeted Therapies in Thoracic Malignancies".

Invited speaker at the "IASLC Small Cell Lung Cancer Workshop", New York 22-24 April 2015: "JAK family signalling in SCLC".

Invited speaker and honorary lecture at the "2nd meeting of the Hellenic and International Society of Molecular Targeted-personalized treatments, Kalamata 1-2 May, 2015: "New horizons in treating lung cancer".

Invited speaker at the Grand Rounds of the Case Western Comprehensive Cancer Center, Cleveland 9 May 2015: "Targets and Targeted Therapies in Thoracic Malignancies".

Invited speaker at the 2015 ASCO Annual Meeting, Chicago 29 May – 2 June 2015, Poster Discussant: "Biomarkers in trial design: "Promise and peril".

Invited speaker at the 16th World Conference on Lung Cancer, Denver September 6-9 2015: "Treatment of thymic malignancies, biology and standard treatment"; Discussant at the Mini Oral session 21, Novel Targets, biology, pathology and molecular testing.

Invited speaker at the 4th Annual Biomedical Informatics Symposium at Georgetown University, Washington DC October 16, 2015: "Next generation sequencing to study rare cancers: thymic epithelial tumors".

Invited speaker at the 2015 Tianjin Lung Cancer Conference, Tianjin October 25, 2015: "Advances in research in non-small cell lung cancer".

Speaker at the Course Lung Cancer 2015: a shifting paradigm with focus on immunotherapy and newer targeted therapies, Washington DC December 5, 2015: "Immunotherapy in other thoracic tumors".

Invited speaker at the 3rd Annual Global Summit on Thoracic malignancies and head and neck cancer", San Juan Puerto Rico December 10-13, 2015: "Mechanisms of acquired resistance to EGFR inhibitors".

Invited speaker at the 13th Annual Winter Lung Cancer Conference, Miami 12-14 February 2016: "Updates on treatment advances in small cell lung cancer, mesothelioma, thymoma and thymic carcinoma".

Invited speaker and co-chair of the "16th Annual Targeted Therapies of the Treatment of Lung Cancer", Santa Monica 17-20 February 2016: "Selinexor – SINE inhibitor"; "Momelotinib and Trametinib"; "Margetuximab".

Invited speaker at the NCI Frederick Grand Rounds, April 1, 2016: "Drug resistance in lung cancer".

Invited speaker at the Japanese Respiratory Society Annual Meeting, Kyoto April 7, 2016: "Immuno-oncology in lung cancer".

Invited speaker at the European Lung Cancer Conference, Geneva April 13-16 2016: "KRAS", "Future perspective on managing resistance mechanisms".

Invited speaker at the "3rd National Conrgess of the Hellenic and International Sociaty of Molecular targeted-personalized treatments", Kalamata 6-7 May 2016: "Novel treatments in lung cancer".

Invited speaker at the Roche Satellite Symposium during the 2016 Taiwan Joint Cancer Conference, Taipei 14-15 May 2016: "Treatment strategies in EGFR mutant NSCLC – efficacy beyond EGFR TKIs"; "From bench to bedside: targeting PD-L1 in cancer immunotherapy".

UNIVERSITY SERVICE:

At Georgetown University (Washington DC)

Role/Function: Co-Chair
Committee Name: Clinical Research Committee
Date(s) of service: July 2015 – present

Role/Function: Associate Director for Clinical Research

Committee Name: Lombardi Comprehensive Cancer Center
Date(s) of service: January 2013 – present

Role/Function: Director of clinical research
Committee Name: Medstar Cancer Network
Date(s) of service: January 2013 – present

Role/Function: Chair
Committee Name: Data & Safety Monitoring Committee
Date(s) of service: July 2013 – 2015 September

Role/Function: Member, Co-Chair starting in August 2015
Committee Name: Protocol Review and Monitoring Committee
Date(s) of service: March 2014 – present

Role/Function: Member
Committee Name: Subcommittee of the Protocol Review Committee
Date(s) of service: April 2013 - present

Role/Function: Chair
Committee Name: Search for Regional Head of Thoracic Surgery
Date(s) of service: August 2013 – 2014

At the Vrije Universiteit (Amsterdam) 1990 - 2007

Department Medical Oncology
Role/Function: Chair
Committee Name: Oncology Tumor Board
Date(s) of service: November 1998 – January 2003

University
Role/Function: Member
Committee Name: CTK (Commissie Top Kader, Commission Selection of Professorships)
Date(s) of Service: March 2003 – March 2007

TEACHING ACTIVITIES:

At the Vrije Universiteit (Amsterdam) 1990 - 2007

Teacher of the University (Opleider) for Medical Oncology – this includes teaching to 4th year medical students and the Master Class Oncology. Classes include 20-30 students.

Other teaching activities:
Teacher at the "Basiscursus voor het verplegen van patienten met een oncologische aandoening", 8 March 1999.
Teacher at the "Basiscursus voor het verplegen van patienten met een oncologische aandoening", 20 September 1999.

Teacher at the Graduate course for medicine students, Vrije Universiteit Amsterdam, "Kankerbehandeling anno 2000", June 8 2000.
Teacher at the "Basiscursus voor het verplegen van patienten met een oncologische aandoening", 5 February 2001.
Teacher at the "Verpleegkundige Vervolgopleiding Oncologie" groep A 2001, 6 April 2001.
Teacher at the "Basiscursus voor het verplegen van patienten met een oncologische aandoening", 10 September 2001.
Teacher at the "Specialistische Vervolgopleiding Oncologie Verpleegkunde", 24 April 2002.
Teacher at the 3rd year medical students "Onderwijs profiel oncologie", July 1 2002: "Long kanker, chemotherapeutische behandeling; experimentele behandelingsvormen".
Teacher at the "Specialistische Vervolgopleiding Oncologie Verpleegkunde", 9 September 2002.
Teacher at the "Profiel Oncologie", June 20 2003: "Long kanker biologie".
Teacher at the Master course Innovative therapies, December 9 2003, "Signal transduction".
Teacher at the Collegeweek Erasmus Universiteit, Rotterdam, May 19 2004, "Nieuwe therapeutische mogelijkheden bij de behandeling van longkanker".
Teacher at the Master's Oncology of the VU Medical Center, December 8 2004: "Signal transduction".
Organization of the 9th Nascholingscursus Oncologie of the VU medical Oncology, Amsterdam 16-17 December 2004.
Organization of the first Italian-Dutch course on thoracic malignancies, Amsterdam 9-10 June 2005 "Translational research in lung cancer", "New drugs".
Teacher at the Master's Oncology of the VU Medical Center, December 9 2005: "Signal transduction".

At Georgetown University (Washington DC) – since 2013

Teacher at the course BCHB-529 Biotechnology-based human diagnostics. April 17, 2013: "Targeted therapies in lung cancer".

Teacher at the course Cancer Pharmacology TBIO, March 18, 2014 : "Targeted therapy and driver mutations".

Teacher at the course Cancer Pharmacology TBIO, February 24, 2015 : "Targeted therapy and driver mutations".

Participation in post-graduate and post-doctoral Courses

Course Anticancer Drug Development organized by the European School of Oncology (ESO), Amsterdam July 8-12, 1991: "Principles of chemotherapy".

Post-Doctoral Course Oncology, organized by the ESO, Amsterdam December 19-21, 1991: "Small cell lung cancer"; "Non-small cell lung cancer".

Post-Doctoral Course Oncology, organized by the ESO, Amsterdam April 5-11, 1992: "Gastro-intestinal tumours".

Post-Graduate Course of the European School of Haematology New approaches to anticancer chemotherapy: from basic concepts to therapeutic strategies, Paris, April 23-25, 1993: "Topoisomerases and topoisomerase inhibitors".

Post-Graduate Course of the European Cancer Center-ESMO Anticancer drug development, Amsterdam September 8-10, 1993: "Principles of chemotherapy".

Post-Graduate Course of the ESO Lung cancer, Moscow September 14-17, 1993: "Modern approaches to the treatment of SCLC".

Post-Graduate Course of the ESO New drugs in cancer therapy, Corfu, September 17-18, 1993: "Taxol in lung cancer"; "CPT-11: phase I and II studies".

Post-graduate Course of the ESO 'Seminar on lung cancer', Vienna November 12-13, 1993: "New drugs in lung cancer".

ESO Course 'Lung Cancer', Athens 29 September - 1 October 1994: "Chemotherapy is effective in NSCLC"; Chairman of the Round Table "Controversies in the treatment of NSCLC".

The OOA course 'Pharmacology of anticancer drugs', Amsterdam October 9-13, 1995: "Topoisomerases"; "Rationale of combination therapies"; "Combination therapies in the clinic".

ESO Course 'Tumors of the Lung', Torino February 27, 1996: "Therapeutic strategy".

Faculty and lecturer at the '43rd Course Genetic and immunochemotherapeutic approaches in cancer treatment' of the Ettore Majorana Centre for scientific culture, International School of Pharmacology, Erice May 21-26, 1996: "Multidrug resistance (P-gp-mediated)".

'Post-graduate course of the Netherlands Cancer Institute', Amsterdam October 25, 1996: "Trials/mogelijkheden in Nederland".

'Postdoctoral Course of the AZVU', Amsterdam, 12-14,

December 1996: "Topoisomerase-remmers anders dan CPT-11: een overzicht van effectiviteit en toxiciteit"; "Nieuwe inzichten in drugresistentie"; "Chemotherapeutische mogelijkheden bij de behandeling van het niet-kleincellig longcarcinoom".

'International Cancer Conference & ESO Educational Course on Lung Cancer', Cairo October 3-5, 1997: Plenary lecture: "Adjuvant treatment in lung cancer".

'Advanced Course on Chest Tumours' organized by the ESO, London October 13-15, 1997: "Small cell lung cancer: lessons from trials - chemotherapy"; "Prospects of chemotherapy for mesothelioma"

'ESMO Postgraduate Course - Clinical Pharmacology for Medical Oncology' Monte Verita' Ascona November 27-30, 1997: "Mechanisms of drug resistance and programmed cell death"; Tutorial - "Methods to detect drug resistance".

Co-organizer of the postgraduate course of the Graduate School of Oncology Amsterdam (OOA), January 19, 26, February 2, 9, 1999. "Topoisomerases as a target for cancer chemotherapy".

Invited speaker at the course '1o Incontro Specialisti in Oncologia', Firenze March 11-13, 1999; "New approaches to the treatment of lung cancer".

Invited lecturer at the post-graduate teaching course, University of Antwerpen, Antwerpen May 29, 2000; "Experimental therapies in oncology".

Invited speaker at the Doorlopende Nascholing Medische Oncologie of the Netherlands Cancer Institute, Amsterdam November 10, 2000: "Tweedelijns chemotherapie bij het niet-kleincellig longcarcinoom".

Invited speaker at the OOVU course 'Pharmacological innovations in cancer treatment', Amsterdam June 11-15, 2001, "EGFR receptor inhibitors".

Teacher at the Nascholingscursus Oncologie, Amsterdam December 13-14, 2001: "Nieuwe inzichten bij het niet-kleincellig long carcinoom", Tyrosinekinase remmers", "Nieuwe fase I middelen".

Post-Graduate Course in Pediatric Oncology ASPO-ESO-SIOP, Amsterdam January 14-18, 2002: "Signal transduction inhibitors".

First Course on "From chemotherapy to molecular targets",

Parma September 20-21, 2002: "EGFR and ras inhibitors".

Faculty of the Mastercourse Oncology of the VUMC, September 30–October 25, 2002: "Metastases".

Invited speaker at the 9de Nascholingscursus Medische Oncologie, Arnhem October 3-4, 2002, "Hoe leidt de remming van kinasen tot celdood?" and chairman and speaker at the Orthobiotech satellite symposium "Anemiemanagement met epo: standaardtherapie?"

"DONAMO Cursus IV", longen/mediastinum, Amsterdam November 1, 2002: "NSCLC: tyrosine kinaseremming in de kliniek – panacee ? ".

Invited speaker at the ESMO Advanced Course 'New perspectives: chest tumours integration of research and treatment', Rhodos June 17-19, 2004: "Controversies in SCLC – biological therapies", "Non-small cell lung cancer: combined chemo-targeted therapy".

Invited speaker at the Nascholingscursus Oncologie, Amsterdam December 16-17, 2004

Speaker at the ESO (European School of Oncology) course "New drugs in oncology: from the lab to the clinic", Bellinzona February 16-19, 2005; "Growth factor receptors and inhibitors".

Invited speaker at the Training Course 'Oncology Drug Development in Practice': "Systemic anticancer agents and their mechanism of action", "Lung cancer". Noordwijk, November 23, 2005.

Molecular Oncology course of the Institute for Cancer Research and Treatment, Turin 25 January 2008: "Lung cancer beyond surgery".

At the National Cancer Institute
Teaching the course TRACO (Translational Research in Clinical Oncology) 2007-2012. Classes are about 150 participants (PhD students, post-docs, clinicians).

At Georgetown University
Co-Director of the CME course "Lung cancer 2013: A multidisciplinary approach". Co-chair and speaker "Targeted therapy and molecular biomarkers". Washington DC 14-15 November 2013.

Co-Director of the CME course "Lung cancer 2015: a shifting paradigm with focus on immunotherapy and newer targeted

therapies", Co-Chair and speaker "Immunotherapy in other thoracic tumors". Washington DC December 5, 2015.

MENTORING:

PhD Mentor at the Vrije Universiteit (Amsterdam 1990 – 2007):

Name of Mentee, title of thesis, Date of thesis defense, Role in the PhD

C. Van Kalken: "Clinical and physiological aspects of P-glycoprotein mediated multidrug resistance", November 13, 1992, Vrije Universiteit Amsterdam, member of commission.

P. Pizao: "Multilayered post-confluent tumor cell cultures as a model for in vitro chemosensitivity tests", December 21, 1992, Vrije Universiteit Amsterdam, copromotor.

E.Klumper: "Drug resistance and relapsed leukemia", February 3, 1995, Vrije Universiteit Amsterdam, member of commission.

M.Huizing: "Bioanalysis and clinical pharmacology of paclitaxel", April 11, 1996, Universiteit Utrecht, member of commission.

E.Gheuens: "Implications of multidrug resistance for chemotherapy and immunotherapy", June 1996, University of Antwerp, member of commission.

R.M. Apolinario Hidalgo: "Expression of p53, Bcl-2 and Bax in operable non-small cell lung cancer. Relation with tumor angiogenesis (CD-31)", July 1996, University of Las Palmas de Gran Canaria, copromotor.

S. Linn: "Clinical probing and reversal of multidrug resistance in solid tumors", January 28, 1998, Vrije Universiteit Amsterdam, copromotor.

S. Kumar-Singh: "Differentiation and progression of malignant mesotheliomas", June 26, 1998, University of Antwerp, member of commission.

A-M. Dingemans: "Prognostic factors for response to chemotherapy in lung cancer", June 7, 2000, Vrije Universiteit Amsterdam, copromotor.

H. Gelderblom: "Pharmacologic aspects of new classes of anti-cancer agents: inhibitors of topoisomerase I or tubulin", September 14, 2001, Erasmus University Rotterdam, member of commission.

I. Klaassen: "Determinants of retinoid sensitivity in head and

neck squamous cell carcinoma", October 15, 2001, Vrije Universiteit Amsterdam, member of commission.

C.G. Ferreira: "Apoptosis in non-small cell lung cancer: implications for sensitivity and prognosis", November 21, 2001, Vrije Universiteit Amsterdam, promotor.

C. Huisman: "Clinical and preclinical chemotherapy studies in lung cancer", April 16, 2002, Vrije Universiteit Amsterdam, promotor.

I. Kolfschoten: "Cellular determinants for drug response in ovarian cancer", September 14, 2002, Vrije Universiteit Amsterdam, member of commission.

M. Huigsloot: "Molecular mechanism of anticancer-induced apoptosis in breast cancer (MTLn3) cells", January 23, 2003, Leiden University, member of commission.

J.R. Kroep: "Preclinical and clinical pharmacology of gemcitabine and combinations with paclitaxel and cisplatin", February 12, 2003, Vrije Universiteit Amsterdam, member of commission.

A.H. van Hattum: "Novel camptothecin derivatives: antitumor efficacy and mechanisms of resistance", May 2, 2003, Vrije Universiteit Amsterdam, member of commission.

H. van der Vliet: "Immunoregulation by CD1d-restricted natural killer T cells", May 2, 2003, Vrije Universiteit Amsterdam, promotor.

D. Heideman: "Towards gene therapy for gastric cancer", June 13, 2003, Vrije Universiteit Amsterdam, member of commission.

B. Kuenen: "Clinical experience with receptor tyrosine kinase inhibitors as anti-angiogenic treatment in cancer patients", September 11, 2003, Vrije Universiteit Amsterdam, member of commission.

L.V. Beerepoot: "Early clinical evaluation of antivascular drugs for cancer treatment", May 28, 2004, Utrecht University, member of commission.

M. de Graaf. "Selective chemotherapy with glycoside prodrugs of anthracyclines", July 2, 2004, Vrije Universiteit Amsterdam, member of commission.

S.D. Baker. "Factors affecting pharmacokinetic variability of docetaxel", September 23, 2004, University of Rotterdam,

member of commission.

J.J. Hornberg: "Towards integrative tumor cell biology – control of MAP kinase signalling", March 29, 2005, Vrije Universiteit Amsterdam, member of commission.

R.H.J. Breuer: "Studies on molecular pathology of lung cancer", April 6, 2005, Vrije Universiteit Amsterdam, member of commission.

M. Ferrer: "Fanconi anemia and cisplatin sensitivity: implications for cancer therapy", September 14, 2005, Vrije Universiteit Amsterdam, promotor.

M.J. Vos: "Evaluation of response, toxicity and outcome in glioma therapy", September 28, 2005, Vrije Universiteit Amsterdam, member of commission.

February 10, 2006, member of commission of the PhD theses of pharmacology of the University of Turin.

G.J.M. Herder "The use of 18FDG PET in NSCLC", April 26, 2006, Vrije Universiteit Amsterdam, member of commission.

J.H. Augustijn-Savonije: "Effects of erythropoietin in cancer patients". July 5, 2006. Vrije Universiteit Amsterdam, promotor.

S. van Schaeybroeck: "EGFR activity as a determinant of response to EGFR-targeted therapy", July 7, 2006, University of Leuven, Belgium, member of commission.

M.L. Janmaat: "Targeting ErbB receptors as anticancer therapy: Factors of sensitivity and resistance", October 12, 2006, Vrije Universiteit Amsterdam, promotor.

B. Vischioni: " Expression and subcellular localization of inhibitors of apoptosis proteins in human tissues: mechanisms and clinical implications", November 14, 2006, Vrije Universiteit Amsterdam, promotor.

A. Checisnka: "Regulation of mitochondria-dependent apoptosis in non-small cell lung cancer: implication for cancer therapy", March 9, 2007, Vrije Universiteit Amsterdam, promotor.

L. Broker: "Novel microtubule-stabilizing agents – preclinical and clinical studies", May 9, 2007, Vrije Universiteit Amsterdam, promotor.

M. Gallegos Ruiz: "Therapeutic targets and biomarkers in lung cancer", April 22, 2008, Vrije Universiteit Amsterdam, promotor.

H. van Cruijsen: "Preclinical and clinical studies on the co-regulation of tumor-induced angiogenesis and dendritic cell suppression", March 26, 2009, Vrije Universiteit Amsterdam, promotor.

I. Petrini: "Genomic aberrations of thymic epithelial tumors", March 15, 2012, University of Pisa, supervisor.

COLLABORATIVE ACTIVITIES:

Joint Grants
none

SCHOLARSHIP AND RESEARCH:

RESEARCH GRANTS

Current Active

Current laboratory research activity is supported by a 3-year start-up funding through the Lombardi Comprehensive Cancer Center.

Agency: Karyopharm
Identifying Number:
Title of Project: KPT-330 in thymic malignancies
Dates of Project Period: 2015
Role on Project: Project Leader
Percent Effort: 10%
Total Dollar Amount: 40k

Agency: Astra-Zeneca
Identifying Number:
Title of Project: Exploration of AZD9291 and SRC inhibitor combination for overcoming Cripto1-mediated resistance to EGFR-TKI in EGFR-mutated NSCLC
Dates of Project Period: 2015 - 2016
Role on Project: Project Leader
Percent Effort: 10%
Total Dollar Amount: 63,545

Agency: Lilly
Identifying Number:
Title of Project: Antitumor effect of LY2940930 (Chk1 inhibitor) with or without cisplatin in acquired cisplatin-resistant SCLC xenografts
Dates of Project Period: 2016
Role on Project: Project Leader
Percent Effort: 10%
Total Dollar Amount: 44,060

Agency: Merck

Identifying Number: GMS GR41087
Title of Project: A Phase II study of MK-3475 in patients with thymic carcinoma
Dates of Project Period: 2015 - 2017
Role on Project: Project Leader
Percent Effort: 20%
Total Dollar Amount: 348k

Agency: Synta
Identifying Number:
Title of Project: A Phase I study of Ganetespib in combination with doxorubicin in solid tumors
Dates of Project Period: 2014 - 2017
Role on Project: Project Leader
Percent Effort: 10%
Total Dollar Amount: 79k plus 50k institutions support

Previous

During my time at the National Cancer Insitute (2007 – 2012) my research activity was supported by the National Cancer Institute Intramural Program

Agency: Dutch Cancer Society 4-year research grant (KWF)
Identifying Number: VU 94-776
Title of Project: Expression of the topoisomerase genes in lung cancer patients treated with topoisomerase inhibitors.
Dates of Project Period: 1995 - 1998
Role on Project: Project Leader
Percent Effort: 30%
Total Dollar Amount: about 400k

Agency: European Cancer Center 1-year grant
Identifying Number:
Title of Project: Apoptosis induced by topoisomerase inhibitors
Dates of Project Period: 1996
Role on Project: Project Leader
Percent Effort: 20%
Total Dollar Amount: about 75k

Agency: ESMO (European Society of Medical Oncology) 1-year grant
Identifying Number:
Title of Project: Detection of circulating tumor cells in breast cancer
Dates of Project Period: 1997

Role on Project: Project Leader
Percent Effort: 20%
Total Dollar Amount: about 75k

Agency: ESMO (European Society of Medical Oncology) 2-year grant
Identifying Number:
Title of Project: Metalloproteinase and natural inhibitors in lung cancer invasion and metastasis
Dates of Project Period: 1999 -2000
Role on Project: Project Leader
Percent Effort: 20%
Total Dollar Amount: about 150k

Agency: Dutch Cancer Society 4-year research grant (KWF)
Identifying Number: VU 2001-2509
Title of Project: The role of caspases in the sensitivity of lung cancer cells to chemotherapy.
Dates of Project Period: 2002 - 2005
Role on Project: Project Leader
Percent Effort: 30%
Total Dollar Amount: about 400k

Agency: ESMO (European Society of Medical Oncology) 2-year grant
Identifying Number:
Title of Project: Nuclear-cytoplasmic shuttling of inhibitor of apoptosis as a regulatory mechanism
Dates of Project Period: 2002 - 2003
Role on Project: Project Leader
Percent Effort: 20%
Total Dollar Amount: about 150k

Agency: Dutch Cancer Society (KWF) 2-year translational research grant
Identifying Number: VU 2005-3445
Title of Project: Mutational and functional analysis of the EGFR pathway in non-small cell lung cancer patients: correlation with prognosis and response to small molecule EGFR inhibitors Dates of Project Period: 2005 - 2006
Role on Project: Project Leader
Percent Effort: 40%
Total Dollar Amount: about 200k

Agency: Dutch Cancer Society 4-year research grant (KWF)
Identifying Number: VU 2006-3567
Title of Project: Cancer therapy with the proteasome inhibitor Bortezomib and the death ligand TRAIL for non-small cell lung cancer.
Dates of Project Period: 2006 - 2009

Role on Project: Co-Project Leader
Percent Effort: 10%
Total Dollar Amount: about 450k

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12. Bruzzone M, Conte PF, Chiara S, Carnino F, Giaccone G, Conio A, Bentivoglio G, Pescetto G, Rosso R. High dose cisplatin after failure of polychemotherapy containing cisplatin in ovarian cancer. Preliminary results. **Chemioterapia** 4, 139-142, 1985.

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Appendix B – Material Considered

Petitioners' Ex. No.	Description
1001	U.S. Patent No. 6,900,221, titled "Stable Polymorph on N-(3-ethylphenyl)-6,7-bis(2methoxyethoxy)-4-S hydrochloride, Methods of Production, and Pharmaceutical uses thereof," issued May 31, 2005
1003	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Amendment dated June 19, 2002.
1004	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Office Action dated August 30, 2002.
1005	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Amendment dated February 28, 2003.
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1007	Provisional Appl. No. 60/164,907, filed November 11, 1999.
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1010	J.B. Gibbs, "Anticancer drug targets: growth factors and growth factor signaling," *The Journal of Clinical Investigation 105*(1):9-13 (Jan. 2000) ("*Gibbs*").
1011	Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the Fiscal Year Ended September 30, 1998 Commission File Number 0-15190 OSI Pharmaceuticals, Inc. ("*OSI 10-K*").
1012	Declaration of Laurence S. Lese, Esq.
1013	A.E. Wakeling *et al.*, "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," *Breast Cancer Research and Treatment 38*:67-73 (1996) ("*Wakeling*").
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