UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
Petitioner,

v.

ASTRAZENECA AB
Patent Owner.

U.S. Patent No. 8,329,680

DECLARATION OF LESLIE OLEKSOWICZ, M.D.

IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 8,329,680

TABLE OF CONTENTS

I. QUALIFICATIONS AND BACKGROUND

A. Education and Experience

1. My name is Leslie Oleksowicz. I am a physician and oncologist with over thirty years of experience, spending over 25 years in clinical practice. Throughout my career I have conducted clinical research in the field of Medical Oncology, participated in over 100 clinical trials, and written over 75 publications in my area of expertise. I have treated hundreds of patients with all stages and subtypes of breast cancer, and I directed a basic science laboratory research effort from 1992–2000 which focused on breast cancer adhesive receptors and their role in tumor metastases. In my role as CEO of Leslie Oleksowicz, M.D., LLC, I have also acted as a consultant to provide strategic intelligence to the financial and pharmaceutical industries, advising expertise to biotech and EMR (electronic health medical record) start-up companies and expert skills in legal cases involving intellectual property in the context of oncologic pharmaceuticals. My full *curriculum vitae* (CV) is attached hereto as Exhibit A and is incorporated herein.

2. I received my B.A. in Biological Sciences from Amherst College in 1978, graduating *magna cum laude* and Phi Beta Kappa. I received my M.D. from Tufts University School of Medicine in 1982.

3. After finishing medical school, I completed postgraduate training Internship and Residency Programs in Internal Medicine in 1985 at the Albert

Einstein College of Medicine (Montefiore University Hospital, Bronx, N.Y.) and was certified by the American Board of Internal Medicine (ABIM) in 1988. Additionally, I received research and clinical training (Fellowship) in the medical specialties of Hematology, completed in 1987 at Mount Sinai Medical Center (New York, N.Y.) and Medical Oncology completed in 1989 at Mount Sinai Medical Center (New York, N.Y). I was certified by the ABIM in Medical Oncology in 1989. From 1989–2015, I held faculty positions as an academic oncologist at Mount Sinai Medical Center, (New York, N.Y.), Montefiore University Hospital, (Bronx, N.Y), Roswell Park Cancer Institute (Buffalo, N.Y.), University of Cincinnati Cancer Institute (Cincinnati, OH), Saint Louis University Cancer Center (Saint Louis, MO) and the Dana Farber Cancer Institute (Boston, MA).

4. I currently serve as Chief Executive Officer of Leslie Oleksowicz, M.D., LLC, which provides strategic intelligence to the financial and pharmaceutical industries, advising expertise to biotech and EMR (electronic health medical record) start-up companies and expert skills in legal cases involving intellectual property in the context of oncologic pharmaceuticals.

5. I have been a member of a number of professional societies, including the American Society of Clinical Oncology (current member), the American Society of Hematology, SWOG (a worldwide network of researchers that designs

and conducts cancer clinical trials), the American College of Physicians, and the National Kidney Cancer Association (current member, editorial advisory board).

6. I have served as an editor for the following journals: Cancer, American Journal of Medical Sciences, Southern Journal of Medicine, Journal of Urology, Kidney Cancer, and Transfusion.

7. I have extensive experience treating patients with breast cancer, including hormone receptor-positive breast cancers. During my 25 years in academic practice, I have directed both basic science and clinical investigations in the area of hormone positive breast cancer. From 1992–2000, I led a basic science research effort studying adhesive glycoprotein receptors expressed by hormone-positive breast tumor cells that participated in the metastatic process. As a principal member of an institution-wide breast malignancy affinity group, I facilitated collaborations amongst clinicians and basic science investigators. My laboratory research was funded by several competitive grant-awarding groups, including the American Cancer Society, the Elsa U. Pardee Foundation, Sandoz Pharmaceuticals, and the Roswell Park Alliance Foundation, with the resultant research generating 11 publications in top-tier peer-reviewed journals. Additionally, as an invited guest speaker, I presented my work at multiple NCI-designated cancer centers including the Albert Einstein Cancer Center, the Mount Sinai Medical Center, the Grace Cancer Drug Center and the Roswell Park Cancer

Institute. In 2003, when I was recruited to the University of Cincinnati Cancer Institute, I directed a clinical trials program, focusing in large part on hormone receptor-positive breast cancer. Over a nine-year interval from 2003–2012, I was principal investigator of 12 breast cancer clinical trials. From 8/2008 – 5/2012, I was principal investigator of the SWOG 1222 trial entitled, *Phase III Randomized Trial of Anastrozole vs. Anastrozole and Fulvestrant as First Line Therapy in Post-Menopausal Women with Metastatic Breast Cancer*, and from 10/2011 – 5/2012, I was principal investigator in the SWOG S1007 trial, which investigated tamoxifen, letrozole, anastrozole and exemestane with or without chemotherapy in patients with invasive breast cancer. Additionally, I directed many other clinical trials evaluating a variety of investigational agents in the setting of early and advanced hormone receptor-positive breast cancer.

8. I have also participated in over 100 clinical trials, in over 80 of which I served as the Principal Investigator. The majority of these involved evaluating different pharmaceutical interventions for cancer treatment. I have served as Principal Investigator on studies evaluating fulvestrant and tamoxifen as treatments for breast cancer in women.

9. I have received a number of awards for my work. I was awarded the Hampden Scholarship during medical school on the basis of my GPA. While directing a basic science laboratory research effort at the Albert Einstein Cancer

Center, I was the recipient of multiple research grants including an American Cancer Society and a National Leukemia Fountain Research Award, grants from multiple pharmaceutical companies including Schering, Chiron, Bristol, Roche, Novartis, and Sandoz, and multiple research grants from national foundations including The Irvin A. Hansen Memorial Foundation, the Carol Solov Abbani Foundation, the Pardee Foundation, and the Bruce Cuvelier Endowed Research Fund. Finally, I was the recipient of a third-prize award at the annual basic science investigator's symposium at Montefiore University Hospital in 1997, and earned a certificate of recognition for outstanding clinical care at Roswell Park Cancer Institute in 2002.

10. I have published my work, and have been named as author or co-author on over 75 articles and abstracts, predominantly concerning cancer pathways and treatments.

B. Materials Considered

11. In connection with forming my opinions and drafting this declaration, I considered my experience, education, and training, as well as the materials identified in this declaration and listed in Exhibit B, attached hereto.

C. Scope of Work

12. I have been retained by counsel for Mylan Pharmaceuticals Inc. ("Mylan") in connection with this matter. I am being compensated at my usual

rate of $650 per hour for my work on this matter. My compensation does not in any way depend on the outcome of this proceeding.

II. SUMMARY OF OPINIONS

13. It is my opinion that, for the reasons stated below, claims 1–20 of the U.S. Patent No. 8,329,680 ("the '680 patent") were obvious over McLeskey [Ex. 1005]. Independent claims 1 and 20 of the '680 patent focus on a dosing regimen of a certain fulvestrant formulation, administered as an intramuscular ("i.m") injection, to treat humans with benign or malignant diseases of the breast or reproductive tract, such as breast cancer. The fulvestrant compound was already known to treat at least hormonal dependent breast cancer in women, and the claimed formulation was specifically disclosed in McLeskey. The remaining elements of the claims, including the route and dose of administration, were already known, and the cited blood plasma fulvestrant concentrations are not limitations to the method of treatment.

14. It is also my opinion that claims 1–20 of the '680 patent were obvious over Howell 1996 [Ex. 1006] in view of McLeskey [Ex. 1005]. Howell 1996 disclosed a long-acting fulvestrant formulation in a castor oil vehicle, administered to human females with breast cancer via a 5 ml monthly intramuscular injection of 250 mg. Howell 1996 disclosed that the fulvestrant treatment was efficacious, well-tolerated, and achieved predicted therapeutic concentrations of fulvestrant for

1 month following a single intramuscular injection. A POSA investigating prior art long-term and/or castor oil-based formulations of fulvestrant would be aware of or find McLeskey, which disclosed the exact formulation claimed in the '680 patent. Therefore, the disclosure of Howell 1996 combined with the specific formulation of McLeskey renders obvious claims 1–20 of the '680 patent.

III. LEGAL STANDARDS

15. I have been informed regarding the relevant legal principles. I have used my understanding of those principles in preparing and forming my opinions set forth in this declaration. My understanding of those legal principles is summarized below.

16. I have been told that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Mylan must show that unpatentability is more probable than not. I have taken this principle into account when forming my opinions here.

17. I have also been told that claims should be construed given their broadest reasonable interpretation in light of the specification, from the perspective of a person of ordinary skill in the art at the time of the invention.

18. I have been informed that the claim scope of a method claim is not limited by a "whereby" or "wherein" clause that simply expresses the intended

result of a process step positively recited. If the whereby clause does not inform how the method is carried out, the whereby clause is generally not given patentable weight.

19. I have been told that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

20. I have been informed that where claimed ranges overlap, lie inside of, or are close to ranges already disclosed in the prior art, the claims are prima facie obvious.

21. I have also been informed that when there is some recognized reason to solve a problem—and there are a finite number of identified, predictable, known solutions—a person of ordinary skill in the art is motivated and has good reason to pursue the known options within her technical grasp. If this approach leads to the expected success, it is likely the product of ordinary skill and common sense rather than the product of innovation. Where a patent simply arranges old elements, with each element performing its known function and the whole yielding no more than would be expected, the combination is obvious.

IV. PERSON OF ORDINARY SKILL IN THE ART

22. As above, I have been informed by counsel that the obviousness analysis is to be conducted from the perspective of a person of ordinary skill in the art (a "person of ordinary skill," or "POSA") at the time of the invention. I have adopted the understanding of a POSA when discussing the teachings of the prior art.

23. I have also been informed by counsel that in defining a POSA the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) speed with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

24. The POSA would have had, as of the earliest priority date, a graduate degree in pharmacy, pharmaceutics, chemistry, or a related discipline, or equivalent experience in drug development and formulation, and would also have familiarity with and knowledge of designing and formulating dosage forms. The POSA would also have access to individuals with expertise in medicine, biochemistry, and pharmacology as part of their drug development and formulation team and would consult with them as appropriate. The POSA's level of experience may come from the POSA's own experience, or may come through the guidance of other individual(s) with experience in the industry, e.g., as members of a research

team or group. The POSA would also be well-versed in the worldwide publications and literature on steroidal hormone formulations and treatments, particularly fulvestrant, that were available as of the priority date.

V. U.S. PATENT NO. 8,329,680 ("THE '680 PATENT") [Ex. 1001]

25. I have read the '680 patent, entitled "Formulation," and its issued claims. The '680 patent was filed on October 15, 2008, and claimed priority to U.S. Patent Application No. 10/872,784 (now the '160 patent) and two foreign applications, [Great Britain 0000313], dated January 10, 2000, and [Great Britain 0008837], dated April 12, 2000. *See* '680 Patent File History [Ex. 1002]. The '680 patent issued December 11, 2012, and named John R. Evans and Rosalind U. Grundy as the sole inventors. AstraZeneca AB was listed as the assignee of the '680 patent.

26. The following table organizes each element by claim:

Table #1. Correlation of Fulvestrant Claim Elements	
Fulvestrant Component	**As Claimed in '680 Patent**
Indications for Fulvestrant	**Claims #1, #9**: hormonal dependent benign or malignant diseases of the human breast or reproductive tract **Claims #3, #6, #11, #14:** breast cancer
Route of Administration	**Claims #1, #4, #7, #9, #12, #15:** i.m. injection
Frequency of Administration	**Claims #5, #8, #13, #16:** once monthly
Volume Formulated Fulvestrant Administered	**Claims #4, #7, #12, #15**: 5 ml
Fulvestrant Dose	**Claims #17–#20:** divided dose
Fulvestrant Concentration	**Claims #1, #9**: about 50 mg/ml

Final Formulation of Fulvestrant	**Claims #1:** "comprising" about 50 $mgml^{-1}$ of fulvestrant about 10% w/v ethanol about 10% w/v benzyl alcohol about 15% benzyl benzoate sufficient amount of a castor oil vehicle
	Claim #9: "consisting essentially of" about 50 $mgml^{-1}$ of fulvestrant about 10% w/v ethanol about 10% w/v benzyl alcohol about 15% benzyl benzoate
Blood Plasma Fulvestrant Concentration Levels and Their Durations	**Claims #1, #9:** at least 2.5 ng/ml for at least 4 weeks
	Claim #2, #10: at least 8.5 ng/ml for at least 4 weeks

27. I understand that Mylan is challenging all claims of the '680 patent, namely claims 1–20. The '680 patent includes 2 independent claims: claims 1 and 9. I also understand that the claim terms in the '680 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable construction in light of the specification of the patent in which they appear.

28. Independent claim 1 recites: "A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation comprising: about 50 $mgml^{-1}$ of fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle; wherein the method achieves a

therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks."

29. Independent claim 9 recites: "A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation consisting essentially of: about 50 $mgml^{-1}$ of fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks."

30. Independent claims 1 and 9 recite the term "a hormonal dependent benign or malignant disease of the breast or reproductive tract." As of January 10, 2000, a POSA would have interpreted the term to include, at minimum, estrogen receptor-positive (ER+ or ER-positive) female breast cancer.

31. Comparing independent claims 1 and 9, the only differences are claim 9's inclusion of "consisting essentially of" and claim 9's omission of "a sufficient amount of castor oil vehicle."

32. Dependent claims 2–8 and 18–19, which directly or indirectly depend from independent claim 1, and dependent claims 12–20, which depend directly or indirectly from independent claim 9, recite a specific type of disease; level and

duration of blood plasma fulvestrant concentration over time; and route, volume, method or frequency of administration.

VI. CLAIM CONSTRUCTION

33. Independent claims 1 and 9 of the '680 patent recite the term "hormonal dependent benign or malignant disease of the breast or reproductive tract . . . [in] a human" in their preamble, and dependent claims 3, 6, 11, and 14 specify that "the benign or malignant disease is breast cancer." Under the broadest reasonable construction to a POSA as of the priority date, this term includes at least hormonal-dependent malignant breast cancer in women.

34. Independent claims 1 and 9 of the '680 patent recite: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Dependent claims 2 and 10 recite that the method achieves a concentration of at least 8.5 $ngml^{-1}$ for at least 4 weeks.

35. As stated previously in paragraph 18, I have been informed that "wherein" clauses that simply express the intended result of a process step, without informing how the method is carried out, are generally not given patentable weight. However, to the extent that such phrases are given patentable weight:

(a) Under the broadest reasonable construction to a POSA as of the priority date, "therapeutically significant" is any blood plasma

fulvestrant concentration greater than or equal to the value specified in the patent (e.g., 2.5 $ngml^{-1}$).

(b) Under the broadest reasonable construction to a POSA as of the priority date, "achieved" means "achieved an average concentration in a patient over the specified time period."

VII. BACKGROUND OF BREAST CANCER AND TREATMENTS

A. Hormone Receptor Positive (HR+) Breast Cancer in Human Females

36. In women, many breast cancer cells are hormone-dependent (or hormone-sensitive), meaning that they can use certain hormones to grow. The breast cancer cells contain proteins known as hormone receptors that can become activated when bound to certain hormones. Once activated, they can lead to the stimulation of cell growth—i.e., cancer.

37. Hormonal-dependent breast cancer in women was known to correlate with three hormone receptors: estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2). Identification of the type of hormone receptors involved in the breast cancer allowed for improved knowledge about how the tumor might act and what treatments were likely to be most effective.

38. Each of these hormone receptors could be "positive" or "negative." Meaning, the breast cancer could be identified as estrogen receptor-positive (ER+) or estrogen receptor-negative (ER-); progesterone receptor-positive (PR+) or

progesterone receptor-negative (PR-); and/or human epidermal growth factor receptor 2-positive (HER2+) or human epidermal growth factor receptor 2-negative (HER2-). ER+ breast cancer is thus a type of hormone receptor-positive or "HR+" breast cancer. HR+ breast cancer *is* hormonal dependent breast cancer.

39. HR+ breast cancer is the most common subtype of invasive breast cancers, and is especially prevalent among post-menopausal women. HR+ breast cancers in women are typically treated with hormone (or endocrine) therapy, which is intended to block the patient's body from producing hormones or otherwise interfering with hormone action, thereby blocking or minimizing hormone receptor cell activation and slowing or stopping tumor growth.

40. Hormone therapies for female HR+ breast cancers may be prescribed as either an adjuvant therapy or in patients with early metastatic disease. In the adjuvant setting, the hormone treatment is given after the main treatment (generally surgery) to reduce the risk of relapse. Adjuvant therapy is a long-term therapy, typically spanning multiple years. In patients with early metastatic disease, the hormone treatment is given to minimize and hopefully prevent further spreading of the disease in the body.

B. Treatment Options for HR+ Breast Cancer in Women Prior to 2000

41. Prior to 2000, several hormone therapies were approved to treat HR+ breast cancer in women. These therapies included selective estrogen receptor

modulators (SERMs), ovarian suppression utilizing gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors (AIs).

42. SERMs bind to estrogen receptors in breast cells, preventing their ability to bind to estrogen and correspondingly proliferate. Notably, however, cells in other body tissues—particularly the bones and uterus—have estrogen receptors with slightly different structures. As the name implies, SERMs were known to have "selective" (or "partial agonist") estrogen activity: they block estrogen binding in breast cells but can activate estrogen receptors in other cells, such as the uterus, and hence increase the risk of uterine cancers. Tamoxifen was the oldest, most well-known, and most-prescribed SERM. *See, e.g.*, Ex. 1018 (Osborne 1995) at 1; Ex. 1033 (BREASTCANCER.ORG, "Selective Estrogen Receptor Modulators (SERMs)," http://www.breastcancer.org/treatment/hormonal/serms).

43. GnRH-agonists downregulate pituitary GnRH receptors, which suppress hormones that stimulate estrogen-production in the ovaries. GnRH agonists can therefore act as a pharmacological alternative to surgical removal of the ovaries (oophorectomy), and are often used in treating pre-menopausal women with breast cancer.

44. AIs block the peripheral production of estrogen via blocking the enzyme aromatase, which converts the hormone androgen into the hormone

estrogen. AIs cannot stop the ovaries from producing estrogen, however, and so are rarely used to treat pre-menopausal women.

45. Prior to 2000, pre-menopausal women with HR+ breast cancer who had intact estrogen-producing ovarian function were conventionally treated with (1) selective estrogen receptor modulators (SERMs), such as tamoxifen; (2) ovarian suppression using GnRH-agonists or ovarian ablation by oophorectomy or irradiation; or (3) combination treatment of (1) and (2).

46. Prior to 2000, post-menopausal women with HR+ breast cancer were typically prescribed a SERM such as tamoxifen, or an AI.

47. Prior to 2000, then, tamoxifen was prescribed for both pre-menopausal and post-menopausal women with HR+ breast cancer. As stated above, tamoxifen was the oldest, most well-known, and most-prescribed SERM. Tamoxifen was prescribed for both adjuvant and metastatic therapies.

48. Although many women with HR+ breast cancer benefited from tamoxifen (in both adjuvant and metastatic settings), tamoxifen was found to be associated with an increased incidence of uterine cancer, which was linked to the drug's partial ER+ agonist activity. *See, e.g.*, Ex. 1013 (O'Regan 1998) at 1.

49. Accordingly, there was a motivation to develop novel endocrine therapies that worked as pure estrogen antagonists and avoided tamoxifen's association with an increased incidence of uterine cancer.

VIII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. McLeskey 1998 [Ex. 1005]

50. McLeskey, titled "Tamoxifen-Resistant Fibroblast Growth Factor-Transfected MCF-7 Cells are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors," was published in CLINICAL CANCER RESEARCH in March 1998. McLeskey was published more than one year before the earliest priority date of the '680 patent. McLeskey was not considered by the Examiner during the prosecution of the '680 patent until Applicants disclosed McLeskey to the Examiner almost three years after the application was filed. After McLeskey was disclosed to the Examiner, the Examiner cited McLeskey in a final rejection, stating that McLeskey disclosed a fulvestrant formulation containing 50 mg/ml fulvestrant in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, broght to volume with castor oil. Ex. 1002 at 313–15 [5–7 of 9/16/11 OA].

51. McLeskey was a murine (i.e., mouse) study looking into potential new treatments for ER+ breast cancers resistant to the partial antiestrogen, tamoxifen. Ex. 1005 (McLeskey) at 1. It was designed to determine if ER signaling remained intact in tamoxifen-resistant tumors. Using fibroblastic growth factor (FGF)-transfected breast cancer cell lines that were rendered resistant to tamoxifen, McLeskey found that estrogen independence was achieved via activation of

alternate oncogenic pathways unrelated to estrogen signaling. McLeskey used the antiestrogen fulvestrant.

52. McLeskey disclosed the exact formulation of fulvestrant claimed in the patents: fulvestrant formulated "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." *Id.* at 2. McLeskey also disclosed that the fulvestrant was formulated to a 50 mg/ml concentration. *Id.*

53. McLeskey disclosed that the above formulation "was supplied by B.M. Vose (Zeneca Pharmaceuticals)," *id.*; Zeneca Pharmaceuticals later became Patent Owner AstraZeneca.

54. McLeskey administered the above formulation of fulvestrant to mice at a dose of 5 mg, delivered subcutaneously every week. *Id.* at 2, 5.

B. Howell 1996 [Ex. 1006]

55. Howell 1996, titled "Pharmacokinetics, Pharmacological and Anti-Tumour Effects of the Specific Anti-Oestrogen ICI 182780 in Women with Advanced Breast Cancer," was published in BRITISH JOURNAL OF CANCER in July 1996. Howell 1996 was published more than one year before the earliest priority date of the '680 patent. The Examiner never relied upon Howell 1996 in any rejection of the claims. *See* Ex. 1002 at 271.

56. Howell 1996 was a study of 19 post-menopausal human females with advanced breast cancer resistant to tamoxifen, meaning HR-positive breast cancer. The stated purpose of Howell 1996 was to "assess the long-term efficacy and toxicity of the specific anti-oestrogen ICI 182780 [*i.e.*, fulvestrant] in patients with advanced breast cancer and to evaluate the pharmacokinetics of the long-acting formulation used." Ex. 1006 (Howell 1996) at 1. Howell 1996 recognized itself as "the first investigation of long-term administration of [fulvestrant] to patients with breast cancer." *Id.* at 6.

57. "[Fulvestrant] was administered as a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock." *Id.* at 2. Patients were administered 250 mg per month; a small cohort of patients were given 250 mg per month after initial "confirmation of lack of local or systemic drug toxicity at the 100 mg dose." *Id.* Patients were monitored for six months. *Id.* at 2–4.

58. The study found that the slow-release fulvestrant formulation provided continuous release of fulvestrant "throughout the one month dosing interval." *Id.* at 3. Measured mean end-of-month serum fulvestrant concentrations ranged from 3.1 $ngml^{-1}$ to 5.6 $ngml^{-1}$, *id.*, although the study recognized that "[t]hese data suggest that lower doses of the drug may be effective in maintaining therapeutic serum drug levels." *Id.* at 6. Data reveal that mean serum blood

concentrations levels at entry ranged from approximately 5.5 to 11.1 $ngml^{-1}$; during the first and sixth months of treatment, mean serum blood concentrations levels ranged from approximately 2.75 to 8.25 $ngml^{-1}$. *Id.* at 4 Fig. 2. No mean serum blood concentrations levels fell below approximately 2.75 $ngml^{-1}$ during the 28 day periods for which data was disclosed. *Id.* Howell 1996 also reports a mean C_{max} of 10.5 $ngml^{-1}$ in patients first-dosed with 250 mg fulvestrant, and a mean C_{max} of 12.8 $ngml^{-1}$ in patients having received six once-monthly 250 mg doses of fulvestrant. *Id.* at 3.

59. The study "demonstrates that predicted therapeutic levels of [fulvestrant], as judged from animal experiments and our previous short Phase I study, can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used." *Id.* at 6 (internal references omitted).

60. The study also confirmed the reliability of previous monkey studies, noting that the pharmacokinetic data in the post-menopausal human females were "similar to those previously demonstrated in adult female monkeys." *Id.* at 6. Howell 1996 specifically predicted that blood plasma fulvestrant concentration levels of 2–3 ng/ml "were consistent with a therapeutic effect in patients with advanced breast cancer." *Id.*

61. Howell 1996 recognized that fulvestrant was "well tolerated during long-term treatment and is active as an anti-tumour agent in patients with advanced breast cancer who have previously relapsed on tamoxifen." *Id.* at 7. Howell 1996 recognized that fulvestrant was devoid of agonist activity, unlike tamoxifen, and that "this new agent may improve the rate and duration of response in patients with advanced breast cancer" and called for further studies into fulvestrant's potential use in treating human females with advanced breast cancer. *Id.*

C. Dukes 1989 [Ex. 1007]

62. The European patent EP 0 346 014 ("Dukes 1989"), granted to Dukes, teaches formulation of fulvestrant (7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17 β-diol) in a castor oil and benzyl alcohol vehicle. Ex. 1007 at 7.

63. The Examiner cited Dukes 1989 in a non-final rejection, stating that Dukes taught that anti-estrogens like fulvestrant were used to treat post-menopausal symptoms and that fulvestrant could be formulated with castor oil and benzyl alcohol in a dosage of 50mg–5g. Ex. 1002 at 252 [2–5 of 12/21/10 OA]. The Examiner also cited Dukes 1989 in a final rejection after the Applicants disclosed McLeskey (Ex. 1005) to the Examiner, again stating that Dukes taught that anti-estrogens like fulvestrant were useful in treating post-menopausal symptoms, that fulvestrant can be formulated in castor oil and benzyl alcohol in a

dosage of 50mg–5 g, and that fulvestrant can be administered intramuscularly. *Id.* at 313–15 [5–7 of 9/16/11 OA].

D. Wakeling 1991 [Ex. 1008]

64. Wakeling 1991, titled "A Potent Specific Pure Antiestrogen with Clinical Potential," was published in CANCER RESEARCH in August 1991 by authors Alan E. Wakeling, Michael Dukes, and Jean Bowler. Wakeling 1991 was published more than one year before the earliest priority date of the '680 patent. Wakeling 1991 was initialed as considered by the Examiner during the prosecution of the '680 patent, but the Examiner never relied upon Wakeling 1991 in any rejection of the claims. *See* Ex. 1002 at 272.

65. Wakeling 1991 studied the effects of fulvestrant in female rats and monkeys, and in MCF-7 breast cancer cells inoculated into the flank of adult female mice. Ex. 1008 at 2. Wakeling 1991 disclosed different types of fulvestrant administration, including a once-per-4-week subcutaneous administration of 5 mg in nude mice. *Id.* at 5; *see generally* 2–5. Wakeling 1991 describes fulvestrant as being a pure anti-estrogen and having "demonstrated excellent growth-inhibitory effects in both cell and animal models of human breast cancer." *Id.* at 1.

66. Wakeling 1991 also recognized "the precedent that many steroids administered parenterally in oil have a sustained duration of action," and so "a

single s.c. [i.e., subcutaneous] bolus dose in oil suspension was tested in adult ovariectomized rats." *Id.* at 3. Wakeling 1991 recognized that "[t]he utility of this approach [i.e., parenteral depot formulations with an extended duration of action]" was demonstrated in ovariectomized, estrogen-treated rats and monkeys, and that "[t]he potential efficacy of 'oil depot' formulations of [fulvestrant] was demonstrated in nude mouse antitumor studies." *Id.* at 6.

67. Wakeling 1991 endorsed fulvestrant as "a prime candidate with which to explore the therapeutic potential of pure antiestrogens in the treatment of breast cancer." *Id.* at 1. It further recognized that fulvestrant "offers significant advantages compared with pure antiestrogens reported previously, particularly with respect to *in vivo* potency," *id.* at 6, and "may find a valuable place in the treatment of breast cancer." *Id.* at 7.

E. Wakeling 1992 [Ex. 1009]

68. Wakeling 1992, titled "ICI 182,780, A New Antioestrogen with Clinical Potential," was published in JOURNAL OF STEROID BIOCHEMISTRY & MOLECULAR BIOLOGY in September 1992 by authors Alan E. Wakeling and Jean Bowler. Wakeling 1992 was published more than one year before the earliest priority date of the '680 patent. The abstract (but not the full article) of Wakeling 1992 was cited by the Examiner in a final rejection during the prosecution of the '680 patent. The Examiner stated that the Wakeling 1992 abstract taught the

administration of fulvestrant demonstrating an antiestrogenic effect for over a one-month period. Ex. 1002 at 313–15 [5–7 of 9/16/11 OA].

69. Fulvestrant was studied in adult female rats, ovariectomized female adult mice, ovariectomized female immature rats, and ER+ MCF-7 human breast cancer cells treated in medium. Ex. 1009 at 2–3. Fulvestrant showed no uterotrophic activity, and it inhibited the growth of ER+ MCF-7 human breast cancer cells in medium. *Id.*

70. Wakeling 1992 recognized fulvestrant was known to have poor oral bioavailability, and therefore a "well-established procedure to mitigate such [rapid metabolism] effects is to administer steroids parenterally in oil," which often permits a "sustained duration of action." *Id.* at 2. This was described as "[a] common means of circumventing the practical constraints consequent on the poor oral bioavailability of steroids." *Id.* at 4. Wakeling 1992 recognized that this depot approach—administering a bolus dose of fulvestrant in arachis oil—had been effective and had sustained anti-estrogenic activity "for in excess of 1 month in both rats and monkeys" *Id.* (citing Wakeling 1991); *see also id.* at 4.

71. Wakeling 1992 recognized that fulvestrant showed enhanced efficacy on breast tumor cells in comparison to tamoxifen, with "excellent antiuterotrophic action." *Id.* Wakeling 1992 recognized that fulvestrant and other pure

antiestrogens "may find a valuable place in the treatment of breast cancer," and that fulvestrant "will be used to test this proposition." *Id.*

F. Dukes 1992 [Ex. 1025]

72. Dukes 1992, titled "Antiuterotrophic Effects of a Pure Antioestrogen, ICI 182,780: Magnetic Resonance Imaging of the Uterus in Ovariectomized Monkeys," was published in JOURNAL OF ENDOCRINOLOGY in November 1992 by authors Michael Dukes, D. Miller, Alan E. Wakeling, and J.C. Wateron. Dukes 1992 was published more than one year before the earliest priority date of the '680 patent. Dukes 1992 was initialed as considered by the Examiner during the prosecution of the '680 patent, but the Examiner never relied upon Dukes 1992 in any rejection of the claims. *See* Ex. 1002 at 271.

73. Dukes 1992 treated adult female ovariectomized monkeys with fulvestrant suspended in arachis oil, administered for 10 days at 1 mg per day. Ex. 1025 at 1, 3. The treatment completely blocked uterotrophic action of estradiol for 3–4 weeks, which researchers characterized as "confirm[ing]" fulvestrant's "sustained antiuterotrophic action." *Id* at 3.

74. Dukes 1992 also investigated a long-acting formulation of fulvestrant, formulated in solution in a castor oil-based vehicle, delivered intramuscularly to adult ovariectomized female monkeys. *Id.* Results "confirmed" that "the duration of action of a single i.m. injection of [fulvestrant] was dose-related." *Id.*

75. Additionally, Dukes 1992 investigated the long-acting fulvestrant formulation in adult ovariectomized female monkeys, given three i.m. injections of 4 mg/kg at 28-day (i.e., approximately monthly) intervals. *Id.*

76. Dukes 1992 characterized fulvestrant as "a fully effective pure antioestrogen in the primate." *Id.* at 9.

G. Wakeling 1993 [Ex. 1028]

77. Wakeling 1993, titled "The Future of New Pure Antiestrogens in Clinical Breast Cancer," published in BREAST CANCER RESEARCH & TREATMENT in January 1993 by Alan E. Wakeling, reflects a plenary lecture given at the 15th San Antonio Breast Cancer Symposium. Wakeling 1993 was published more than one year before the earliest priority date of the '680 patent. Wakeling 1993 was not considered by the Examiner during the prosecution of the '680 patent.

78. Wakeling 1993 identifies two pure antiestrogens: ICI 164,384 and ICI 182,780 (fulvestrant).

79. Wakeling 1993 recognizes the "rationale of seeking to identify new pure antiestrogens was based on the recognition that existing antiestrogens, exemplified by tamoxifen, all possess partial agonist (estrogenic) activity." Ex. 1028 at 4; *see also id.* at 5. Fulvestrant, a pure antiestrogen, was recognized as potentially being important in the "therapeutic application in the treatment of breast cancer." *Id.* at 4. Wakeling 1993 recognized that "experimental data . . .

predict[s] efficacy in patients whose disease recurs during tamoxifen treatment," and that clinical trials with fulvestrant would confirm whether fulvestrant could be more efficacious than tamoxifen in first-line treatment of advanced breast cancer. *Id.* at 4; *see also id.* at 5. In particular, Wakeling 1993 notes that fulvestrant peripheral selection of action could have "highly beneficial effects in premenopausal patients," and that fulvestrant seemed to lack tamoxifen's problematic uterotrophic action. *Id.* at 5.

80. Wakeling 1993 recognized that fulvestrant's low oral bioavailability required alternative administration, and recognized the "potential therapeutic utility of such oil-depot formulations" of fulvestrant, as demonstrated previously by Wakeling 1991, *id.* at 10, and that the "[t]he likely dose and frequency of treatment in [human] breast cancer patients" had been assessed using monkeys. *Id.* Wakeling 1993 recognized that "therapeutic studies with the oil depot formulation of [fulvestrant] in patients" were soon intended. *Id.*

81. Wakeling 1993 noted that "[f]unctional disablement of the ER signaling capacity by pure antiestrogens produces effects on human breast cancer cells which have *profound therapeutic implications*." *Id.* at 4–5 (emphasis added). Wakeling 1993 recognized that if fulvestrant's apparent pure anti-estrogenic activity "translates to the clinical setting, one might anticipate significant benefits in the rate and extent of tumor remission following pure antiestrogen therapy

compared with other 'antiestrogenic' therapies. . . . Thus, there is a powerful rationale which argues the superiority of pure antagonists [including fulvestrant] over other treatments." *Id.* at 5.

82. Wakeling 1993 presented several studies, arguing that the presented experimental data "may have important clinical applications" and that there was a "sound rationale" for treating patients who relapse during adjuvant tamoxifen therapy with pure antiestrogens, e.g., fulvestrant. *Id.* at 10. Ultimately, "[m]odel studies with human breast cancer cells *in vitro* and *in vivo* predict that [fulvestrant and ICI 164,384] have the potential to be more effective therapeutically than currently available treatments for breast cancer." *Id.* at 11.

H. Dukes 1993 [Ex. 1026]

83. Dukes 1993, titled "Antiuterotrophic Effects of the Pure Antioestrogen ICI 182,780 in Adult Female Monkeys (*Macaca nemstrina*): Quantitative Magnetic Resonance Imaging," was published in JOURNAL OF ENDOCRINOLOGY in August 1993 and authored by Michael Dukes, J.C. Waterton, and Alan E. Wakeling. Dukes 1993 was published more than one year before the earliest priority date of the '680 patent. Dukes 1993 was initialed as considered by the Examiner during the prosecution of the '680 patent, but the Examiner never relied upon Dukes 1993 in any rejection of the claims. *See* Ex. 1002 at 271.

84. Dukes 1993 describes the results of a study of fulvestrant on mature, intact (uterus-having) female pigtail monkeys with regular menstrual cycles, with the goal of determining fulvestrant's anti-uterotrophic activity in premenopausal human females. Ex. 1026 at 1.

85. The monkeys were administered a "long-acting castor oil-based solution [of fulvestrant] given as a single i.m. injection" of 2.5 or 4 mg/kg, or alternatively a daily dosing regimen of fulvestrant formulated in a propylene glycol vehicle to provide rapid release *in vivo*. *Id.* at 2, 6. The volumes of the monkey endometrium and myometrium were studied via quantitative MRI. *Id.* at 2.

86. Dukes 1993 found that both 2.5 mg/kg and 4.0 mg/kg fulvestrant doses showed anti-uterotrophic effects, but that only the 4.0mg/kg dose "fully block[ed] the trophic action of endogenous oestrogens on the endometrium in the second half of the cycle." *Id.* at 7.

87. Dukes 1993 confirmed the findings of Dukes 1992, which had demonstrated that fulvestrant would "sustain blockade of the uterotrophic action of oestradiol in ovariectomized monkeys for approximately 1 month." *Id.* Dukes 1993 determined the Dukes 1992 findings to be "entirely consistent with the findings of the present study with respect to the duration of action, the apparent dose-response, and the longer sustained blockade of myometrial than endometrial growth." *Id.*

I. DeFriend 1994 [Ex. 1027]

88. DeFriend 1994, titled "Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer," was published in CANCER RESEARCH in January 1994 by authors including David J. DeFriend, Anthony Howell, John F. Robertson, and Alan E. Wakeling. DeFriend 1994 was published more than one year before the earliest priority date of the '680 patent. DeFriend 1994 was not considered by the Examiner during the prosecution of the '680 patent.

89. DeFriend 1994 was a clinical study "to assess [fulvestrant's] tolerance, pharmacokinetics, and short term biological effects in women with primary breast cancer." Ex. 1027 at 1. DeFriend 1994 characterized itself as "the first investigation of short term administration of ICI 182780 to women with primary breast cancer," *id.* at 5, and recognized that fulvestrant was "the first therapeutic agent to be investigated in clinical trials with the potential to completely deprive breast tumors of estrogenic stimulation." *Id.* at 6.

90. DeFriend 1994 treated 56 post-menopausal women with primary breast cancer in a study spanning October 1991 through November 1992. Patients were administered i.m. injections into the buttock of a short-acting 20mg/ml fulvestrant formulation in a propylene glycol-based vehicle, with patients receiving 6 mg or 18 mg doses for 7 days prior to primary breast surgery. *Id.* at 1–3.

91. DeFriend 1994 found that the short-acting fulvestrant formulation was well-tolerated and that adverse events were "mostly considered" unrelated to fulvestrant. *Id.* at 3, 5, 6. The study found that blood serum fulvestrant concentration was "dose dependent." *Id.* at 3. DeFriend 1994 disclosed that fulvestrant showed no agonist activity of serum gonadotropin levels at the pituitary, in contrast to tamoxifen, which reduces LH (luteinizing hormone) and FSH (follicle-stimulating hormone) levels in post-menopausal women due to its agonist activity on the pituitary, and demonstrated no agonist or antagonist activity in the liver, again in contrast to the estrogen-like action of tamoxifen. *Id.* at 5.

92. DeFriend 1994 also recognized that fulvestrant "produced a significant decline in the expression of ER and PgR [i.e., progesterone receptor] in primary breast cancers." *Id.*

93. DeFriend 1994 recognized that future studies "are planned with a different, long-acting, formulation of [fulvestrant] contained in a castor-oil vehicle," *id.*, and that "Phase II trials with a long-acting formulation of [fulvestrant] are now in progress." *Id.* at 6.

J. Osborne 1995 [Ex. 1018]

94. Osborne 1995, titled "Comparison of the Effects of a Pure Steroidal antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer," was published in JOURNAL OF THE NATIONAL CANCER INSTITUTE in May 1995 by

authors including C. Kent Osborne and Alan E. Wakeling. Osborne 1995 was published more than one year before the earliest priority date of the '680 patent. The Examiner cited Osborne 1995 in two rejections, stating that Osborne taught that fulvestrant was useful in treating human breast cancer. Ex. 1002 at 252, 313.

95. Osborne 1995 compared the inhibitory tumor-effects of fulvestrant, tamoxifen, and estrogen withdrawal on the growth of established tumors and on tumorigenesis, using ER+, human, MCF-7 breast tumor cells grown in female athymic (i.e., thymus-removed) nude mice. Ex. 1018 at 1–2. For the established tumor studies, the mice were administered fulvestrant formulated in castor oil, administered subcutaneously once a week; for the tumorigenesis studies, mice were administered 5 mg of fulvestrant once a week. *Id.* at 2.

96. Osborne 1995 demonstrated that fulvestrant inhibited estrogen-dependent growth of MCF-7 tumors "in a dose dependent manner." *Id.* It found that fulvestrant suppressed tumor growth for a "significantly longer duration" than tamoxifen or estrogen withdrawal, as well as "significantly delayed" tumorigenesis. *Id.* at 2, 4.

97. Osborne 1995 recognized that fulvestrant was unlikely to increase a patient's risk of endometrial cancer, as with tamoxifen, and that "[f]urther clinical study . . . is clearly indicated." *Id.* at 5.

K. Howell 1995 [Ex. 1012]

98. Howell 1995, titled "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer," was published in THE LANCET in January 1995 by authors Anthony Howell, David DeFriend, John Robertson, Roger Blarney, and Peter Walton. Howell 1995 was published more than one year before the earliest priority date of the '680 patent. Howell 1995 was initialed as considered by the Examiner during the prosecution of the '680 patent, but the Examiner never relied upon Howell 1995 in any rejection of the claims. *See* Ex. 1002 at 271.

99. Howell 1995 was a study of 19 post-menopausal patients with advanced, tamoxifen-resistant breast cancer. Ex. 1012 at 1.

100. The patients were administered 5 mL of "a long-acting [fulvestrant] formulation in a castor oil-based vehicle by monthly intramuscular injection into a buttock." *Id.* at 1–2. To appraise fulvestrant's safety, four patients received only 100 mg for the first month, with 250 mg doses thereafter; the remaining 15 patients received 250 mg every month from the outset. *Id.* at 1.

101. Howell 1995 found no serious drug-related events and that the long-acting fulvestrant formulation was well-tolerated at the site of injection, "despite the relatively large 5 mL volume administered." *Id.*at 2.

102. Howell 1995 recognized that, in primates and in short-term studies in women, fulvestrant inhibited endometrial proliferation at a similar serum concentration as in Howell 1995, and that "[i]f a similar inhibitory effect of [fulvestrant] were shown in longer-term studies, this would be a further therapeutic advantage of the specific antioestrogen, since tamoxifen is known to be associated with proliferation and endometrial cancer." *Id.*

103. Howell 1995 "suggest[ed] that [fulvestrant] may improve rate and duration of response when used as a first-line treatment for advanced breast cancer, since it has no demonstrable agonist activity," and "the lack of toxicity or effect on serum lipids" made fulvestrant a candidate for adjuvant therapy in humans. *Id.*

L. O'Regan 1998 [Ex. 1013]

104. O'Regan 1998, titled "Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182780 on Endometrial Cancer Growth," was published in JOURNAL OF THE NATIONAL CANCER INSTITUTE, in October 1998 by primary author Ruth M. O'Regan. O'Regan 1998 was published more than one year before the earliest priority date of the '680 patent. O'Regan 1998 was not considered by the Examiner during the prosecution of the '680 patent.

105. Knowing that tamoxifen caused a twofold to threefold increase in the incidence of endometrial cancer, O'Regan 1998 was designed to study the growth of human endometrial cancer with fulvestrant treatment. Ex. 1013 at 1, 5.

106. Athymic and ovariectomized mice, implanted with human endometrial tumors, were treated with fulvestrant, tamoxifen, or estrogen. *Id.* at 1.

107. The fulvestrant compound was "dissolved in ethanol" and administered in a peanut oil vehicle "to a final concentration of 50 mg/mL," and "injected subcutaneously at a dose of 5 mg (0.1 mL peanut oil) per animal per week." *Id.* at 2.

108. O'Regan 1998 recognized that "[c]linically," meaning in humans, fulvestrant "must be given by depot intramuscular injection because of low oral potency." *Id.*

109. O'Regan 1998 found that fulvestrant inhibited endometrial cancer, both in the presence and absence of estrogen, which suggested that fulvestrant would "prevent further tumor growth in patients with tamoxifen-stimulated endometrial cancer." *Id.* at 5–6. O'Regan 1998 recognized that prior studies had demonstrated no estrogen actions of fulvestrant on the rodent or primate uterus, and "[t]here is every indication that [fulvestrant] will control growth of both breast cancer and endometrial cancer in patients." *Id.* at 6.

IX. FULVESTRANT WAS A WELL UNDERSTOOD COMPOUND BY JANUARY 10, 2000

A. Fulvestrant Was Well Known in the Prior Art.

110. By 1987—prior to the patent's priority date of January 10, 2000—fulvestrant was a known pharmaceutical compound. Exs. 1029; 1007 (Dukes 1989

EP patent application, proposed claims 2, 4). For example, fulvestrant was one of a number of steroidal antiestrogens claimed in a patent assigned to Imperial Chemical Industries (predecessor to AstraZeneca) that issued in 1987. Ex. 1029 at 2, 21 (claim 8). Further, a European patent application published on December 13, 1989, which listed Michael Dukes (of Imperial Chemical Industries) as the inventor, proposed claims for "7α-[9-(4,4,5,5,5-pentafluropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol." Ex. 1007, proposed claims 2, 4. This is the chemical name for fulvestrant. Moreover, the patent application described fulvestrant as a "pure antioestrogen." *Id.*

B. Fulvestrant's Pharmacological Usefulness Was Well Known in the Prior Art.

111. By the early 1990s, researchers were aware of the drawbacks to partial estrogen antagonists like tamoxifen, wanting "antagonist molecules which bind to oestrogen receptors (ER) with high affinity," which would be "distinctly different from tamoxifen-like ligands" and "would offer the chance of achieving complete blockade of oestrogen action." Ex. 1009 (Wakeling 1992) at 1. Researchers recognized that a pure anti-estrogen, unlike tamoxifen, could provide "*complete* ablation of the estrogen-mediated tumor growth," which was "a desirable objective since it might be anticipated to provide more rapid, more complete, or longer-lasting tumor responses." Ex. 1028 (Wakeling 1993) at 5. Put simply, researchers

were aware that a pure anti-estrogen might provide anti-tumor activity superior to tamoxifen in certain human females with breast cancer.

112. Around the same time, fulvestrant—a steroidal, pure anti-estrogen—was already being recognized as a "prime candidate" for research in ER+ female breast cancer. Ex. 1008 (Wakeling 1991) at 1; 1009 (Wakeling 1992) at 1.

113. And, by 1995, human females with breast cancer were already being treated with fulvestrant in a clinical research setting. Ex. 1012 (Howell 1995) at 1; 1006 (Howell 1996) at 2; 1027 (DeFriend 1994) at 1.

C. Fulvestrant's Pre-Clinical Anti-Tumor and Anti-Uterotrophic Effects Were Well Known in the Prior Art.

114. Early pre-clinical studies published in the 1990s demonstrated that fulvestrant's pure ER antagonist activity, together with its lack of significant uterotrophic (uterine and endometrial growth) effects, rendered it a "prime candidate" for further development in patients with ER+ breast cancer. Ex. 1008 (Wakeling 1991) at 1; 1009 (Wakeling 1992) at 1; *see also* 1028 (Wakeling 1993) at 7.

115. Fulvestrant was demonstrated to be an estrogen receptor downregulator (ERD). Unlike partial anti-estrogens like tamoxifen, fulvestrant is a "pure" ER antagonist: it was known to block binding in estrogen receptors, without having the partial estrogen agonist activity (particularly in uterine and bone tissue)

of SERMs such as tamoxifen. For example, fulvestrant's binding affinity for the ER was significantly superior to tamoxifen. *See* Ex. 1008 (Wakeling 1991) at 1–2.

116. In the early development of an anti-estrogen, an immediate concern is possible trophic effects on normal uterine tissues—which, in the case of tamoxifen, was associated with an increased risk of endometrial cancer. To this end, early studies were focused on assessing potential uterotrophic effects of fulvestrant in murine and primate models. After investigation, fulvestrant was found to have significant anti-uterotrophic activity.

117. In a study published in 1991, researchers studied the effects of fulvestrant on ovariectomized rats and monkeys as well as on ER+ "MCF-7" cells (a particular ER+ breast cancer cell line) transplanted into adult female nude mice. *See generally* Ex. 1008 (Wakeling 1991). The study recognized two ways fulvestrant showed therapeutic relevance: fulvestrant's enhanced efficacy compared to tamoxifen on breast tumor cells and fulvestrant's "excellent antiuterotrophic action" achieved without altering body weight or sex hormone secretion. Ex. 1008 (Wakeling 1991) at 6; *see also* Ex. 1009 (Wakeling 1992) at 4. In short, Wakeling 1991 found that fulvestrant had no estrogenic uterotrophic action in the rodent model.

118. In the Dukes 1992 and 1993 studies, fulvestrant was confirmed to be "a fully effective pure antioestrogen in the primate." Also encouraging, fulvestrant

was confirmed to have no uterine stimulating activity—which was not the case with tamoxifen. Ex. 1025 (Dukes 1992) at 1, 9; 1026 (Dukes 1993) at 1, 6–7. In the 1992 study, a fulvestrant formulation demonstrated a 3–6 week sustained blockade of hormone-induced proliferation of the uterine endometrium and myometrium in female ovariectomized primates (a "post-menopausal" primate model). *See generally* Ex. 1025 (Dukes 1992) and at 1. The subsequent 1993 study also found that treatment with fulvestrant prevented the growth of the uterine endometrium and myometrium, this time in a "pre-menopausal" intact female primate model. *See generally* Ex. 1026 (Dukes 1993) and at 1. In both Dukes 1992 and Dukes 1993, then, fulvestrant was found to have substantial anti-uterotrophic effects in both ovariectomized and intact female primates. Ex. 1025 (Dukes 1992); 1026 (Dukes 1993).

119. As a pure estrogen antagonist, fulvestrant induced anti-uterotrophic effects, and without the "castration-like" increases in certain plasma hormonal (gonadotropin) levels. Ex. 1028 (Wakeling 1993) at 7. Hence, "if these observations [we]re paralleled in [human] patients," side effects commonly seen with tamoxifen, GnRH-agonists, and AIs—such as hot flashes, insomnia, and the psychologic consequences of estrogen withdrawal—were not expected to occur with fulvestrant. *Id.* Moreover, unlike the GnRH agonists and AIs, no reduction in bone density was observed in animals treated with fulvestrant. *See, e.g.*, Ex. 1008

(Wakeling 1991) at 7 (noting research). All told, fulvestrant was expected to have a superior tolerability profile to tamoxifen.

120. In Osborne 1995, a 1995 study of ER+ MCF-7 breast cancer cells (studied in nude mice), fulvestrant was found to be more effective than tamoxifen in reducing the expression of estrogen-related genes. Ex. 1018 (Osborne 1995). Specifically, fulvestrant was found to "possess[] a great ability to suppress estrogen-sensitive gene expression and greater antitumor activity than the partial estrogen antagonist tamoxifen." *Id.* at 4. Fulvestrant also showed "significantly delayed" MCF-7 tumorigenesis and a "significantly longer duration" of suppressed growth of established tumors than treatment by tamoxifen and estrogen withdrawal (or estrogen withdrawal alone). *Id.* at 4–5. So, according to Osborne 1995, fulvestrant also exhibited promise in ER-related gene expression and superior anti-tumor activity to tamoxifen.

121. Yet another study, McLeskey 1998, showed that in certain tamoxifen-resistant patients, an agent targeting the ER—such as fulvestrant—could theoretically be effective as second-line therapy. Ex. 1005 (McLeskey).

122. This result was confirmed in a subsequent study investigating the activity of fulvestrant on tamoxifen-resistant breast cancer cells. Results showed that fulvestrant showed a profound inhibitory effect on tumor proliferation, which was ascribed to its pure ER antagonistic activity. Ex. 1036 (Lykkesfeldt 1994).

123. A 1998-published study, O'Regan 1998, was designed to further investigate the effect of fulvestrant on the growth of human endometrial cancer. Ex. 1013 (O'Regan 1998) at 1. Athymic (thymus gland-removed) and ovariectomized mice transplanted with human endometrial tumors and treated with estrogen, followed by either tamoxifen or fulvestrant. While the tamoxifen-treated mice showed increases in uterine tumor growth, the mice implanted with tamoxifen-stimulated endometrial tumors and given fulvestrant treatment demonstrated inhibited uterine tumor growth. Additionally, fulvestrant was found not to increase the growth of endometrial cancers when administered alone, and in the presence of post-menopausal levels of estradiol, fulvestrant inhibited tamoxifen-stimulated endometrial growth. Meaning, researchers found that fulvestrant inhibited endometrial cancer, with or without the presence of estrogen, and that therefore it was not expected to increase the incidence of endometrial cancer. *Id.* at 1, 6. These findings supported the notion that fulvestrant could control growth of both ER+ breast and ER+ endometrial tumors. *Id.* at 6.

124. These preclinical reports demonstrated the potent anti-tumor efficacy of fulvestrant in the preclinical setting. Fulvestrant was found to be superior to tamoxifen in its affinity for the ER, its lack of ER agonist activity, its safety, and its anti-uterotrophic effects. Accordingly, a POSA would have expected fulvestrant to be safer than tamoxifen, in particular in minimizing development of

uterine cancer, making fulvestrant a possible candidate to treat, at minimum, ER+ malignant diseases of female breast tissue.

D. Fulvestrant's Clinical Efficacy in Human Females With Breast Cancer Was Well Known in the Prior Art.

125. Because fulvestrant was recognized as a "potent" pure antiestrogen with a projected favorable safety profile, "excellent growth-inhibitory effects in animal and *in vitro* models of human breast cancer and appear[ing] to have no demonstrable intrinsic agonist activity," researchers conducted a series of studies designed to evaluate the tolerance, pharmacokinetics, and short term biologic effects of fulvestrant in human females. Ex. 1027 (DeFriend 1994) at 1, 5. Fulvestrant, when administered to post-menopausal human females with ER+ breast tumors, was found to be well-tolerated, produced demonstrable anti-estrogenic effects in human breast tumors *in vivo*, and show no evidence of agonist (e.g., uterotrophic) activity. *Id.* at 1, 5–6. The blood serum concentration of fulvestrant was determined to be dose-dependent and fulvestrant was also found to produce a "significant decline" in breast cancer expression of ER+ and PgR+ in the human female subjects. *Id.* at 5. DeFriend 1994 recognized that Phase II trials with a long-acting fulvestrant formulation were already in progress. *Id.* at 6.

126. Also prior to 2000, fulvestrant was studied in a Phase II trial of 19 post-menopausal women with tamoxifen-resistant breast cancer to determine fulvestrant's pharmacologic effects and the drug's anti-tumor activity. An initial

published study recognized that fulvestrant was well-tolerated, lacked toxicity, and had no demonstrable agonist (e.g., uterotrophic) activity, making it a good candidate for "first-line treatment for advanced breast cancer." Ex. 1012 (Howell 1995) at 2. A later publication—"the first investigation of long-term administration of [fulvestrant] to patients with breast cancer"—recognized that fulvestrant produced few side effects, demonstrated predicted therapeutic levels as judged from animal experiments, and had the "potential to improve the rate and/or duration of response to anti-oestrogen therapy in breast cancer." Ex. 1006 (Howell 1996) at 6, 7.

127. Hence, data from these early human clinical trials were very promising. These trials not only demonstrated fulvestrant's robust anti-tumor activity in tamoxifen-resistant female ER+ breast cancers, but also suggested that fulvestrant was potentially more efficacious than tamoxifen.

E. Fulvestrant's Efficacy in Human Females with ER+ Breast Cancer was Well Known in the Prior Art.

128. A 1991 study found pure antiestrogens such as fulvestrant "may find a valuable place in the treatment of breast cancer." Ex. 1008 (Wakeling 1991) at 7.

129. Researchers in 1993 recognized that although "[t]he clinical usefulness of [fulvestrant] remains to be determined," fulvestrant "may prove superior to conventional partial agonist antioestrogens in the treatment of breast cancer." Ex. 1026 (Dukes 1993) at 1, 7.

130. In a 1993 presentation on pure antiestrogens, Dr. Wakeling recognized that pure antiestrogens, specifically including fulvestrant, could "have profound therapeutic implications," that "one might anticipate significant benefits in the rate and extent of tumor remission" by fulvestrant compared to other therapies, and that there "[wa]s a powerful rationale which argues the superiority of pure agonists over other treatments." Ex. 1028 (Wakeling 1993) at 8. Indeed, Dr. Wakeling stated that "[b]ased on the experimental precedents discussed above, there is a sound rationale for treating patients who relapse during adjuvant [tamoxifen] therapy with pure antiestrogens." *Id.* at 10.

131. Likewise, in a 1998-published study, researchers stated that "[t]here is every indication that [fulvestrant] will control growth of both breast cancer and endometrial cancer in patients," Ex. 1013 (O'Regan 1998) at 1557, further noting that "a large randomized, international clinical trial is under way." *Id.* at 2.

132. Not all anti-tumor agents that are effective in the metastatic setting are equally effective in the adjuvant setting, during which patients typically remain on the drug for years. Publications such as Howell 1996, which proposed investigating the activity of fulvestrant as an adjuvant treatment for [ER+] breast cancer, Ex. 1006 (Howell 1996) at 7, and O'Regan 1998, which proposed evaluating fulvestrant's potential as an adjuvant therapy for early stage endometrial

cancer, Ex. 1013 (O'Regan 1998) at 5–6, further underscored the optimism regarding fulvestrant's future usefulness.

F. Fulvestrant Formulations and Its Intramuscular Route of Administration Were Established in the Prior Art.

133. From the late 1980s up until 2000, multiple preclinical and clinical publications demonstrated not only the clinical efficacy of fulvestrant in the setting of ER+ breast cancer, but also documented its route and schedule of administration, formulation, optimal dose, volume and concentration, and blood plasma serum fulvestrant concentration levels.

1. Indication

134. As stated above, fulvestrant was developed to address the known limitations of tamoxifen, a treatment for ER+ breast cancer. *See supra* ¶¶ 48–49. Fulvestrant was administered in multiple pre-clinical studies directed to the treatment of hormonal dependent breast cancer. *See generally* Ex. 1008 (Wakeling 1991); 1009 (Wakeling 1992); 1018 (Osborne 1995); 1028 (Wakeling 1993); 1025 (Dukes 1992); 1026 (Dukes 1993). Multiple publications also disclosed fulvestrant administration to human females as a potential treatment for breast cancer, namely hormonal dependent (HR+) breast cancer. *See generally* Ex. 1006 (Howell 1996); 1012 (Howell 1995); 1027 (DeFriend 1994).

2. Excipients and Percent w/v Concentrations

135. It is my opinion that a POSA, who would be familiar with prior art showing fulvestrant formulations in castor oil, often accompanied with benzyl benzoate and ethanol, would look to the specific concentrations provided by Zeneca Pharmaceuticals and disclosed in McLeskey. *See* Ex. 1005 (McLeskey) at 2.

136. McLeskey 1998 disclosed the *exact* formulation of fulvestrant, 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, and castor oil claimed in the '680 patent:

Table #2: Comparison of McLeskey and '680 Patent		
McLeskey 1998	**'680 patent (claims 1 and 9)**	
" . . . 50 mg/ml preformulated [fulvestrant] drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil . . ."	Claim 1	" . . . fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of a castor oil vehicle . . ." (col. 12 ll. 46–50 (claim 1))
	Claim 9	" . . . fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; [and] about 15% w/v of benzyl benzoate" (col. 13 ll. 11–15 (claim 9))

137. I have also reviewed the expert declaration of Dr. Laird Forrest, Ph.D., and agree with his analysis as to the formulation of fulvestrant and a POSA's expected reliance on McLeskey.

3. Route and Schedule of Administration

138. Intramuscular monthly doses of fulvestrant were repeatedly disclosed in the art. O'Regan 1998 disclosed that, "[c]lincally, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Ex. 1013 (O'Regan) at 2.

139. Several other human studies or disclosures reiterated this same route of administration for humans. For example, Dukes 1989 disclosed the fulvestrant compound and its administration in humans to be "dosed as an intramuscular depot injection." Ex. 1007 at 6. DeFriend 1994 also disclosed a formulation of fulvestrant administered i.m. into the buttock. Ex. 1027 at 1.

140. Large-animal studies also disclosed i.m. administration. For example, Dukes 1992 disclosed i.m. administration of long-acting fulvestrant in monkeys, with injections of fulvestrant in castor oil given at 28-day intervals (i.e., approximately monthly). Ex. 1025 at 3, 7. Dukes 1993 likewise disclosed a long-acting castor oil solution, given i.m. to monkeys. Ex. 1026 at 2.

141. Several studies also touted the benefits of oil-based fulvestrant formulations in providing sustained anti-estrogenic activity. Wakeling 1992, for

example, disclosed that an oil-formulated "bolus dose" of fulvestrant provided "sustained antioestrogenic activity for in excess of 1 month in both rats and monkeys." Ex. 1009 at 2.

142. Several small-animal studies used a subcutaneous dose. *See, e.g.*, Ex. 1005 (McLeskey 1998) at 2; 1008 (Wakeling 1991) at 2; 1013 (O'Regan 1998) at 2. However, a POSA would understand that—when scaled up and translated to humans—a large-volume dose would preferably be given intramuscularly. I.M. administration would be expected to enhance the long-term release and to avoid the skin irritation and sensitivity typical of giving a large-volume dose s.c., just beneath the skin.

143. Regarding dosing schedule, Howell 1995 disclosed a long-acting fulvestrant formulation in castor oil, delivered by monthly intramuscular injection into a buttock. Ex. 1012 at 2. Howell 1996 likewise disclosed a "long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection into the buttock." Ex. 1006 at 2; *see also id.* at 1 ("administered as a monthly depot intramuscular injection")] Howell 1996 also described its results as showing that therapeutic levels of fulvestrant "can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used." *Id.* at 6.

144. Accordingly, recognizing fulvestrant's "low oral potency," Ex. 1013 (O'Regan 1998) at 2, a POSA would have expected to administer fulvestrant

parenterally. Human and animal studies consistently and repeatedly adopted either a subcutaneous dose or an intramuscular dose. Because the disclosed dose of fulvestrant was a larger volume (typically 5 ml, *see infra*) and was intended to exhibit a long-term or depot release (*see infra*), a POSA would expect to administer fulvestrant intramuscularly in humans, not subcutaneously. Animal studies using subcutaneous administration would not dissuade a POSA from this understanding.

4. Dose of Fulvestrant As-Formulated

145. A POSA would have known that oily intramuscular injections were typically given in volumes of significantly less than 10 ml, and usually 6 ml or less. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 ("The usual volumes injected range from 1.0 to 3.0 ml, with volumes up to 10.0 ml sometimes being given (in divided doses) in the gluteal or thigh areas . . . ."); 1038 (Rodger & King) at 6; 1054 (Newton) at 3; *see also* Ex. 1020 (GB '286) at 3 ("The volumes intramuscularly injected of the oily solutions of the present invention are normally 1 to 6 ml. The oily solutions are thus advantageously made up in unit dosage form, 15 each dosage unit having a volume within the range of from 1 to 6 ml for example a volume of 1, 2, 3 or 4 ml.").

146. Indeed, the specification of the'680 patent admits that injection volumes of 5 ml were known in the art: "[c]urrent[] guidelines recommend that no

more than 5 mls of liquid is injected intramuscularly in a single injection." Ex. 1001 at col. 5, ll. 64–66. Thus, the Patent Owner recognized the state of the art—that typically, i.m. injections did not exceed 5 ml.

147. In studies of fulvestrant in human females, the medical art disclosed an injectable dose of 5 ml. Howell 1995 disclosed an i.m. injection of 5 ml, noting that "[fulvestrant] appeared well tolerated at the site of injection despite the relatively large 5 mL volume administered." Ex. 1012 at 2.

148. Howell 1996 likewise disclosed a long-acting formulation administered by "monthly i.m. injection (5 ml) into the buttock" Ex. 1006 at 2, with the same disclosure of being "well tolerated." *Id.* at 4.

149. With the POSA's general understanding of recommended dosages, and with knowledge of prior art disclosing fulvestrant intramuscular injections of 5 ml or 6 ml in human patients and that such administration was "well tolerated," a POSA would have expected success in administering a 5 ml formulation of fulvestrant.

5. Divided Dose

150. Likewise, as stated above, a POSA would understand that larger injection volumes may be given in a divided dose. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 (intramuscular "volumes up to 10.0 ml [are] sometimes . . . given (in divided doses) in the gluteal or thigh areas . . . .").

151. Although Howell 1995 and Howell 1996 described a 5 ml administration as "well tolerated," they also recognized that 5 ml was a "relatively large . . . volume." Ex. 1012 (Howell 1995) at 2; 1006 (Howell 1996) at 4. A POSA would also be aware that such an injection could alternatively be given in a divided dose, *see, e.g.*, Ex. 1037 (Modern Pharmaceutics) at 7, and would expect a divided dose to exhibit similar efficacy.

6. Fulvestrant Concentration of About 50 $mgml^{-1}$

152. McLeskey specifically disclosed a preformulated fulvestrant concentration of "50 mg/ml." Ex. 1005 at 2. A preformulated fulvestrant concentration of 50 $mgml^{-1}$ is "about 50 $mgml^{-1}$."

7. Fulvestrant Total Dose of 250 mg

153. Dukes 1989 disclosed an i.m. injection of 50 mg to 5 g of fulvestrant. Ex. 1007 at 7.

154. Howell 1995 and Howell 1996 disclosed i.m. doses of 250 mg, both from the outset of the study for one patient cohort and beginning on month two for another Ex. 1006 (Howell 1996) at 2–3 (after an initial dose of 100 mg "[f]or appraisal of drug safety"); Ex. 1012 (Howell 1995) at 1("following confirmation of lack of local or systemic drug toxicity at the 100 mg dose").

155. McLeskey 1998 disclosed a 50 mg/mL preformulated dose, Ex. 1005 at 2, and O'Regan 1998 similarly disclosed a dose of 50 mg/mL. Ex. 1013 at 2. A

50 mg/1mL dose of fulvestrant, when scaled up to 5 mL, *see supra* Section IX.F.4, is a 250 mg dose.

X. UNPATENTABILITY OF THE '680 PATENT

156. Independent claims 1 and 9 of the '680 patent recite (1) a formulation of fulvestrant containing specific excipients, (2) administered to humans via intra-muscular injection, (3) as a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract, with (4) a given blood plasma fulvestrant concentration over time.

157. Dependent claims 2 and 10 recite a blood plasma fulvestrant concentration level of 8.5 ng/ml for 4 weeks.

158. Dependent claims 3, 6, 11, and 14 name the hormonal dependent benign or malignant disease to be breast cancer.

159. Dependent claims 4, 7, 12, and 15 recite an intramuscular injection of 5 ml of formulation.

160. Dependent claims 5, 8, 13, and 16 recite once monthly administration of the formulation.

161. Dependent claims 17–20 recite that the formulation is administered in a divided dose.

A. Claims 1–20 of the '680 patent were obvious over McLeskey.

162. In my opinion, claims 1–20 of the '680 patent were obvious to a POSA in view of McLeskey, which disclosed the precise formulation of fulvestrant claimed in the patent.

1. McLeskey disclosed the claimed fulvestrant formulation.

163. A POSA investigating therapeutic applications of fulvestrant would have been aware of the formulations known in the art, including "long-acting" and "castor oil-based" formulations. A POSA seeking therapeutic formulations of fulvestrant would find McLeskey, which disclosed every element of the claimed formulation.

164. McLeskey disclosed the exact concentrations of excipients claimed in independent claims 1 and 9: 10% w/v of ethanol, 10% w/v of benzyl alcohol, 15% w/v of benzyl benzoate, and a sufficient amount of a castor oil vehicle. Ex. 1005 at 2.

165. For these reasons, those stated above in Section IX.F.1, and the reasons given in the declaration of Dr. Forrest [Ex. 1003], it is my opinion that the formulation component of independent claims 1 and 9 was obvious.

2. The prior art disclosed the use of fulvestrant to treat human females having HR+ breast cancer.

166. McLeskey disclosed the use of fulvestrant as a possible alternative for tamoxifen in the treatment of ER+ breast cancer, and recognized the need for new clinical treatments for human patients. Ex. 1005 at 1.

167. Moreover, it was well-established in the medical art that fulvestrant was expected to treat, at minimum, ER+ breast cancer in human females. *See, e.g.*, Ex. 1008 (Wakeling 1991) at 7; 1025 (Dukes 1992) at 1, 7, 9; 1028 (Wakeling 1993) at 8, 10–11; 1013 (O'Regan 1998) at 2, 6; *see also supra*, Section IX.E. ER+ breast cancer *is* hormonal-dependent/hormone receptor-positive (HR+) breast cancer. Using a fulvestrant formulation to treat "hormonal dependent benign or malignant disease of the breast or reproductive tract," or specifically "breast cancer" in women, was neither new nor unexpected.

168. Knowing the exact fulvestrant formulation concentrations disclosed in McLeskey, a POSA would expect success in administering the formulation of fulvestrant to, at least, human females with HR+ breast cancer. Thus, in my opinion, McLeskey renders obvious claims 1, 3, 6, 9, 11, and 14 of the '680 patent as they relate to treating hormone-dependent breast cancer in humans.

3. The prior art disclosed delivering fulvestrant intramuscularly to humans.

169. With regard to the route of administration, it would have been obvious to a POSA that fulvestrant administration in humans should be by intramuscular injection rather than subcutaneous delivery, as in McLeskey's murine study. First, for murine models, large volume injections are optimally given subcutaneously—in contrast to humans, where i.m. injection is the administrative route of choice for large drug volumes. For example, for a 20-gram mouse, a recommended volume for an i.m. injection is 0.001 ml, whereas the recommend volume for an s.c. injection is 0.2 ml—200 times the volume of the i.m. injection. Ex. 1039 (Machholz) at 8. One reason for this difference is the small muscular volume of the mouse will not support a large volume injection. *Id.* Second, intramuscular injections can be very painful for animals and, therefore, laboratory guidelines recommend anesthesia to minimize discomfort. This is labor intensive for the investigator and adds another layer of complexity to the experiment, which can be avoided by simply administering the drug subcutaneously.

170. Furthermore, where a steroid sex hormone is formulated in oil, as it was in McLeskey, a POSA would understand that the typical route of administration in humans is by i.m. injection. I.M. injections enable prolonged release of the drug and thereby reduce the number of required injections, which is preferable for patients and physicians/clinicians. *See, e.g.*, Ex. 1025 (Dukes 1992)

at 7 ("1 month, a dosing interval likely to be clinically convenient in therapeutic studies in breast cancer patients").

171. Accordingly, a POSA would expect McLeskey's formulation to be administered to humans intramuscularly, rather than subcutaneously, thus rendering obvious the "intra-muscular" component of independent claims 1, 4, 7, 9, 12, and 14.

4. The prior art disclosed administering a formulation having a concentration of about 50 mg/ml of fulvestrant to human females having breast cancer.

172. McLeskey disclosed the administration of a "50 mg/ml" fulvestrant formulation. Ex. 1005 at 2; *see also supra*, Section IX.F.5.

173. For the reasons stated above in Section X.A.2, it would have been obvious to a POSA to administer McLeskey's fulvestrant to human female for the treatment of, at minimum, HR+ breast cancer.

174. A POSA looking to McLeskey for the specific components and concentrations of the excipients in the fulvestrant formulation would also look to the disclosed formulated fulvestrant concentration of 50 mg/ml. Therefore, it would have been obvious to a POSA to administer McLeskey's fulvestrant formulation to a human female with hormonal dependent breast cancer at the disclosed concentration of 50 mg/ml.

175. Under the broadest reasonable interpretation of the claims, 50 mg/ml is a fulvestrant formulation comprising "about 50 $mgml^{-1}$".

176. Accordingly, it is my opinion that the elements of claims 1 and 9 of the '680 patent, which claim a fulvestrant formulation of "about 50 $mgml^{-1}$ of fulvestrant," were obvious over McLeskey, which teaches a formulated fulvestrant concentration of 50 mg/ml.

5. A POSA knew from the prior art to administer to humans a 5 ml volume of formulated fulvestrant.

177. It was well known in the prior art that oily intramuscular injections were typically given to humans in volumes of significantly less than 10 ml, and usually less than 6 ml. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 (up to 10 ml); 1038 (Rodger & King) at 6 (up to 5 ml); 1054 (Newton) at 3 (up to 5 ml).

178. Indeed, the specification of the '680 patent admits that injection volumes of 5 ml were known in the art: "[c]urrent[] guidelines recommend that no more than 5 mls of liquid is injected intramuscularly in a single injection." Ex. 1001 at col. 5, ll. 64–66. Further, prior art specifically relating to fulvestrant administration in humans disclosed ranges around 5–6 ml. *See* Ex. 1012 (Howell 1995) at 2 (5 ml); 1006 (Howell 1996) at 2 (5 ml); 1020 (GB '286) at 3 (1 to 6 ml).

179. Accordingly, it was obvious to a POSA to administer a dose to humans of 5 ml, as disclosed in claims 4, 7, 12, and 15. Thus, a POSA would find obvious the formulated fulvestrant volume element of claims 4, 7, 12, and 15.

6. A POSA would have understood that the 5 ml of formulated fulvestrant could have been administered to a human female in a divided dose.

180. Claims 17–20 of the '680 patent claim the above-described formulation, "administered in a divided dose."

181. As stated previously, a POSA understood that larger injection volumes could be given in a divided dose. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 (intramuscular "volumes up to 10.0 ml [are] sometimes . . . given (in divided doses) in the gluteal or thigh areas . . . .").

182. Although some prior art described a 5 ml administration to humans as "well tolerated," it also recognized that 5 ml was a "relatively large . . . volume." Ex. 1006 (Howell 1996) at 4; 1012 (Howell 1995) at 2. A POSA would also be aware that a larger-volume injection could alternatively be given in a divided dose, *see, e.g.*, Ex. 1037 (Modern Pharmaceutics) at 7, and would expect a divided dose to exhibit similar efficacy in the patient.

183. In my opinion, the divided dose elements of claims 17–20 of the '680 patent were obvious in view of the knowledge of a POSA at the time of invention.

7. A POSA would have understood that the fulvestrant formulation could have been administered monthly.

184. Dependent claims 5, 8, 13, and 16 of the '680 patent further claim that the fulvestrant formulation is administered "once monthly."

185. As explained above, a POSA would have been familiar with the number of prior art references specifically disclosing intramuscular monthly and/or "depot" doses of fulvestrant. *See, e.g.*, Ex. 1006 (Howell 1996) at 2 ("*monthly* i.m. injection into the buttock") (emphasis added); *see also id.* at 1 ("*monthly* depot intramuscular injection") (emphasis added); 1009 (Wakeling 1992) at 4 (noting "parenteral *depot* formulations with an extended duration of action") (emphasis added); 1025 (Dukes 1992) at 7–8 (28-day intervals); 1013 (O'Regan 1998) at 2 (need for "*depot* intramuscular injection" in clinical setting) (emphasis added).

186. Likewise, a POSA would have been familiar with the several prior art references that disclosed that fulvestrant exhibits a therapeutic/anti-estrogenic effect of at least 1 month, thus informing a POSA of the expected success of a once-monthly fulvestrant formulation. *See, e.g.*, Ex. 1009 (Wakeling 1992) at 2 (oil-based fulvestrant formulation "sustained antioestrogenic activity for in excess of 1 month in both rats and monkeys"); 1025 (Dukes 1992) at 7 (anti-estrogenic action for 1 month in monkeys); 1026 (Dukes 1993) at 7 (same); 1006 (Howell 1996) at 6 (therapeutic levels of fulvestrant "can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used").

187. A POSA would also know that monthly doses of anti-estrogens would be preferable for both patients and physicians/clinicians. *See, e.g.*, 1025 (Dukes 1992) at 7 ("1 month, a dosing interval likely to be clinically convenient in therapeutic studies in breast cancer patients").

188. Accordingly, in my opinion, claims 5, 8, 13, and 16 of the '680 patent were obvious over the knowledge of a POSA and the prior art.

8. A POSA would have understood that the claimed blood plasma fulvestrant concentrations were not limitations of the patent.

189. After providing the specific components and percentages of formulated fulvestrant, claims 1 and 9 of the '680 patent state: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Dependent claims 2 and 10 require a blood plasma fulvestrant concentration of at least 8.5 $ngml^{-1}$ for 4 weeks.

190. As stated previously, I have been informed that the claim scope of a method claim is not limited by a "whereby" or "wherein" clause that simply expresses the intended result of a process step positively recited. If the clause does not inform how the method is carried out, the whereby or wherein clause is generally not given patentable weight.

191. The '680 patent neither claims nor discloses measuring blood plasma fulvestrant concentration levels as a component of the method of treatment. Neither is a POSA informed of any necessary titration or dosing (e.g., volume, schedule) adjustment based on blood plasma fulvestrant concentration levels. To the contrary, the POSA would be informed that if the as-claimed method of treatment is followed, the specified therapeutic plasma levels will be achieved. And, by correlate, to the extent specific blood plasma fulvestrant concentrations are desired, a POSA would understand to adjust, e.g., the volume or frequency of fulvestrant administered. These adjustments would have been routine to a POSA in treating a patient with hormonal dependent breast cancer with fulvestrant. In 1996, the prior art had already disclosed blood plasma fulvestrant concentration levels higher than 8.5 ng/mL extending for at least one week, along with blood plasma fulvestrant concentration levels higher than approximately 5.5 ng/mL for at least four weeks. Ex. 1006 (Howell 1996) at 3–4. A POSA would have known from this disclosure—as well as the general knowledge in the art that fulvestrant formulations in castor oil depots achieved a long-acting effect (*see, e.g.*, Exs. 1003 at ¶¶ 58–61; 1012; 1007; 1025; 1026; 1018; 1027 at 5)—that blood plasma fulvestrant a blood plasma fulvestrant concentration level of up to 8.5 ng/mL could have been achieved through routine optimization of the method of treatment.

These adjustments could have included, *inter alia*, adjusting the dosage or frequency of administration.

192. Accordingly, it is my opinion that a POSA would not understand the "wherein" clause to add an informative step, and thus that the claimed blood plasma fulvestrant concentration levels are not actually limitations of the patent. However, even if they were considered limitations, they would still all be met by the prior art.

B. All claims of the '680 patent were obvious over Howell 1996 in view of McLeskey.

193. In my opinion, claims 1–20 of the '680 patent were obvious over at least Howell 1996, which disclosed administering fulvestrant to female humans with primary breast cancer (with the goal of understanding fulvestrant's "[p]harmacokinetic[], pharmacological and anti-tumour effects"), in view of McLeskey, which disclosed the precise formulation of fulvestrant claimed in the patents. In my opinion, a POSA would understand Howell 1996's administration and results, with McLeskey's specific fulvestrant formulation, to meet every claim of the '680 patent. My discussion of the obviousness of claims 1–20 of the '680 patent over McLeskey, *see supra* Section X.A, is incorporated herein.

1. Howell 1996 disclosed using fulvestrant to treat breast cancer in a human female.

194. Howell 1996 disclosed that the study's aim was "to assess the long-term efficacy and toxicity of the specific anti-oestrogen [fulvestrant] in [human female] patients with advanced breast cancer and to evaluate the pharmacokinetics of the long-acting formulation uses." Ex. 1006 at 1.

195. As stated above, it was well-established in the medical art that fulvestrant was expected to treat, at minimum, ER+ breast cancer in human females. *See, e.g.*, Ex. 1008 (Wakeling 1991) at 7; 1025 (Dukes 1992) at 5, 6; 1028 (Wakeling 1993) at 8, 10; 1013 (O'Regan 1998) at 2, 6; *see also supra*, Section IX.E. Using a fulvestrant formulation to treat "hormonal dependent benign or malignant disease of the breast or reproductive tract," or specifically "breast cancer," in human females was neither new nor unexpected.

196. It would have been obvious to a POSA in view of Howell 1996 that a fulvestrant formulation could be used to "treat[] a hormonal dependent benign or malignant disease of the breast of reproductive tract" in humans as claimed in independent claims 1 and 9. Likewise, it would have been obvious to a POSA that a fulvestrant formulation could be specifically used to treat hormonal dependent (HR+) breast cancer, as claimed in dependent claims 3, 6, 11, and 14. In my opinion, therefore, the above-described disease components of claims 1, 3, 6, 9, 11, and 14 of the '680 patent were obvious over Howell 1996.

2. Howell 1996 in view of McLeskey disclosed administering McLeskey's complete fulvestrant formulation to a human, particularly a human female.

197. Howell 1996 disclosed a "long-acting formulation [of fulvestrant] contained in a castor oil-based vehicle [administered] by monthly i.m. injection into the buttock." Ex. 1006 at 2.

198. When considering possible formulations based on Howell 1996, a POSA would be aware of other formulations of fulvestrant disclosed in the art, as well as formulations for other steroidal hormones. In particular, a POSA would be aware of other fulvestrant or steroidal hormone formulations that were or could be "long-acting," i.m.-injectable, "depot," and/or contained in castor oil-based vehicles.

199. One such publication was McLeskey. McLeskey disclosed a specific castor oil-based formulation of fulvestrant: "50 mg/ml preformulated [fulvestrant] drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1005 at 2.

200. And for at least the reasons stated above in Section X.A.2, it would have been obvious to a POSA to administer McLeskey's fulvestrant to human female for the treatment of, at minimum, HR+ breast cancer.

201. A POSA, therefore, would understand that McLeskey's castor-oil based fulvestrant formulation, and its specific excipient components, could be

administered to humans as was accomplished in Howell 1996. A POSA would furthermore understand that McLeskey's fulvestrant formulation could be useful for at least the treatment of human females with hormonal dependent breast cancer, as in Howell 1996.

202. It was therefore obvious to use McLeskey's specific fulvestrant formulation in administration to a human, as disclosed in Howell 1996. In my opinion, the formulation components of claims 1 and 9 were therefore obvious over Howell 1996 in view of McLeskey.

3. Howell 1996 in view of McLeskey disclosed administering 5 ml of fulvestrant intramuscularly to a human female with breast cancer.

203. The '680 patent claims an "intramuscular[]" route of (claims 1, 4, 7, 9, 12, 15) at a volume of 5 ml (claims 4, 7, 12, 15).

204. Howell 1996 specifically disclosed a long-acting formulation administered by "monthly i.m. injection (5 ml) into the buttock" of a human female with breast cancer. Ex. 1006 at 2. Howell 1996 recognized that the 5 ml dose showed efficacy and "appeared well tolerated locally at the site of injection despite the relatively large 5 mL volume administered." *Id.* at 4, 6–7.

205. Other prior art disclosures buttressed this understanding. For example, Howell 1995 recognized that administration of 5 ml of formulated fulvestrant to a human female "appeared well tolerated locally at the site of

injection despite the relatively large 5 mL volume administered." Ex. 1012 (Howell 1995) at 2. GB '286 disclosed a dosage of 1 to 6 ml—not inconsistent with the 5 ml used by Howell 1996 and Howell 1995. Ex. 1020 at 3.

206. And it was well-known in the prior art that oily intramuscular injections were typically given to humans in volumes of significantly less than 10 ml, and usually less than 6 ml. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 (up to 10 ml); 1038 (Rodger & King) at 6 (up to 5 ml); 1054 (Newton) at 3 (up to 5 ml). Indeed, the specification of the '680 patent admits that injection volumes of 5 ml were known in the art: "[c]urrent[] guidelines recommend that no more than 5 mls of liquid is injected intramuscularly in a single injection." Ex. 1001 at col. 5, ll. 64–66.

207. Moreover, a POSA would understand that a 5 mL injection of a steroid hormone, formulated in oil and intended to be long-acting, should preferably be given intramuscularly: it would provide an extended release profile and avoid the contraindications (e.g., skin irritation, sensitivity) of giving the volume subcutaneously.

208. Although McLeskey administered her formulation of fulvestrant subcutaneously, a POSA would understand that subcutaneous is a common route of administration in mice because murine intramuscular administrations are not preferred. However, when translating the treatment to a human, a POSA would

expect to give a steroid hormone formulated in oil, and expect it to be long-acting, via intramuscular injection. *See supra* 142, 169–170

209. Therefore, it would have been obvious to a POSA in view of Howell 1996 to administer McLeskey's fulvestrant formulation to a human female via a 5 ml intermuscular injection. In my opinion, therefore, that the intramuscular injection element of '680 patent claims 1, 4, 7, 9, 12, and 15 was obvious to a POSA over Howell 1996, alone or in view of McLeskey. Likewise, the total volume element of '680 patent claims 4, 7, 12, and 15 was obvious to a POSA in view of Howell 1996.

4. A POSA would have known to administer the 5 ml of formulated fulvestrant in a divided dose.

210. Claims 17–20 of the '680 patent claim the above-described formulation, "administered in a divided dose."

211. As stated previously, a POSA understood that larger injection volumes could be given in a divided dose. *See, e.g.*, Ex. 1037 (Modern Pharmaceutics 1996) at 7 (intramuscular "volumes up to 10.0 ml [are] sometimes . . . given (in divided doses) in the gluteal or thigh areas . . . .").

212. Although Howell 1996 and Howell 1995 described a 5 ml administration to human females as "well tolerated," they also recognized that 5 ml was a "relatively large . . . volume." Ex. 1012 (Howell 1995) at 2; 1006 (Howell 1006) at 4. A POSA would also be aware that such an injection could alternatively

be given in a divided dose, *see, e.g.*, Ex. 1037 (Modern Pharmaceutics) at 7, and would expect a divided dose to exhibit similar efficacy.

213. In my opinion, claims 17–20 of the '680 patent were obvious in view of the knowledge of a POSA at the time of invention.

5. A POSA would have known to administer the fulvestrant formulation to a human monthly.

214. Dependent claims 5, 8, 13, and 16 of the '680 patent further claim that the fulvestrant formulation is administered "once monthly."

215. Howell 1996 disclosed monthly injections of formulated fulvestrant. Ex. 1006 at 1, 2. It also recognized "therapeutic levels of [fulvestrant] . . . can be achieved and maintained for 1 month following a single i.m. injection of the log-acting formulation used." *Id.* at 6.

216. Likewise, a POSA would have been familiar with a number of other prior art references that disclosed fulvestrant's administration and/or its effects approximately monthly. *See, e.g.*, Ex. 1025 (Dukes 1992) at 7–8 (administration at 28-day intervals and anti-estrogenic action for 1 month in monkeys); 1026 (Dukes 1993) at 7 (same); 1013 (O'Regan 1998) at 2 (need for "*depot* intramuscular injection" in clinical setting (emphasis added)); 1009 (Wakeling 1992) at 4 (noting "parenteral *depot* formulations with an extended duration of action" (emphasis added)); *id.* at 174 (oil-based fulvestrant formulation "sustained antioestrogenic activity for in excess of 1 month in both rats and monkeys").

217. A POSA would also know that monthly doses of anti-estrogens would be preferable for both patients and physicians/clinicians. *See, e.g.*, Ex. 1025 (Dukes 1992) at 7 ("1 month, a dosing interval likely to be clinically convenient in therapeutic studies in breast cancer patients").

218. Accordingly, in my opinion, claims 5, 8, 13, and 16 of the '680 patent were obvious over Howell 1996 and the knowledge of a POSA and the prior art.

6. Howell 1996 in view of McLeskey disclosed administering a fulvestrant formulation of 50 mg/ml concentration to a human female with breast cancer.

219. McLeskey disclosed the administration of a "50 mg/ml" fulvestrant formulation. Ex. 1005 at 2.

220. For reasons as stated above in Sections X.A.2 and X.B.2, it would have been obvious to a POSA to administer McLeskey's fulvestrant to a hunan female for the treatment of, at minimum, HR+ breast cancer. A POSA looking to McLeskey for the specific components and concentrations of the excipients in the fulvestrant formulation would also look to the disclosed concentration of 50 mg/ml. Therefore, it would have been obvious to a POSA to administer McLeskey's fulvestrant formulation to a human female with breast cancer at the disclosed concentration of 50 mg/ml.

221. Administration of 50 $mgml^{-1}$ matches "about 50 $mgml^{-1}$." Accordingly, it is my opinion that the elements of claims 1 and 9 of the '680

patent, which claim a fulvestrant formulation comprising "about 50 $mgml^{-1}$" of fulvestrant, were obvious over Howell 1996 and McLeskey.

7. A POSA would have understood that the claimed blood plasma fulvestrant concentrations were not limitations of the patent.

222. After providing the specific components and percentages of formulated fulvestrant, claims 1 and 9 of the '680 patent state: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Dependent claims 2 and 10 recite a blood plasma fulvestrant concentration of at least 8.5 $ngml^{-1}$, "wherein" it is achieveed for 4 weeks.

223. As stated previously, I have been informed that the claim scope of a method claim is not limited by a "whereby" or "wherein" clause that simply expresses the intended result of a process step positively recited. If the clause does not inform how the method is carried out, the whereby or wherein clause is generally not given patentable weight.

224. The patent neither claims nor discloses measuring blood plasma fulvestrant concentration levels as a component of the method of treatment. Neither is a POSA informed of any necessary titration or dosing adjustment based on blood plasma fulvestrant concentration levels. To the contrary, a POSA would

be informed that if the as-claimed method of treatment is followed, the specified therapeutic plasma levels will be achieved.

225. Accordingly, it is my opinion that a POSA would not understand the "whereby"/"wherein" clause to add an informative step, and thus that the claimed blood plasma fulvestrant concentration levels of claims 1–2 and 9–10 of the '680 patent are not actually limitations of the patent that must be separately rendered obvious.

8. Even to the extent the claimed blood plasma fulvestrant concentrations are limitations, they were disclosed by Howell 1996, alone or in view of McLeskey.

226. To the extent the blood plasma fulvestrant concentrations could be interpreted as claim limitations, they were obvious over Howell 1996's disclosures of mean serum fulvestrant concentrations. Ex. 1006 at 3–4, 6. Howell 1996 disclosed a long-acting formulation of fulvestrant administered monthly to human females with breast cancer, and reports pharmacokinetic data for patients administered a monthly 250 mg dose. *Id.* at 3–4, 6.

227. Independent claims 1 and 9 of the '680 patent state, "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Dependent claims 2 and 10 alter the concentration to 8.5 $ngml^{-1}$ for at least 4 weeks.

228. Howell 1996 disclosed mean serum fulvestrant concentration levels of at least 2.5 $ngml^{-1}$ for the duration of 28 days after injection. Ex. 1006 at 4 Fig. 2. Howell 1996 also described its results as showing that therapeutic levels of fulvestrant "can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used." *Id.* at 6. As Howell 1996 disclosed these two elements, and as the administration of the claimed fulvestrant formulation to human females with breast cancer was obvious over at least Howell 1996 and McLeskey, the serum fulvestrant concentration elements of claims 1 and 9 were obvious in view of Howell 1996.

229. Howell 1996 disclosed a long-acting formulation of fulvestrant which reached C_{max} levels of 10.5 to 12.8 $ngml^{-1}$ after 7 days. Howell 1996 depicts mean serum fulvestrant concentrations of 8.5 $ngml^{-1}$ for approximately 7 days, when administered in a once-monthly 250 mg dose. *Id.* at 3–4. It would be a routine and predictable method of optimization for a POSA to measure a patient's blood plasma fulvestrant concentration and to adjust the amount and frequency of fulvestrant administered to achieve concentrations at or above 8.5 $ngml^{-1}$ for 4 weeks, as in claims 2 and 10. This is particularly true where claims 2 and 10 impose no restrictions on the frequency of dosing. As Howell 1996 disclosed mean serum fulvestrant concentrations at and above 8.5 $ngml^{-1}$, and as it would be routine for a POSA to achieve these levels for a longer duration such as 4 weeks by

altering the dose and/or frequency of administration (*see* Section X.A.8, *supra*), the serum fulvestrant concentration elements of claims 2 and 10 were obvious in view of Howell 1996 and the knowledge of a POSA.

XI. CONCLUSION

230. For the foregoing reasons, it is my opinion that claims 1–20 of the '680 patent were obvious over McLeskey. Independent claims 1 and 9 focus on a method of treating hormonal dependent benign or malignant disease of the breast or reproductive systems by intramuscular administration of a specific fulvestrant formulation. The specific formulation claimed in claims 1 and 9 was disclosed in McLeskey, and the remaining independent claim elements were either within the knowledge and experience of a POSA or are not limitations to the claims.

231. Furthermore, claims 1–20 of the '680 patent were also rendered obvious by Howell 1996 in view of McLeskey. Howell 1996 disclosed the intramuscular administration of 5 ml (250 mg of fulvestrant) of a castor oil-based fulvestrant formulation for the treatment of human females with advanced, hormonal dependent breast cancer. That disclosure, combined with the specific castor oil-based fulvestrant formulation disclosed in McLeskey (50 mg/ml of 10% ethanol, 10% benzyl benzoate, 15% benzyl alcohol, brought to volume with castor oil) and the knowledge of a POSA, renders all claims of the '680 patent obvious. A POSA would not interpret any remaining independent claim elements, such as

serum blood plasma concentration, to be additional limitations; to the extent they could be so construed, they are nonetheless obvious over Howell 1996 in view of McLeskey and the knowledge of a POSA.

232. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Dated: 6/29/2016

By: _____
Leslie Oleksowicz, M.D.

EXHIBIT A

Curriculum Vitae
Leslie Oleksowicz, M.D.

Date Prepared:	**7/1/2015**
Name:	**Leslie Oleksowicz, M.D.**
Home Address:	**1623 Beechshire Drive**
	Cincinnati, OH 45255
Phone:	**HOME: 513-620-8685; I-phone: 860-460-9975**
Email:	leslie.oleksowicz@gmail.com
	loleksowicz@earthlink.net
Place of Birth &	**Ware, MA 01082**
Citizenship	**U.S Citizen**

Education

9/1974 - 6/1978	BA Magna Cum Laude Phi Beta Kappa	Biology	Amherst College Amherst, Massachusetts
9/1978 - 6/1982	MD	Medicine	Tufts University School of Medicine Boston, Massachusetts

Postdoctoral Training

7/1982-7/1985	Residency	Internal Medicine	Montefiore Hospital/ Albert Einstein College of Medicine, Bronx, New York
7/1985-7/1987	Fellowship	Hematology	Mount Sinai Medical Center, New York, New York
7/1987-7/1989	Fellowship	Medical Oncology	Mount Sinai Medical Center, New York, New York.

Current Employment

1/2015-present	Leslie Oleksowicz, M.D, LLC, Consultant	DBL, 207 Thomas More Parkway Crestview Hills, KY

Faculty Academic Appointments

7/1989-11/1991	Instructor	Medical Oncology	Mount Sinai Medical Center, New York, New York
6/1992-7/1998	Assistant Professor of Medicine	Medical Oncology	Montefiore Hospital/ Albert Einstein College of Medicine Bronx, New York
9/1998-7/2003	Associate Professor of Medicine	Medical Oncology	Roswell Park Cancer Institute Buffalo, New York
9/2003-5/2012	Associate Professor of Medicine	Hematology/Oncology	University Hospital/University of Cincinnati Cincinnati, Ohio
8/2012-4/2013	Professor of Medicine	Hematology/Oncology	Saint Louis University Medical Center, Saint Louis, Missouri

9/16/2013-12/31/2014	Attending Clinician	Hematology/Oncology	Dana Farber Cancer Institute Boston, Massachusetts

Appointments at Hospitals/Affiliated Institutions

7/1989-11/1991	Clinical Assistant	Medical Oncology	Mount Sinai Medical Center
6/1992-7/1998	Assistant Attending	Medical Oncology	Montefiore Hospital
9/1998-7/2003	Associate Attending	Internal Medicine/Medical Oncology	Roswell Park Cancer Institute
9/2003-5/2012	Associate Attending	Internal Medicine/Medical Oncology	University Hospital, University of Cincinnati
9/2003-5/2012	Associate Attending	Internal Medicine/Medical Oncology	University Point Practice, Satellite facility of University of Cincinnati, West Chester, OH
12/2004-6/2010	Courtesy Associate Attending	Internal Medicine/Medical Oncology	Christ Hospital, Cincinnati, OH
9/2003-5/2012	Associate Attending	Internal Medicine/Medical Oncology	West Chester Medical Center, West Chester, OH (hospital owned by University of Cincinnati)
4/2009-5/2012	Associate Attending	Internal Medicine/Medical Oncology	University Point Surgical Hospital, West Chester, OH
8/2012-4/2013	Attending Professor	Internal Medicine/Medical Oncology	Saint Louis University Hospital
9/2013-12/2014	Faculty Clinician	Medical Oncology	Dana Farber Cancer Institute Boston, MA
9/2013-12/2014	Clinician	Hematology/Oncology	Lawrence and Memorial/Dana Farber Community Cancer Center, Waterford, CT Lawrence and Memorial Hospital, New London, CT

Current Licensure

1985	New York (active)	#158402-1
2003	Ohio (active)	#35-083335
2012	Missouri (inactive)	#2012021332
2013	Connecticut (inactive)	#052051

Certification

10/1987	Board Certified Diplomat in Internal Medicine
8/1989	Board Certified Diplomat in Medical Oncology

Other Professional Positions

1/1997-3/1997	Consultant	Merck Pharmaceutical: Evaluation of clinical and laboratory data related to COX-2 inhibitor.
10/1996-3/1998	Course Director	Practical Reviews in Cancer Management. Monthly review of recent clinical studies in medical oncology
8/2002-present	Advisory Board Member	National Kidney Cancer Association
7/22/2006	Course Director	First Annual University of Cincinnati Genitourinary Symposium
9/2007-9/2008	Advisory Board Member	Novartis (Interleukin-2)
7/2120/07	Course Director	Second Annual University of Cincinnati Genitourinary Symposium
9/2007-9/2008	Member speaker bureau	Bayer/Onyx
2/2008-5/2012	Advisory Board Member	Association of Community Cancer Center
7/26/2008	Course Director	Third Annual University of Cincinnati Genito-Urinary Symposium
8/2008-4/2013	Principal Investigator of SWOG	University of Cincinnati and University of Saint Louis
9/2009-10/2010	Advisory Board Member	Pfizer
7/26/2009	Course Director	Fourth Annual University of Cincinnati Genitourinary Symposium
6/2011-6/2012	Advisory Board Member	Centacore-Ortho

Major Administrative Leadership Positions

Local

9/1998-7/2003	Director of GU Oncology	Roswell Park Cancer Institute
9/1998-7/2003	Director of Melanoma and Sarcoma Oncology	Roswell Park Cancer Institute
9/1998-7/2003	Director of High Dose IL-2 Service	Roswell Park Cancer Institute

7/2003-5/2012	Director of GU Oncology	University of Cincinnati Medical Center
7/2003-5/2012	Director of Melanoma and Sarcoma Oncology	University of Cincinnati Medical Center
7/2003-520/12	Director of High Dose IL-2 Service	University of Cincinnati Medical center
9/2008-7/2009	Director of Gastrointestinal Oncology	University of Cincinnati Medical Center
8/2012-4/2013	Director of GU Oncology	University of Saint Louis Medical Center
8/2012-4/2013	Director of Melanoma and Sarcoma Oncology	University of Saint Louis Medical Center

Committee Service

Local

9/1992-6/1998	Transfusion Committee 9/92-6/1998	Montefiore Hospital/Albert Einstein College of Medicine Member
9/1995-6/1998	Cancer Center Protocol Review Committee 9/1995-6/1998	Albert Einstein Cancer Center Vice Chair
9/1995-6/1998	Cancer Center Protocol Audit Committee 9/1995-6/1998	Albert Einstein Cancer Center Coordinator
9/1992-6/1998	Hematology Malignancy Working Group 9/1992-6/1998	Montefiore Hospital/Albert Einstein Member
9/1992-6/1998	Breast Malignancy Affinity Group 9/1992-6/1998	Member Montefiore Hospital/Albert Einstein
10/1998-10/1999	CME Advisory Board 10/1998-10/1999	Roswell Park Cancer Institute Member
5/1999-6/2000	Morbidity and Mortality Committee 5/1999-6/2000	Roswell Park Cancer Institute Member
5/1999-6/2000	Quality Improvement Committee 5/1999-6/2000	Roswell Park Member
1/2001-1/2002	IRB 1/2001-1/2002	Roswell Park Member
9/2003-4/2012	Hematology/Oncology Grand Rounds 9/2003-4/2012	University of Cincinnati Director, Coordinator and Master of Ceremonies
9/2003-5/2006	Scientific Review Protocol Committee 9/2003-5/2006	University of Cincinnati Member
9/2004-6/2006	Ethics Committee 9/2004-6/2006	University of Cincinnati Co-Chair
9/2003-8/2008	Hematology/Oncology Clinical Research Forum 9/2003-8/2008	University of Cincinnati Director
9/2004-7/2007	Prostate Cancer Affinity Group 9/2004-7/2007	University of Cincinnati Member
5/2008-5/2012	Medical Center Fund of Cincinnati 5/2008-5/2012	University of Cincinnati Member

Regional

1985-1987	Society for the Study of Blood 1985-1987	Teaching Hospitals in the Greater New York Area Member

National and International

11/002-11/2003	Advisory Board on Cancer Related Fatigue 11/2002-11/2003	NCCN Member
8/2002-present	Advisory board 8/2002-present	National Kidney Cancer Association Member

Professional Societies

1/1990-9/2003	American Society of Hematology 1/1990-9/2003	Member
1996-present	American Society of Clinical Oncology 1996-present	Member
9/1998-6/2003	Cancer and Leukemia B (CALGB) 9/1998-6/2003	Member
6/1992-7/1998	Eastern cooperative Group (ECOG)	Member

	6/1992-7/1998	
1985-present	Phi Delta Epsilon Fraternity 1985-present	Member
1982-1987	American College of Physicians 1982-1987	Member
8/2002-present	National Kidney Cancer Association 8/2002-present	Member, Editorial Advisory Board
10/2003-4/2013	SWOG	Member

Editorial Activities

Cancer
Transfusion
Southern Journal of Medicine
Journal of Urology
American Journal of Medical Sciences

Other Editorial Roles

2009-present	Editorial Advisory Board	Kidney Cancer

Honors and Prizes

6/1978	Webster Prize	Amherst College	Undergraduate Thesis
9/1978-9/1982	Simpson Fellowship	Tufts University School of Medicine	Scholarship based on GPA
9/1978-9/1982	Hampden Scholarship	Tuft University School of Medicine	Scholarship based on GPA
2/1997	Third Prize awarded at basic investigators research symposium	Albert Einstein college of Medicine	Third prize for best scientific paper
11/2002	Certificate of recognition	Roswell Park	Excellence in clinical practice

Report of Funded and Unfunded Projects

Funding Information

Past

1/1999-6/2003	A Phase II Pilot Study of Dose –Intensive IL-2, DTIC and IFN in Patients with Metastatic Malignant Melanoma. **Leslie Oleksowicz,: P.I.**; $60,000 from Schering Pharmaceuticals
1/1999-6/2003	A Phase II Study of Dose-Intensive IL-2 by IV Bolus and Low Dose Immunomodulating IFN as Therapy for Patients with Metastatic or Unresectable RCC. **Leslie. Oleksowicz, P.I. Investigator-initiated**. $40,000 from Schering Pharmaceuticals
1/1999-6/2003	An adjuvant Dose-intensive Trial of High Dose bolus IL-2 in Patients with High Risk Renal Cell Carcinoma. **Leslie. Oleksowicz, P.I. Investigator Initiated**. $20.000 from Chiron Pharmaceuticals
1/1999-6/2003	A Phase II Study of Post-Transurethral Resection M-VAC and Taxol/Gemcitabine Chemotherapy in Patients with Invasive Transitional Cell Bladder Cancer. **Leslie Oleksowicz, P.I.** $50,000 from Bristol Pharmaceuticals.
1/2003-6/2004	A Phase II Trial Investigating the Efficacy of High Dose-Intensive IL-2 in Combination with Capecitabine in Patients with Stage IV Renal Cell Carcinoma. **Leslie Oleksowicz, P.I.** $75,000 from Roche Pharmaceuticals.
04/2005-5/2006	A Phase II Trial of Fludarabine and High Dose Bolus Interleukin-2 in Patients with Stage IV or Surgically Unresectable Renal Cell Carcinoma. **Leslie Oleksowicz, P.I. Investigator-initiated**; $150,000 from Chiron.
04/2005	A Phase II Trial of Taxotere, Gleevec, Complete Androgen Blockade and Zometa in Patients with a Rising PSA s/p Definitive Treatment. **Leslie Oleksowicz, P.I. Investigator-Initiated.** $120,000 from ***Novartis (Trial was never initiated and never accrued any patients).***
7/1992-7/1993	The Role of IL-6 on Platelet Function. **Leslie Oleksowicz, P.I**. $20,000 from Sandoz Pharmaceuticals
7/1993-6/1996	The Mechanisms of Anti-Tumor Activity of IL-2 and Il-6: The Relationships between the Hemostatic and Immune Systems. **Leslie Oleksowicz, P.I.;** $150,000 from American Cancer Society.
7/1993-6/1996	The Role of IL-6 on Platelet Function. **Leslie Oleksowicz, P.I**. $60,000 from Sandoz Pharmaceuticals.
7/1993-6/1996	Research in Platelet Function. **Leslie Oleksowicz, P.I**. $25,000 from Irving A Hansen Memorial Foundation.
7/1994-4/1995	Impedance Agregometry Investigating Platelet Tumor Interactions. **Leslie Oleksowicz, P.I.**, $30,000 from Carol Solar Abbani Foundation.
7/1994-4/1995	Ex vivo Platelet Functional Studies in Patients with Advanced Breast Carcinoma Who have Undergone Autologous Bone Marrow Transplantation and have been Treated with IL-6 or Placebo. **Leslie Oleksowicz, P.I.;** $30,000 from

	Sandoz Pharmaceuticals.
1/1996-12/1997	Characterization of Immunorelated GPIb Expression by Myelogenous Leukemia Cells. **Leslie Oleksowicz, P.I.**, $30,000, National Leukemia Research Association.
7/1997-7/1998	The Role of Tumor GPIbα in Platelet-Tumor Adhesive Interactions and Metastasis. **Leslie Oleksowicz, P.I.** $80,000 from the Elsa U. Pardee Foundation.
1/1999-1/2001	The Role of GP1b Expressed by Renal Carcinoma Cells in Primary Adhesive Interactions Required for the Metastatic Process. **Leslie Oleksowicz: P.I.**, $30,000 from the Bruce Cuvelier Endowed Research Fund in Urology.
11/1999-10/2000	Tumor Expression of the Immunorelated Platelet Adhesive receptor: GP1bα and α2β3: Novel Targets for Anti-Neoplastic Strategies. **Leslie Oleksowicz: P.I.** $50,000 from the Roswell Park Alliance Foundation.

Additional Clinical Trials

7/1992-7/1993	Co-Investigator: A Compassionate Study of High Dose IL-2 by I.V. Bolus in Patients with Metastatic or unresectable Renal Cell Carcinoma. Investigator-Initiated Trial.
5/1992-11/1993	Co-Investigator: A Phase I Study of Interleukin-6 (IL-6, SDZ ILS 969) Administered by 120-Hour Continuous Intravenous Infusion. Sponsored by the Cytokine Working Group and Sandoz Pharmaceuticals
8/1993-10/1995	Co-Investigator: Open-Label, Multicenter Trial of Actimmune Interferon Gamma-1b (IFN-γ1b) in Patients with Metastatic Renal Cell Carcinoma. Sponsored by Genentech.
7/1994-8/1995	Co-Investigator: A Phase III Randomized Double Blind, Placebo-Controlled Study or CT-1501R and High Dose Intermittent Interleukin-2 in the Treatment of Patients with Advanced Renal Cell or Metastatic Malignant Melanoma. Sponsored by Cell therapeutics.
1/1994-1/1996	Co-investigator: Chemo-Immunotherapy of Metastatic Renal Cell Carcinoma with IL-2, Interferon-α2b, and 5-FU. Sponsored by the Cytokine Working Group.
10/1994-9/1998	Co-Investigator: Randomized Phase II Trial of Chemotherapy and Outpatient Biotherapy in Metastatic Malignant Melanoma. Sponsored by the Cytokine Working Group.
6/1996-11/1997	Co-Investigator: A Multicenter Phase II Evaluation of Combination Therapy of Targretin Oral Capsules (LGD 1069) and Intron A in patients with Advanced Renal cell Carcinoma. Sponsored by Ligand Pharmaceuticals and the Schering
7/1996-9/1997	Co-Investigator: A Phase II Study of Moderate Dose IL-2 by I.V. Bolus and Subcutaneous GM-CSF in Patients with Metastatic or unresectable Renal Cell Carcinoma. Investigator-initiated study.
11/1996-2/1997	Co-Investigator: Open-Label Randomized, Dose-Escalating Study of Recombinant Human Interleukin-12 administered by sub-cutaneous Injection in Patients with Advanced Malignancies. Sponsored by Genetics Institute and Wyeth-Ayerst.
7/1997-3/1999	Co-Investigator. A Randomized Phase III Trial of High-Dose IL-2 Versus Subcutaneous Interleukin-2/IFN in Patients with Metastatic Renal Cell Carcinoma. Sponsored by the Cytokine Working Group.
5/1997-6/1998	Co-Investigator: Open-Label, Non-Randomized, Dose-Escalating Study of Recombinant Human Interleukin-12 by IV injection in Patients with Untreated or Previously Treated Advanced RCC. Sponsored by Genetics Institute and Wyeth-Ayerst.
7/1999-5/20000	A Multi-Center, Escalating dose Phase I Study of IV DENSPM administer daily for 5 days as a Loading dose followed by thrice weekly maintenance dosing for two weeks. Sponsored by Parke-Davis.
7/2002-6/2003	Co-Investigator. Phase I Study of Intravenous Tumor Necrosis Factor-alpha Plus Doxorubicin in Patients with Advanced Solid tumors. A Pilot Study.
7/2002-6/2003	Co-Investigator. Phase I Study and Pharmacokinetics of Irinotecan in Combination with Fixed Dose Celecoxib in Patients with Advanced Colorectal Cancer. Instituion-sponsered trial.
7/2002-6/2003	Co-Investigator. A Phase I Trial of Subcutaneous and Oral Calcitriol (1,25-$(OH)_2D_3$) & Carboplatin in Advanced Solid Tumors. Sponsored by Abbott, Hoffman-LaRoche, CapCURE.
2/2003-5/2003	**Principal Investigator**. A Phase II Study of Capecitabine (IND #62761) Plus Gemcitabine for Metastatic Renal Cell Carcinoma. CALGB 9008.
5/2002-7/2003	Principal Investigator. Multi-Center Randomized, Controlled, Double-Blind Parallel-Group Study to Compare the Efficacy and Safety of Two CC-5013 Dose Regimens in Subjects with Metastatic Malignant Melanoma whose Disease has progressed on Treatment with DTIC, IL-2, IFNα or IFNβ. Sponsored by Celgene.
9/2003-5/2006	Co-Investigator. Prospective Phase II Clinical Trial: Interferon-alpha, Tamoxifen and Thalidomide for the Treatment of Advanced Renal Cell Carcinoma. Sponsored by Celgene.
3/2004-11/2007	Co-Investigator. A Randomized Double Blind, Placebo Controlled Phase III Trial of Immunotherapy with Autologous Antigen-Presenting Cells Loaded with PA2024 (Provenge, APC8015) in Asymptomatic Subjects with Gleason Sum <7,Metastatic Androgen independent Prostate Cancer . Sponsored by Dendreon Corporation.
11/2004-2/2006	**Principal Investigator**. Phase II Randomized, Open-Label, Three-Arm, Multicenter Study of Medi-522, A Humanized Monoclonal Antibody Directed against the αvβ3 Integrin, in Combination with Docetaxel, Prednisone and Zolendronic acid in the Treatment of Patients with Metastatic Androgen Independent Prostate Cancer. Sponsored by

	Medimmune.
1/2005-1/2007	**Principal Investigator**: Clinical Protocol CA183001. A Phase II Study of I.V. Vinflunine in Patients with Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelium. Bristol/Myers/Squibb.
7/2005-3/2006	**Principal Investigator**: A Phase III Randomized Open-Label Study of CG1940 and CG8711 vs. Docetaxel and Prednisone in Patients with Metastatic Hormone Refractory Prostate Cancer who are Chemotherapy-Naïve. Sponsored by Cell Genesys.
12/2005-1/2007	**Principal Investigator**: SWOG 0508. Phase II Trial of Combination Thalidomide plus Temozolomide in Patients with Malignant Melanoma. SWOG-0508.
10/2006-9/2007	**Principal Investigator**: Clinical Protocol CA184024. A Multicenter Randomized Double-Blind Two Arm Phase III Study in Patients with Untreated or Stage IV Melanoma Receiving DTIC plus 10 mg/kg Ipilimumb vs. DTIC with Placebo. BMS.
5/2006-5/2007	**Principal Investigator:** SWOG 0306. A Phase II Study of Irinotecan in Patients with Advanced Transitional Cell Carcinoma of the Urothelium. SWOG 0306.
1/2005-5/2007	Co-Investigator: Phase III trial of High Dose Interferon vs. Cisplatin, Vinblastine, DTIC plus IL-2 and Interferon in Patients with High Risk Melanoma.
5/2006-2/2020	Co-Investigator: A Phase III Protocol of Androgen Suppression and 3DCRT/IMRT vs. AS and 3DCRT/IMRT Followed by Chemotherapy with Docetaxel and Prednisone for Localized High Risk Prostate Cancer. Sponsored by RTOG.
1/2007-2/2011	**Principal Investigator:** ASSURE TRIAL. ECOG 2805. A Randomized Double Blind Phase II Trial of Adjuvant Sunitnib vs. Sorafinib vs. Placebo in Patients with Resected Renal Cell Carcinoma. Sponsored by ECOG 2805.
1/2006-10/2009	Co-Investigator: SWOG 0512. Phase II trial of BAY 43-9006 (Sorafinib) in Combination with Carboplatin and Paclitaxel in Patients with Uveal Melanoma. SWOG 0512.
1/2006-9/2008	Co-Investigator: SWOG 0505. Phase II trial of BAY 43-9006 in Advanced Soft Tissue Sarcoma. SWOG 0505.
7/2007-9/2010	**Principal Investigator**: Lenalidomide in Treating Older patients with AML. SWOG
1/2007-10/2010	**Principal Investigator:** A Randomized Double Blind Placebo Controlled Phase III study of Early vs. Standard Zolindronic Acid to Prevent Skeletal Related Events in Men with Prostate Cancer Metastatic to the Bones. CALGB 90202.
2/2007-3/2010	Co-Investigator: SWOG 0421. Phase III study of Docetaxel and Altrasentan vs. Docetaxel and Placebo in Patients with Advanced Hormone Refractory Prostate Cancer. SWOG 0421.
3/2008-7/2010	**Principal Investigator:** Multi-institutional Consortium: The High Dose Aldesleukin (IL-2) "SELECT" Trial in Patients with Metastatic Renal Cell Carcinoma. NOVARTIS.
1/2007-5/2009	**Principal Investigator:** High Dose Interferon Alpha in Treating Patients with Stage II or Stage III Melanoma. SWOG.
1/2007-1/2009	**Principal Investigator:** Androgen Ablation Therapy with or without Chemotherapy in Treating Patients with Metastatic Prostate Cancer. Intergroup Trial.
8/2008-5/2012	**Principal Investigator**: Phase III Randomized Trial of Anastrozole vs. Anastrozole and Fulvestrant as First Line Therapy in Post-Menopausal Women with Metastatic Breast Cancer. SWOG.
8/2008-9/2009	**Principal Investigator**: Phase II Studies of Two Different Schedules of Dasatinib in Bone Metastasis Predominant Metastatic Breast Cancer. SWOG-0622.
8/2008-10/2010	**Principal Investigator**: Phase III Trial of Irinotecan-Based Chemotherapy Plus Cetuximab with or without Bevacizumab as Second line Therapy in Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, OPTIMOX or XELOX. SWOG-0600.
8/2008-5/2012	**Principal Investigator**: A Phase III Prospective Randomized Comparison of Depot Octreotide plus Interferon alpha vs. Depot Octreotide plus Bevacizumab in Advanced Poor Prognosis Carcinoid Patients. SWOG-0518
10/2008-11/2009	**Principal Investigator:** Gemtuzumab and Combination Chemotherapy in Treating Patients with Previously Untreated APL. SWOG.
8/2009-7/2010	**Principal Investigator**: A Randomized Double Blind Placebo Controlled Phase III Study of Early vs. Standard Zeledronic Acid to Prevent Skeletal-Related Events in Men with Prostate Cancer Metastatic to Bone. SWOG 90202.
10/2008-8/2010	**Principal Investigator**: Acetyl-Carnitine in Preventing Neuropathy in Women with Stage I, II or IIIA Breast Cancer Undergoing Chemotherapy. SWOG.
11/2008-7/2010	**Principal Investigator:** Capecitabine, Gemcitabine and Radiation Therapy in Treating Patients with Cholangiocarcinoma of the Gallbladder or Bile duct. SWOG.
5/2008-9/2010	**Principal Investigator:** Erlotinib and Bevacizumab in Treating Patients with Stage IIIb or Stage IV Primary Non-Small Cell Lung Cancers Who Have Never Smoked. SWOG.
9/2008-5/2020	**Principal Investigator**: Cytogenetic Studies in Leukemia Patients, Ancillary SWOG 9007 and Leukemia Centralized Reference Laboratories and Tissue Repositories. Ancillary SWOG 9910.
8/2008-3/2010	**Principal Investigator**: A Phase II Study of Lenalidomide for Previously Untreated Non-M3, Deletion 5q Acute AML in Patients age 60 or Older Who Decline Remission Induction Chemotherapy. SWOG 0605.
8/2008-11/2010	**Principal Investigator:** A Phase IIb Study of Molecular Responses to Imatinib at Standard or Increased Doses for Previous Untreated Patients with CML in the Chronic Phase. SWOG 0325.
8/2008-9/2009	**Principal Investigator:** A Phase II Study of ATRA, Arsenic Trioxide and Gentuzumab Ozogamicin in Patients with Previously Untreated High Risk Acute Promyelocytic Leukemia. SWOG 0535.
8/2008-5/2023	**Principal Investigator:** Lung Cancer Specimen Repository Protocol, Ancillary. SWOG 9925
8/2008-5/2012	**Principal Investigator:** Phase III Chemo-Prevention Trial of Selenium Supplementation in Patients with Resected Stage I NSCLC. SWOG E5597.

8/2008-11/2009	**Principal Investigator:** A Pilot Phase I Study of Weekly Docetaxel and Cetuximab Chemo radiation for Poor Risk Stage III NSCLC. SWOG 0429.
8/2008-10/2009	**Principal Investigator**: Phase II Trial of combination of OSI-774 (Erlotinib) and Bevacizumab in Never Smokers with Stage IIIb and IV Primary Lung Adenocarcinoma. SWOG 0636.
7/2008-10/2009	**Principal Investigator:** Phase II Trial of Combination of OSI-774 (Erlotinib) and Bevacizumab in Stage IIIB and IV Bronchoalveolar Carcinoma and Adenocarcinoma with MAC Features. SWOG 0635
9/2008-5/2012	**Principal Investigator:** Central Lymphoma Serum Repository Protocol. SWOG 8947.
8/2009-9/2011	**Principal Investigator**: A Phase III Trial of CHOP + Rituxumab vs. CHOP +Iodine-I131-Labelled Monoclonal Anti-B1 Antibody (Tositumomab) for Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphoma. SWOG 0016.
8/2009-9/2011	**Principal Investigator:** Evaluation of CHOP Plus Involved Field Radiotherapy followed by Yttrium-90 Ibritumomab Tiuxentan for Stage I, IE and non-bulky Stage II and IIE Positive, High Risk Localized Histologies of NHL. SWOG 0313.
11/2008-5/2010	**Principal Investigator:** Gemcitabine and Cisplatin in Treating Patient with Stage I Non-small cell lung Cancer that was Removed by Surgery. SWOG.
9/2008-11/2009	**Principal Investigator:** Phase II Trial of Standard Dose Cyclophosphamide, Doxorubicin, Vincristine, prednisone (CHOP) and Rituximab plus Bevacizumab for Advanced Stage DLBCL. SWOG 05154.
2/2008-6/2010	**Principal Investigator**: Gemcitabine and Erlotinib with or without Monoclonal Antibody Therapy in Treating Patients with Metastatic Pancreatic Cancer that Cannot be Removed by Surgery. SWOG.
9/2008-5/2009	**Principal Investigator:** Phase II Study of PXD101 in Relapsed and Refractory Aggressive B-Cell Lymphoma. SWOG 50520
9/2008-3/2011	**Principal Investigator:** Phase III Randomized Study of Four weeks of High Dose IFN-alpha2B in Stage T2b, N0, T3a-bN0 and T1-4,N1a, 2a, 3 (microscopic) Melanoma. SWOG E1697.
9/2009-8/2020	**Principal Investigator**: Phase II Trial of BAY 43-9006 in combination with Carboplatin and Paclitaxel in Patients with Metastatic Uveal Melanoma. SWOG 0512.
4/2008-7/2009	**Principal Investigator**: Azacitidine and Gemtuzumab in Treating Older Patients with Previously Untreated AML. SWOG.
9/2009-5/2012	**Principal Investigator:** Myeloma Specimen Repository Protocol. SWOG 0309
6/2009-5/2012	**Principal Investigator**: Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extra Hepatic Cholangiocarcinoma. SWOG 0809.
6/2009-5/2012	**Principal Investigator:** Phase III Randomized Study of Imatinib with or without Bevacizumab in Patients with Metastatic or Unresectable GIST. SWOG 0502.
8/2008-11/2010	**Principal Investigator**: Phase II Study of the Efficacy of Amifostine in Reducing the Incidence and Severity of oxaliplatin-induced Neuropathy in Patients with Colorectal Cancer. Sponsored by Medimmune.
06/2009-7/2010	**Principal Investigator:** A Pilot Phase I Study of Weekly Docetaxel and Cetuximab Chemo Radiation of Poor Risk Small Cell Lung Cancer. SWOG 0429.
6/2009-7/2010	**Principal Investigator:** A Pilot Phase I Study of Weekly docetaxel and Cetuximab Chemo Radiation of Poor Risk Stage III NSCLC. SWOG 0429
6/2009-5/2012	**Principal Investigator**: Collecting and Sorting Blood Samples from Patients with Previously Untreated Non-Hodgkin's Lymphoma. SWOG.
6/2009-5/2012	**Principal Investigator**: Collecting and Storing Blood and Bone Marrow Samples from Patients with Hematologic Cancers. SWOG.
1/2009-3/2010	**Principal Investigator:** Topotecan with or without Aflibercept in Treating Patients with Extensive Stage Small Cell Lung Cancer. SWOG.
6/2009-5/2012	**Principal Investigator**: Collecting and Storing Blood and Bone Marrow Samples from Patients with Myeloma, Waldenstroms Macroglobulinemia, Amyloidosis or Monoclonal Gammopathy of Undetermined significance. SWOG.
1/2009-3/2010	**Principal Investigator**: Topotecan with or without Aflibercept in Treating Patients with Extensive Stage Small Cell Lung Cancer. SWOG.
4/2009-1/2012	**Principal Investigator**: Osteonecrosis of the Jaw in Patients with Cancer Receiving Zoledronic Acid for Bone. SWOG.
2/2009-4/2011	**Principal Investigator:** Dasatinib in Treating Patients with Stage IV Breast Cancer that has Spread to the bones. SWOG.
6/2009-7/2010	**Principal Investigator:** A Randomized Phase III Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX-GM-CSF Compared to Subcutaneous Administration of GM-CSF in Previously Treated Melanoma Patients with Unresectable Stage 3b, 3c and 4 Disease. Sponsored by BIOVEX.
2/2012-5/2012	**Principal Investigator:** A Randomized Phase II Trial of BAY 43-9006 with either CCI-779 or R1I5777 (tipifarnib) Metastatic Melanoma. SWOG S0438.
10/2010-5/2012	**Principal Investigator**: Randomized Placebo-Controlled Trial of Acetyl L-Carnitine for the Prevention of Taxane Induced Neuropathy. SWOG S0715.
10/2010-5/2012	**Principal Investigator**: Phase II Studies of Two Different Schedules of Dasatinib in Bone-Metastasis Predominantly Metastatic Breast Cancer. SWOG 0622.
10/2010-5/2012	**Principal Investigator:** A Randomized Phase III Trial to Test the Strategy of Changing Therapy vs. Maintaining Therapy for Metastatic Breast Cancer Patients who have Elevated Circulating Tumor cell Levels at First Follow-up Assessment. SWOG 0500.

10/2010-5/2012	**Principal Investigator:** Phase III Trial of Irinotecan-Based Chemotherapy plus Cetuximab with or without Bevacizumab as Second Line Therapy for Patients with Metastatic Colorectal Cancer who have Progressed on Bevacizumab with either FOLFOX, Optimox or Xelox. SWOG 0600.
10/2010-5/2012	**Principal Investigator**: CHAARTED: Chemo Hormonal Therapy vs. Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer. CTSU E3805.
2/2010-5/2012	**Principal Investigator**: A Randomized, Double-Blind. Phase III Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer that have Received Prior Treatment with Docetaxel. BMS-CA184-043.
5/2010-5/2012	**Principal Investigator:** A Phase II Trial of Azacitidine plus Gemtuzumab as Induction and Post-Remission Therapy in Patients older than 60 and older with Previously Untreated non-M3 Acute Myeloid Leukemia. SWOG.
10/2010-5/2012	**Principal Investigator:** Phase II ERCC1 and RRMI-Based Adjuvant Therapy Trial in Patients with Stage I Non-Small Cell Lung Cancer. SWOG 0720.
10/2010-5/2012	**Principal Investigator**: A Randomized Phase II Trial of Weekly Topotecan with and without AVE005 in Patients with Platin-Treated Extensive Stage Small Cell Lung Cancer. SWOG 0820.
9/2011-5/2012	**Principal Investigator:** Treatment Decision Making Based on Blood Levels of Tumor Cells in Women with Metastatic Breast Cancer Receiving Chemotherapy. SWOG S0500.
11/2011-5/2012	**Principal Investigator:** Chemotherapy with or without Bevacizumab in Treating Patients with Stage IB , Stage II or Stage IIIa Non-Small Cell Lung Cancer that was Removed by Surgery. SWOG E1505.
11/2011-5/2012	**Principal Investigator:** Study of Bone Marrow and Blood Samples from Patients with Leukemia or Other Hematopoietic cancers. SWOG S9007.
3/2011-5/2012	**Principal Investigator:** Erlotinib with or without Carboplatin and Paclitaxel in Treating Patients with Stage IIIB or Stage IV NSCLC. SWOG S0709.
11/2011-5/2012	**Principal Investigator:** Gemcitabine after Surgery in Treating Patients with Newly diagnosis or Recurrent Bladder Cancer. SWOG S9910.
10/2011-5/2012	**Principal Investigator**: Tamoxifen Citrate, Letrozole, Anastrozole, or Exemestane with or without Chemotherapy in Treating Patients with Invasive RxPONDER Breast Cancer. SWOG S1007.
7/2011-5/2012	**Principal Investigator**: Carboplatin and Paclitaxel with or without Bevacizumab and/or Cetuximab in Treating Patients with Stage IV or Recurrent Non-Small Cell Lung Cancer. SWOG S0819.
6/2011-5/2012	**Principal Investigator**: Radiation Therapy in Treating Women who have undergone Surgery for Ductal Carcinoma in Situ for Stage I or Stage II Breast Cancers. SWOG-NSABP-B-39.
4/2011-5/2012	**Principal Investigator**: Capecitabine, Gemcitabine and Radiation Therapy in Treating Patients with Cholangiocarcinoma of the Gallbladder or Bile Duct. SWOG S0808.
6/2011-5/2012	**Principal Investigator:** R04929097 in Treating Patients with Stage IV Melanoma. SWOG S0933.
5/2011-5/2012	**Principal Investigator**: Epratuzumab, Cytarabine and Clofarabine in Treating Patients with Relapsed or Refractory Acute Lymphoblastic leukemia. SWOG 50910.
7/2011-5/2012	**Principal Investigator**: Hormone Therapy With or Without Combination Chemotherapy in Treating Women who have Undergone Surgery for Node-Negative Breast Cancer (THE TAILORx Trial). SWOG/INTERGOURP CDR0000472066, ECOG-PACCT-1
9/2011-5/2012	**Principal Investigator:** Study of Palifosfamide-tris in Combination with Doxorubicin in Patients with Front-Line Metastatic Soft Tissue Sarcoma. Ziopharm IPM30091.
10/2011-5/2012	**Principal Investigator**: A Phase III Randomized Study of Adjuvant Ipilimumab anti-CTLA4-therapy vs. High Dose IFN for Resected High Risk Melanoma. CTSU E1609
12/2011-5/2012	**Principal Investigator:** A Phase III blinded study of immediate post-TURBT Instillation of Gemcitabine vs. Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer. SWOG S0337.
2/2011-5/2012	**Principal Investigator**: A Randomized Double blind Phase III study comparing Gemcitibine, cisplatin and Bevacizumab to Gemcitibine cisplatin and placebo in patients with advanced TCC. CALGB 90601

Report of Local Teaching and Training

Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs)

7/1994-5/1998	Biology of Cytokines and Clinical Management of Patients receiving High dose IL-2	monthly
9/2003-5/2012	Management of Patients receiving high Dose IL-2	quarterly

Clinical Supervisory and Training Responsibilities

7/1993-6/1998	Montefiore Hospital Fellows' Hematology/Oncology Clinic	Supervised one day per week
9/2003-5/2012	University Cincinnati Hospital Ward Attending	4 months/year
9/2003-5/2012	University of Cincinnati Consult Attending	3 months/year
9/2005-5/2012	Cincinnati VA Hematology/Oncology Clinic Supervisor	2 months per year
8/2012-4/2013	University of Saint Louis Hospital Ward Attending	3 months per year
8/2012-4/2013	University of Saint Louis Hospital Consult Attending	3 months per year

Laboratory and Other Research Supervisory and Training Responsibilities

6/93-6/98	Supervised 2 high school seniors' basic lab projects, 1 post-doc with basic science skills, and 4 medical oncology fellows (see below)	Daily laboratory supervision

Formally Supervised Trainees

6/1993-8/1993	**Priya Kota**: Forest Hill High School. Summer Research Intern. Minority High School Apprentice Program. IL-6 platelet functional studies. Completed project submitted for Westinghouse Award.
4/1994-6/1995	**Dina Zuckerman, Ph.D.**: Post-Doc Fellow. Tumor-Platelet Adhesive Studies: Expression of platelet Immunorelated GP1b□ by tumor cells. Multiple papers published (see list of publications)
7/1994-6/1995	**Yelana Novik, M.D.**: Second Year Oncology Fellow. Laboratory Research: IL-3 and IL-11 Effects on Platelet function, in vitro and in vivo studies. Published several abstracts and paper.
6/1995-8/1995	**Sandra Bazelaise:** DeWitt Clinton High School. Summer Research Intern. Minority High School Apprentice Program. Studies of tumor-induced platelet aggregation using whole blood as a substrate.
6/1995-8/1995	**Jung-Gon Suh, M.D.:** Second Year Oncology Fellow. Clinical Elective, Intensive Training on IL-2/Cytokine service. Clinical project: A review of Dermatologic toxicities associated with IL-2 administration.
2/1997-7/1998	**Niyati Bhagwati, M.D.:** Second Year Oncology Fellow. Laboratory Research: The Expression of GPIbα by human breast carcinoma specimens. Published several papers.
7/1997-6/1998	**Machour Yousef, M.D.:** Third Year Oncology Fellow. Laboratory Research: The Expression of GPIbα by Blasts from patients with acute leukemia. Published abstract.
11/1997-6/1998	**Harry Deshpandi, M.D.**: Second Year Oncology Fellow. Clinical Research: A Retrospective In-House Analysis and correlation of IL-2 dose intensity in combination bio-chemotherapy protocols and response rates.
2/2006-2/2008	**Irum Khan, M.D.** Second Year Medical Resident. Supervised preparation of resident clinical vignette for presentation at University Hospital and abstract for Ohio chapter of American College of Medicine 10/07 on the topic of mature mediastinal teratoma in Kleinfelters syndrome.
2010	**Sadia Ali, M.D.** Supervised preparation of Abstract for Presentation at American Endocrine Society, "Uneventful pregnancy after incidental mitotane exposure". Abstract was selected for presentation at the Endocrine Society's 92nd annual Meeting and Exposition.

Formal Teaching of Peers (e.g., CME and other continuing education courses)

11/6/ 2004	Annual Greater Cincinnati Prostate Cancer Forum presented by the Barrett Cancer Center	Conference panelist
3/25/2006	University of Cincinnati Cancer Education, Knowledge for Life, "Prostate Cancer: Frequently asked questions and answers".	Conference panelist
7/22/2006	First Annual University of Cincinnati Genitourinary Symposium: "Novel Targeted Therapies for the Treatment of Genitourinary Malignancies'.	Course Director
7/21/2007	Second Annual university if Cincinnati Genitourinary symposium: "Overview of Novel Targeted Therapies for the Treatment of Genitourinary Malignancies".	Course Director and Speaker
7/26/2008	Third Annual University of Cincinnati Genitourinary Symposium: New Directions in the Treatment of Genitourinary Malignancies. Dr. Oleksowicz: Course Director and speaker, presenting "Overview of Targeted Therapies"	Course Director and Speaker
7/26/2009	Fourth Annual University of Cincinnati Genitourinary Symposium: Evolving Treatment Paradigms for Genitourinary Malignancies. Dr. Oleksowicz: Course Director and Speaker. Presenting "Review of New Targeted Agents for the Treatment of Advanced Renal Cell Carcinoma".	Course Director and Speaker
2/17/2007	University of Cincinnati Community Cancer Education Day- Knowledge for Life. Dr. Oleksowicz on "Prostate Cancer: Frequently Asked Questions and Answers".	Conference panelist
9/10/1999	Medical Oncology Syllabus Review Lecture, "Metastatic Melanoma".	Lecturer

Roswell Park Cancer Institute. Buffalo, New York

Local Invited Presentations

8/1/1991	Medical Research Seminar, "Mechanisms of Anti-Tumor Activity of IL-2 and IL-6: The Relationship Between the Hemostasis and Immune Systems". Vermont Comprehensive Cancer Center, Burlington, VT.
9/5/1991	Oncology Research Seminar, "Mechanisms of Anti-Tumor Activity of IL-2 and IL-6: The Relationship Between the Hemostatic and Immune systems". Winthrop-University Hospital, Minneola, N.Y.
2/21/1994	Symposium sponsored by Sandoz Pharmaceuticals. "Mechanisms of anti-tumor activity of IL-2 and IL-6. The Relationship between the Hemostatic and Immune Systems". East Hanover, N.J.
12/10/1994	Medical Grand Rounds, "Platelet Activation Induced by IL-6: Evidence for a Mechanism Involving Arachidonic Acid Metabolism". Montefiore University Hospital, Bronx, N.Y.
12/20/1994	Oncology Grand Rounds, "The Effect of IL-6 on Platelet Function: *In Vitro* and *In vivo* Studies." Montefiore Hospital, Bronx, New York.
2/7/1995	Guest Lecturer, "The Role of Platelets in the Metastatic Process." February 1995. Carol Solar Abbani Foundation Annual Meeting, New York, N.Y.
3/15/1995	Oncology Grand Rounds, "Autologous Immunomodulation." March 1995. Department of Oncology, Montefiore Hospital, Bronx, New York.
5/6/1995	Oncology Grand Rounds, "Cytokine Interactions among Hematopoietic Cells." May 1995. Weiler Hospital of the Albert Einstein College of Medicine, Bronx, N.Y
1/29/1996	Guest Lecturer, "Characterization of Immunorelated GPIb Expression by Myelogenous Leukemia Cells." National Leukemia Research Association Annual New York Chapter Meeting, Garden City, N.Y.
1/20/1997	Hematology Grand Rounds, "Human Breast Carcinoma Cells Synthesize a Protein Immunorelated to Platelet GPIbα with Different Functional Properties". Montefiore Hospital, Division of Hematology, Bronx, N.Y.
4/22/1997	Hematology Grand Rounds, "Human Breast Carcinoma Cells Synthesize a Protein Immunorelated to Platelet GPIbα with Different Functional Properties". Mount Sinai Hospital, Division of Hematology, New York, N.Y.
4/13/1997	Oncology Grand Rounds, "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal cell carcinoma", Stanley S. Scott Cancer Center, LSUMC, New Orleans, LA
9/5/1997	Research Seminar, "High-Dose Bolus Interleukin-2: A Forth Treatment Modality for Advanced Renal Cell Carcinoma". F. Lee Moffitt Cancer Center, Tampa, FL.
2/26/1998	Clinical Research Seminar, "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal Cell Carcinoma". Ireland Cancer Center of the Case Western Reserve university. Division of Hematology/Oncology, Cleveland, OH
4/19/1998	Oncology Grand Rounds, "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal Cell Carcinoma". University of Minnesota, Division of Transplant, Hematology and oncology, Minneapolis, MN.
5/2/1998	Cadenza Foundation Invited Guest Lecture, "Human Breast Carcinoma Cells Synthesize a Protein Immunorelated to platelet GPIbα with Different Functional Properties. Thomas Jefferson School of Medicine, Philadelphia, Pennsylvania.
6/5/1998	Oncology Grand Rounds, "High-Dose Bolus Interleukin-2: A Fourth Treatment modality for Advanced Renal Cell Carcinoma". Department of Medicine, Roswell Park Cancer Institute. Buffalo, N.Y.
2/7/1999	Chiron-Sponsored Seminar. "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for advanced renal cell carcinoma. Buffalo, New York
5/27/1999	Hematology/Oncology Grand rounds. "High Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal Cell carcinoma". Syracuse University, Syracuse, N.Y.
8/9/1999	Basic Seminar: "The Role of Tumor GPIb and Plasma von Willebrand's Factor in Adhesive Interactions Regulating Metastasis Formation". Roswell Park Cancer Institute, Grace Cancer Drug Center; Buffalo, N.Y.
9/10/1999	Medical Grand Rounds, "The Role of Tumor GPIb and Plasma von Willebrand's Factor in Adhesive Interactions Regulating Metastasis Formation". Roswell Park Cancer Institute. Buffalo, N.Y.
4/18/2001	Medical Grand Rounds. "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal Cell Carcinoma." Erie County Medical Center, Department of Urology, Buffalo, New York.
3/12/2003	Medical Grand Rounds. "High-Dose Bolus Interleukin-2: A Fourth Treatment Modality for Advanced Renal cell Carcinoma". Milton S. Hershey Cancer Center, Hershey, PA
4/17/2003	Division of Hematology/Oncology Grand Rounds, "High Dose Bolus Interleukin-2: A Forth Treatment Modality for Advanced Renal cell Carcinoma". University of Cincinnati, Cincinnati OH.
4/25/2003	Division Seminar "Treatment Modalities for Advanced Renal Cell Cancer." University of Cincinnati Medical Center. Cincinnati, OH.
2/11/2004	Department of Radiation Oncology Grand Rounds, "An Overview of High Dose IL-2 & New Therapeutic Treatment Modalities for Advanced Renal Cell Carcinoma". Barrett Cancer Center, University of Cincinnati, Cincinnati, OH
2/13/2004	Division of Hematology/Oncology Grand Rounds, "An Overview of High Dose IL-2 and New Therapeutic Modalities for the Treatment of Advanced Renal Cell Carcinoma". University of Cincinnati medical Center, Cincinnati OH
2/18/2004	Department of Surgery Grand Rounds at Cincinnati University Hospital, "Overview of the medical genitourinary Oncology Program at University Hospital". University of Cincinnati, Cincinnati, OH
7/14/2004	Department of Internal Medicine Grand Rounds. University of Cincinnati Medical Center. "An Overview of High Dose IL-2;

	New Therapeutic Treatment Modalities for Advanced Renal Cell Carcinoma". University of Cincinnati, Cincinnati, OH
8/6/2004	Division of Hematology/Oncology Grand Rounds. Fellow and Resident Lecture Series: "Up-Date on Prostate Cancer Management and New Approaches to Treatment." University of Cincinnati, Cincinnati, OH.
11/17/2004	4th Annual Greater Cincinnati Prostate Cancer Forum, "Treatments for Hormone Resistant Prostate Cancer". Cincinnati Marriot Northeast , Mason, OH.
6/5/2005.	Division of Hematology/Oncology Grand Rounds, American Society of Clinical Oncology Annual Meeting Proceedings. "Update on the Treatment and Management of Renal Cell Carcinoma". University of Cincinnati, Cincinnati, OH
12/6/2005	Prostate Cancer Working Group Symposium. 12/05. "The Role of Chemotherapy in advanced Prostate Cancer". Kingsgate Marriott Conference Center, Cincinnati, OH
6/15/2006	Division of Medicine Departmental Meeting. June 2006. "An Overview of High Dose Interleukin-2 and New Therapeutic Modalities for the Treatment of Advanced Renal Cell Carcinoma". University of Cincinnati, Cincinnati, OH
8/10/2006	Division of Hematology/Oncology Grand Rounds. Fellow and Resident Lecture Series: "Up-date on Prostate Cancer Management. New Approaches to Treatment". University of Cincinnati, Cincinnati, OH.
8/22/2006	Division of Hematology/Oncology Grand Rounds, "Management of High Dose IL-2". University of Cincinnati, Cincinnati, OH
8/28/2007	Division of Hematology/Oncology Grand Rounds. Fellow and Resident Lecture Series. "Review of Prostate Cancer Management and New Approaches to Treatment". University of Cincinnati, Cincinnati, OH
9/5/2007	Division of Hematology/Oncology Grand Rounds, "High Dose IL-2 Management for Renal Cell Carcinoma. Identifying Appropriate Candidates for Treatment". University of Cincinnati, Cincinnati, OH.
9/14/2007	Division of Hematology/Oncology Grand Rounds. Fellow and Resident Lecture Series. "Review of Prostate cancer Management and New Approaches to Treatment". University of Cincinnati, Cincinnati, OH
9/19/2007	Division of Urology Grand Rounds, "An Overview of New Therapeutic Modalities for the Treatment of Metastatic Renal Cell Carcinoma". University of Cincinnati, Cincinnati, OH
5/3/2008	Overview of Prostate and RCC. Speaker at University of Cincinnati Community Cancer Education day. University Point, West Chester,. OH
6/22/2008	Hematology/Oncology Grand Rounds. Division of Hematology/Oncology Grand Rounds, "Current Trends in the Treatment of Advanced Melanoma". University of Cincinnati, Cincinnati, OH
9/5/2009	Grand Rounds Division of Hematology/Oncology: "Clinical Management of High Dose Interleukin-2". University of Cincinnati, Cincinnati, OH
8/20/2009	Faculty Speaker for Regional GU Symposium, "Evaluating and Treating Genitourinary Malignancies, Evolving Treatment Paradigms in Advanced Renal Cell carcinoma". Cincinnati Marriott in Mason OH
11/18/2009	Urology Grand Rounds. University of Cincinnati. "Prostate Cancer Up-Date". University of Cincinnati, Cincinnati, OH
9/11/2010	Grand Rounds, Division of Hematology/Oncology. "New Clinical Strategies for the Treatment of Prostate Cancer". University of Cincinnati, Cincinnati, OH
2/10/11	Genitourinary Research 2011 Symposium. 2/10/2011. "Dose Intensity High dose Interleukin-2: A Strategy for Improved Patient Outcomes." Kingsgate Marriot, University of Cincinnati, Cincinnati, OH
3/8/2012	Hematology/Oncology Rounds. "Evolving Treatment Paradigms in Renal Cell Carcinoma". Saint Louis University, St. Louis, MO
4/25/2012	Hematology/Oncology Grand Rounds at Mayo Clinic. "Metastatic Melanoma: New paradigms for Targeted Treatment". Scottsdale, AZ
5/17/2011	Dinner Lecture sponsored by Prometheus: "Overview of High Dose Interleukin-2 in the Age of Targeted Therapy". Cincinnati, OH
5/18/2012	Faculty Lecture Series. "Management of Testicular Tumors: A Standard for Success with Cytotoxic Chemotherapy", University of Cincinnati, Cincinnati, OH
6/5/2012	Dinner Lecture sponsored by Prometheus: "Evolving Treatment Paradigms in Renal Cell Carcinoma". Louisville KY
6/6/2012	Dinner Lecture sponsored by Prometheus: "Evolving Treatment Paradigms in Renal Cell Carcinoma", Lexington, KY.
10/9/2012	Hematology/Oncology Grand Rounds. "New Clinical Strategies for the Treatment of Prostate Cancer". Saint Louis, MO
1/20/2013	Dinner lecture sponsored by Medivation. "Enzalutamide, A New Therapeutic Option for Patients with Metastatic Prostate Cancer. Cape Girardeau, MO.
2/13/2013	Hematology/Oncology Grand Rounds. New Treatment Paradigms for Advanced Melanoma". Saint Louis MO.

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

Regional

2/1999	Second Annual Regional Cancer Center Consortium for Biologic Therapy of Cancer. "Thirty-Two-Month Follow-up Analysis of a Phase II Trial of Dose-Intensive Interleukin-2 in Metastatic Renal Cell Carcinoma." February 1999. Rochester, N.Y.
10/1999	Cancer Genetics Regional Conference. "The Role of Tumor GPIb and Plasma Von Willebrands Factor in Adhesive

Interactions Regulating Metastasis Formation". Buffalo, N.Y.

National

4/1994	Annual Meeting of the American Association for Cancer Research, "Characterization of IL-6 Effects on Platelet Activation and Functional Properties in Phase I clinical Trials". San Francisco, CA
12/1997	Annual meeting of the American Society of Hematology, "Breast Carcinoma GPIbα-Related Protein is Regulated by a PKC Sensitive Mechanism". San Diego, CA
12/1998	Annual Meeting of the American Society of Hematology "Elevated Levels of Highly Polymeric Forms of von Willibrands Factor are Associated with Disseminated Malignancies". Miami, FL

International

7/1993	International Society of Hematology, "Functional Platelet Aberrations in Patients Receiving IL-2 as Immunotherapy. New York, N.Y.

Report of Clinical Activities

Practice Activities

8/92-7/98	High Dose IL-2 Service	Montefiore Hospital	3 days/week
9/98-6/03	Ward Attending	Roswell Park	One week every month
9/98-6/03	Clinic Attending	Roswell Park	3 days/week
9/98-6/03	High dose IL-2 Service	Roswell Park	4 days/week
9/03-5/12	Ward Attending	University Hospital (Cincinnati)	4 months/year
9/03-5/12	Consult Attending	University Hospital (Cincinnati)	4 months/year
9/03-5/12	Clinic Attending	University Hospital (Cincinnati)	3 days/week
9/03/5/12	High dose IL-2 Service	University Hospital (Cincinnati)	7 days/week
8/12-4/13	Ward Attending	Saint Louis University Hospital;	4 months per year
8/12-4/13	Consult Attending	Saint Louis University Hospital	4 months per year
8/12-4/13	Clinic Attending	Saint Louis University Hospital	3 days/week

Report of Education of Patients and Service to the Community

Activities

2/7/2004	The Wellness Community of Cincinnati. Invited Guest Lecture." Up-Date on Novel Treatments for Advanced Renal Cell Carcinoma". 4918 Cooper Road, Blue ASH, OH
5/20/2006	Prostate Cancer Networking Group of the Wellness Community of Greater Cincinnati. "Novel and Emerging Treatments for Prostate Cancer". 4918 Cooper Road, Blue ASH, OH
9/19/2009	The Wellness Community of Cincinnati. Invited Guest Lecture. "Innovative Cancer Treatments". 4918 Cooper Road, Blue ASH, OH
2/11/2011	The Wellness Center at Blue Ash. "Targeted Anti-tumor Therapies: a New Paradigm for Successful Cancer Treatment". 4918 Cooper Road Blue Ash, OH
10/9/2012	Saint Louis Cancer Center Support Group Lecture Series. "New Discoveries in Cancer". Saint Louis, MO

Recognition

11/2002	Certificate of recognition	Roswell Park	Excellence in clinical practice

Report of Scholarship

Publications

Oleksowicz L, Bruckner HW: Prophylaxis of 5-Fluorouracil-Induced Coronary Vasospasm with Calcium Channel Blockers. *American Journal of Medicine.1988; 85:750-751.*

Oleksowicz L, Morris JC, Phelps RB, Bruckner HW: Pulmonary Carcinoid Presenting as Multiple Subcutaneous Nodules. *Tumori 1990;* 76: 44-47.

Paciucci PA, Mandeli J, **Oleksowicz L**, Holland JF: Thrombocytopenia During Immunotherapy with IL-2 by constant Infusion. *American*

journal of Medicine 1990; 89: 308-312.

Oleksowicz L, Paciucci PA, Zuckerman D, Colorito A, Rand JH, Holland JF: Alterations of Platelet Function Induced by IL-2. *Journal of Immunotherapy 1991;10: 363-370.*
Oleksowicz L, Zuckerman D, Lomazova KD, Burychkafska LE, Astrina OC, Slavina EG: The Role of Interleukin-2 and Mononuclear Cells in Platelet Tumor Interactions. *Invasion and Metastasis*.1993; 13: 119-131.
Oleksowicz L, Zuckerman D, Puszkin E, Dutcher JP: Effects of Interleukin-2 Administration on Platelet Function in Cancer Patients. *American Journal of Hematology 1994; 45: 224-231.*
Oleksowicz L, Mrowiec Z, Zuckerman D, Isaacs R, Dutcher JP, Puszkin E: Platelet Activation Induced by IL-6: Evidence for a Mechanism Involving Arachidonic Acid Metabolism. *Thrombosis and Haemostasis* 1994:72:302-308.
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Oleksowicz L, Mrowiec Z, Isaacs R, Dutcher JP, Puszkin E: Morphologic and Utrastructural Evidence for IL-6 Induced Platelet Activation. American Journal of Hematology 1995; 48:92-99.
Mrowiec ZR, **Oleksowicz L**, Dutcher JP, DeLeon-Fernandez M, Lalezari P, Puszkin EG: A Novel Technique for Preparing Improved Buffy Coat Platelet Concentrates. *Blood Cells, Molecules and Diseases*,1995; 21: 25-33.
Oleksowicz L, Mrowiec Z, Schwartz E, Khorshidi M, Dutcher JP, Puszkin E: Characterization of Tumor-Induced Platelet-Aggregation: The Role of Immunorelated GPIb and GPIIb/IIIa Expression by MCF-7 Breast Cancer Cells. Thrombosis Res 1995; 79: 261-274.
Weiss GR, Margolin KA, Sznol M, Atkins MB, **Oleksowicz L**, Isaacs R, Fisher RI: A Phase II Study of a 120-hour Continuous Intravenous Infusion of Interleukin-6 for Metastatic Renal Cell Carcinoma. *J of Immunother* 1995; 18: 52-56.
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EXHIBIT B

Exhibit	Description
1001	U.S. Patent No. 8,329,680
1002	File History For U.S. Patent No. 8,329,680
1005	McLeskey *et al.*, "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors," CLIN. CANCER RESEARCH 4:697–711 (1998) ("McLeskey")
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1008	Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential," 51 CANCER RESEARCH 3867–3873 (1991) ("Wakeling 1991")
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1012	A. Howell, "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer," LANCET 345: 29–30 (1995) ("Howell 1995")
1013	O'Regan et al., "Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth," 90 J. NAT'L CANCER INST. 1552–1558 (1998) ("O'Regan 1998")
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1038	Rodger & King, "Drawing up and administering intramuscular injections: a review of the literature," 31(3) J. ADVANCED NURSING 574–582 (2000) ("Rodger & King")
1039	Machholz et al., "Manual Restraint and Common Compound Administration Routes in Mice and Rats," 67 J. VISUALIZED EXPERIMENTS 1–8 (2012) ("Machholz")