UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, LLC

Petitioner

v.

ASTRAZENECA AB

Patent Owner

Case IPR2017-00900

U.S. Patent 8,329,680 B2

DECLARATION OF JOHN F. R. ROBERTSON, M.D. IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

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I, John F. R. Robertson, M.D., do hereby make the following declaration:

I) INTRODUCTION

1. I am over the age of eighteen and competent to make this declaration.

2. I have been retained as an expert witness on behalf of AstraZeneca AB for the above-captioned *inter partes* review (IPR). I am being compensated at my customary rate of £600 per hour for my consultation in connection with this matter. My compensation is in no way dependent on the outcome of my analysis or opinions rendered in this matter. A copy of my curriculum vitae, which includes my academic background, work experience, and select publications and presentations, is attached to this declaration as Exhibit A.

II) QUALIFICATIONS AND EXPERIENCE

3. My name is John Robertson, M.D. I am a physician specializing in breast cancer and surgery, and I have Specialist Accreditation in General Surgery. I trained and have worked as a general surgeon, focusing primarily on breast cancer, for thirty-five years, through which I have acquired extensive clinical experience in breast disease. Since August 1998, I have been Professor of Surgery at the University of Nottingham, initially based at the City Hospital, Nottingham (1988 - 2011) and then based at the Royal Derby Hospital, Derby (2011 - present). Prior to that, since 1992, my appointments included Senior Lecturer and Reader in Surgery, both based at the City Hospital, Nottingham. I

have clinical experience across the continuum of breast care, from preventive care for high risk patients and routine screening, to diagnosis and treatment of primary breast cancer, to diagnosis and treatment of locally advanced and metastatic disease, to palliative care.

4. I received my M.B. Ch.B. (Bachelor of Medicine, Bachelor of Surgery), B.Sc. (Bachelor of Science) and M.D. (in the UK, a postgraduate research degree in medicine) all from the University of Glasgow. I also was awarded F.R.C.S. (Fellowship of the Royal College of Surgeons) by the Royal College of Physicians and Surgeons of Glasgow.

5. My knowledge concerning the treatment of breast cancer, more specifically hormonal dependent breast cancer, and the use of hormone (i.e., endocrine) therapies has been gained through my training and personal and professional experiences. More specifically, these experiences include my own medical practice for over thirty-five years, research that I have conducted (both laboratory research and clinical trial research), consultancy positions I have held, and advisory boards and committees that I have served on or been a member of. In my medical practice, I have gained extensive experience over the last thirty-five years with every class of approved endocrine agent used to treat hormonal dependent breast cancer. Over my career, I have treated thousands of women with hormone dependent breast cancer.

6. In terms of research, I have been involved in both laboratory research and clinical trials of all major classes of new endocrine therapies in hormonal dependent breast cancer over thirty years. I have consulted for and served on or chaired advisory boards to major pharmaceutical companies researching and developing drugs for hormonal dependent breast cancer.

7. One of my major clinical and laboratory research interests is breast cancer, particularly hormonal dependent, or hormone receptor positive, breast cancer and the role of endocrine therapy. I have also had a focus on advanced disease—both locally advanced and metastatic breast cancer. As a surgical oncologist with both a major clinical and laboratory interest in endocrine and growth factor therapies, I find myself in a central position providing a link between surgical and non-surgical (clinical and medical) oncologists, which ensures seamless continuity of care for patients and a rich base from which clinical and laboratory research can proceed. At the University of Nottingham, my group's interest in systemic therapies has placed it at the vanguard of surgical units performing pre-surgical ("window of opportunity") studies which allows us to combine our skill sets in surgery and systemic therapies into a translational research program investigating biological changes in breast cancers, which matches our therapeutic clinical trials in advanced disease. I am currently one of the three Chief Investigators on the largest trial of peri-operative endocrine

therapy in the world (the POETIC trial). I have been Chief Investigator, or local Principal Investigator, in a large number of multicenter trials for new drugs produced by a variety of pharmaceutical companies including AstraZeneca, Novartis, Amgen, GlaxoSmithKline, Schering, and Bayer.

8. I have published extensively in the field of cancer, principally, although not exclusively, on topics related to cancer of the breast with a particular focus on hormonal dependent breast cancer and endocrine therapies. I currently have over 300 peer-reviewed publications. I have also published book chapters on the treatment of breast cancer and a book titled, Endocrine Therapy of Breast Cancer.

9. I have attended, over the last thirty years, a large number of professional oncology conferences, with a primary focus on breast cancer. I have presented at a number of professional conferences regarding my research related to breast cancer. In addition to presenting laboratory and clinical trial research, I have given invited lectures at both national and international conferences. I am frequently invited to lecture at international cancer meetings. Between 2009 and September 2016, I gave invited lectures at fifty-five international cancer meetings, often giving multiple lectures at a single meeting. One of the major topics of invited lectures has been the treatment of breast cancer and the use of hormone therapies, otherwise known as endocrine therapies.

10. I am a member of several learned societies, including: the Society of Academic and Research Surgery, the British Association of Surgical Oncology, the Association of Breast Surgery, and the British Association of Cancer Research. I am also a member, or have been a member, of several scientific committees as well as committees affiliated with universities and health care centers. I have reviewed manuscripts for a number of journals and was the founding Editor-in-Chief of the journal, Breast Cancer Online.

11. I have extensive teaching experience, including in the subject of breast cancer. In addition, I have supervised a number of under- and post-graduate medical trainees and non-clinical scientists, including nearly twenty such physicians and students during the past five years.

12. I have significant experience in the areas of breast cancer diagnosis and treatment, breast cancer clinical trial research, hormonal dependent, or hormone receptor positive, breast cancer, and hormonal therapies. Therefore, I believe that I am qualified to render the opinions set forth in this declaration.

13. In the past four years, I have testified in the following litigation: *AstraZeneca Pharmaceuticals LP v. Sagent Pharmaceuticals, Inc.*, No. 14-cv-03547-RMB-KMW (D.N.J.).

III) MY UNDERSTANDING OF THE PROCEEDING

14. I have been informed that this proceeding is an *inter partes* review

("IPR") before the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("the Board"). I have been informed that an IPR is a proceeding to review the patentability of one or more issued claims in a United States patent on the grounds that the patent is the same as or rendered obvious in view of the prior art.

15. I have been informed that InnoPharma Licensing, LLC ("InnoPharma") filed a Petition requesting IPR ("Petition") of U.S. Patent No. 8,329,680 (the '680 Patent"), which issued to John R. Evans and Rosalind U. Grundy on December 11, 2012 and is assigned to AstraZeneca AB. I have reviewed the Petition, and understand that it alleges that claims 1-3 and 6 of the '680 Patent are unpatentable over Howell 1996 (Ex. 1007) and, alternatively, over the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008) and O'Regan (Ex. 1009), and the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), O'Regan (Ex. 1009), and DeFriend (Ex. 1038).

IV) MY OPINIONS AND THEIR BASES

16. I have been asked to give my opinion on whether or not a person of ordinary skill in the art ("POSA") would understand claims 1-3 and 6 of the '680 Patent to be rendered obvious by: (1) Howell 1996 (Ex. 1007); (2) the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008); (3) the combination of

Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008) and O'Regan (Ex. 1009); or (4) the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), O'Regan (Ex. 1009), and DeFriend (Ex. 1038). Most of my opinions herein are a direct repeat of the opinions in my declaration submitted in support of AstraZeneca's Preliminary Patent Owner Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325 (P.T.A.B. Oct. 6, 2016) attached hereto for the Board's convenience as Ex. 2136 (Robertson Mylan Decl.). Critically, and as described in more detail throughout this declaration, InnoPharma has essentially presented the same evidence as Mylan. Furthermore, InnoPharma's experts did not address many of the arguments in my previous declaration. At the same time, I think it is important to note that the majority of the opinions in InnoPharma's expert declarations are conclusory and/or wholly unsupported by any evidence (e.g., in many instances, full pages of opinions do not contain a single citation to literature or merely cite to other expert declarations (similarly unsupported)). I have tried to note in my declaration (1) the repetition by InnoPharma of evidence previously considered in the Mylan IPR and also (2) the lack of support throughout InnoPharma's declarations, but both are so pervasive throughout the declarations that I feel it is necessary to highlight upfront.

17. As part of this opinion, I considered the level of ordinary skill in the art around January 2000, which represents the filing date of GB 0000313, to which

the '680 Patent claims priority.

V) DOCUMENTS CONSIDERED

18. The materials that I have considered, in addition to the exhibits to the Petition, are those cited herein (which are also listed in Exhibit B). My opinions as stated in this Declaration are based on the understanding of a POSA in the art as defined below.

VI) THE '680 PATENT CLAIMS

19. I have been informed that the priority date of the '680 Patent was January 10, 2000.

20. Independent claim 1 of the '680 Patent is provided below.

> 1. 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.

21. Dependent claims 2-3 and 6 limit claim 1 to a method: wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$ (claim 2); and wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer (claims 3 and 6).

VII) PERSON OF ORDINARY SKILL IN THE ART

22. I have been asked to provide my opinion on the novelty and obviousness of the asserted claims, from the perspective of a person of ordinary skill in the relevant art. The skilled person with respect to the '680 Patent is a person having a bachelor's or advanced degree in a discipline such as pharmacy, pharmaceutical sciences, endocrinology, medicine or related disciplines, and having at least two years of practical experience in drug development and/or drug delivery, or the clinical treatment of hormone dependent diseases of the breast and reproductive tract. Because the drug discovery and development process is complicated and multidisciplinary, it would require a team of individuals including, at least, medical doctors, pharmacokineticists, and formulators.

23. As considered from the perspective of the medical doctor member of that team, the invention of the '680 Patent is novel, and not obvious, for the following reasons.

VIII) LEGAL PRINCIPLES

24. I am not a lawyer, and I have relied on the explanations of counsel for an understanding of certain principles of U.S. patent law that govern the determination of patentability. The discussion set forth below regarding the law of obviousness is intended to be illustrative of the legal principles I considered while preparing my declaration, and not an exhaustive list.

25. I am informed by counsel that InnoPharma must show unpatentability by a preponderance of the evidence, and preponderance of the evidence means "more probable than not." I understand that to institute an *inter partes* review InnoPharma must show that there is a reasonable likelihood that it would prevail in an *inter partes* review.

26. I am informed by counsel that for a patent claim to be invalid as anticipated by a prior art reference, that reference must disclose every limitation of the claim. Thus, if the inventions of a patent claim were already disclosed, in their entirety, by a prior art reference, that claim is anticipated and not novel.

27. I am informed by counsel that for an invention to be obvious, the patent statute requires that the differences between the invention and the prior art be such that the "subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which such subject matter pertains."

28. I understand that the obviousness evaluation must be from the perspective of the time the invention was made. The obviousness inquiry must guard against slipping into use of hindsight.

29. I understand that even in circumstances where each component of an invention can be found in the prior art, there must have been an apparent reason to combine the known elements in the fashion claimed by the patent at issue. For an invention to be found obvious, to protect against the distortion caused by hindsight bias, there must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

30. For the method of treatment to be obvious, it must have been among a finite number of identified, predictable solutions to the problems at hand.

31. For the reasons explained below, in my opinion, InnoPharma has not shown that there is a reasonable likelihood that it would prevail in an *inter partes* review of claims 1-3 and 6 of the '680 patent.

IX) CLAIM CONSTRUCTION

32. All of the claims of the '680 Patent are expressly directed to methods of treatment. The methods of treatment include choice of an active ingredient, a method of administration (i.e., a combination of excipients and active injected intramuscularly), and the amount of the active to be delivered to the blood in a

sustained release fashion to treat hormonal dependent disease of the breast and reproductive tract.

33. A medical doctor would understand that the blood plasma level limitations of the '680 Patent claims are indeed limitations of the claims and should be given their plain and ordinary meaning. These limitations are in claims 1 and 2: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks"; "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$." A clinician would understand these limitations to mean that the specified blood plasma fulvestrant concentrations of at least 2.5 $ngml^{-1}$ or 8.5 $ngml^{-1}$ are achieved and maintained for the specified amount of time. This is consistent with the Board's finding in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Paper No. 11 (P.T.A.B. Dec. 14, 2016) (Ex. 1011) which InnoPharma does not dispute. Ex. 1011 (PTAB Decision) at 18 ("[W]e interpret 'achieves' in the wherein clauses as meaning that the concentration of fulvestrant in a patient's blood plasma is at or above the specified minimum concentration for the specified time period."); Petition at 17. Further, these limitations give meaning to and provide defining characteristics of the method of treatment. Indeed, as the Board previously held, "rather than merely stating the result of intramuscularly administering the recited formulation, [] the wherein clause dictates both the

administration duration and dose of the formulation, i.e., an amount sufficient to provide a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Ex. 1011 at 17. And, "[t]hat these parameters are further limited in claim[] 2, [] ('the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$') further indicates that the wherein clauses provide defining characteristics." *Id.* InnoPharma does not dispute this finding. Petition at 18.

X) STATE OF THE RELEVANT ART

A) Problem To Be Solved

34. Breast cancer was a problem at the time of the invention. Approximately 184,200 people in the United States were expected to be diagnosed with breast cancer in 2000, with over 41,000 deaths expected from the disease. Ex. 2008 (Greenlee) at 6-7. At the time of the invention, a variety of treatments existed for patients with breast cancer, one of which was endocrine therapies. Such therapies seek to alter hormone levels in a patient and/or the hormone receptor levels in the tumor to influence the progression of hormonal dependent breast cancer. Breast cancer is divided into hormone dependent and hormone independent subtypes. Approximately 46-77 percent of cases of breast cancer were considered hormone dependent. Ex. 2009 (Robertson 1996) at 1. The remaining one-third of breast cancer cases are hormone independent. This classification of

breast cancer as hormone independent and hormone dependent is important because it guides the clinicians as to which type of treatment may be appropriate for a particular patient.

35. Of the endocrine therapies available prior to the invention of the '680 Patent, tamoxifen ("Nolvadex®") was "the most important hormonal antitumor agent for breast cancer." Ex. 2010 (Fornier) at 4; Ex. 2011 (Jordan Supp. 1995) at 1 ("Tamoxifen [] is the endocrine therapy of choice for selected patients with all stages of breast cancer."). Indeed, tamoxifen was "the most widely used first-line hormonal agent in patients with metastatic breast cancer." Ex. 2012 (Hortobagyi Cancer Investigation 1998) at 5. "Tamoxifen is a synthetic antiestrogen that blocks estrogen binding to the estrogen receptor (ER)." Ex. 2010 (Fornier) at 4.

36. Tamoxifen was known to be a partial agonist/antagonist. It blocked estrogen from fueling breast cancer tumors in breast tissue. But in other tissues like bone and the heart it acted like estrogen, providing beneficial protection. Ex. 1039 (Osborne 1995) at 5. Other references similarly described the importance and benefits of tamoxifen's partial agonist/antagonist properties. Ex. 2022 (Minton) at 1; Ex. 2023 (Grese 1998) at 1-2. Tamoxifen was available as a once a day oral pill.

37. The success of tamoxifen led to attempts to improve the less desirable aspects of the drug. A significant clinical problem was that tamoxifen treatment

eventually resulted in tumor resistance. Ex. 2010 (Fornier) at 4 ("Unfortunately, breast cancer in most patients will eventually become resistant to tamoxifen."). In other words, "most tumours that respond [to tamoxifen] eventually develop acquired resistance and start to regrow." Ex. 2013 (Johnston 1997) at 1.

38. Thus, prior to 2000, there was a need for (1) improved treatments for hormone dependent breast cancer, and (2) improved treatment options for patients following tamoxifen failure. Ex. 2014 (Pritchard 1997); Ex. 2015 (Buzdar Clin. Oncol. 1998); Ex. 1050 (Buzdar Clin. Cancer Res. 1998); Ex. 2013 (Johnston 1997); Ex. 2017 (Jordan 1995); Ex. 2018 (Morrow); Ex. 2019 (Wiebe); Ex. 2020 (Jordan Supp. 1992); Ex. 2021 (Jordan 1992). Metastatic breast cancer is an incurable condition so an endocrine therapy that could extend a woman's life and/or give her a better quality of life was desired.

39. An improved treatment would have to be either more effective or at least as effective but safer than tamoxifen. In addition, it should be as convenient, i.e., a once a day pill. Dr. Harris disagrees, instead arguing (without any literature support) that "IM injections are [] favored because they ensure compliance" and "patients will tolerate pain for lifesaving drugs like cancer treatments." Ex. 1015 at ¶¶ 75, 160-161. This is contrary to the literature at the time which, indeed, indicates that physicians thought that patients would not accept any treatment but a once a day pill. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should

be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative."). Dr. Harris describes this in emotive language "[w]hen given the choice is between an IM injection that may cause pain but can cure cancer where other treatments have failed, patients will accept this tradeoff." Ex. 1015 at ¶ 161. Advanced breast cancer in 2000 and even up to the present day is an incurable condition and so this "choice" that Dr. Harris describes is not a realistic clinical choice which either the patient or doctor have been or are currently faced with and, as noted above, it was reported at the time that oral medication was "well tolerated" and an "essential component of any strategy to introduce a new antiestrogen." Ex. 2020 at 4.

40. Within the endocrine therapies category, the prior art taught several different approaches, such as "improved" tamoxifens (other selective estrogen receptor modulators (SERMs)), aromatase inhibitors (AIs), and oral pure antiestrogens. Other approaches being used were antiprogestins and high dose estrogens, the latter which included approved and marketed products at the time.

41. In my view, InnoPharma's experts, Drs. Harris and El-Ashry provide an incomplete analysis of endocrine therapy (Ex. 1015 at ¶¶ 67-101; Ex. 1014 at ¶¶ 24-31), for at least the following reasons:

- They ignore whole classes of promising endocrine therapies, e.g.,

antiprogestins, progestins and high dose estrogens.

- They fail to describe the important advantages of the SERMs currently used at the time (e.g., cardiovascular effects).
- They focus solely on an ***uncommon*** negative effect of tamoxifen (uterine cancer). This is somewhat surprising since O'Regan whom InnoPharma has referenced stated "[i]ndeed, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, recently stated that no patient should stop taking tamoxifen because of concerns about the risk of endometrial cancer and that the benefits of tamoxifen use far outweigh any risks." Ex. 1009 at 1. In other words, while endometrial cancer was an acknowledged risk of tamoxifen treatment it was not deemed sufficient risk to stop any patient from taking tamoxifen.
- They fail to discuss the extensive research that was ongoing to assess new "designer" SERMs, which were being developed to optimize the beneficial agonistic properties of SERMs while minimizing potential harmful agonistic properties.
- They fail to recognize that, even beyond the designer SERMs, the aromatase inhibitors had become the new and preferred focus for pharmaceutical companies and clinical researchers seeking new and

more effective endocrine agents, including the second and third generation aromatase inhibitors that were being developed for various clinical indications in breast cancer.

- In terms of pure antiestrogens, they do not acknowledge the other pure antiestrogens being developed immediately prior to 2000, of which one in particular, EM-800, was more potent, orally active, had phase II clinical data, and had started phase III clinical trials.

42. For the reasons described above and below, a skilled artisan would not have begun with fulvestrant as the active ingredient, nor would a skilled artisan have expected such an approach to succeed.

B) The Prior Art Taught and Provided a Promising Scientific Rationale and Experimental Candidates for Many Different Systemic Therapy Approaches to Treating Breast Cancer

1) Selective Estrogen Receptor Modulators (SERMs)

43. Given the success of tamoxifen and the benefits of its mixed agonist/antagonist activity, one of the promising areas was the search for a new tamoxifen with a better balance of activities. As of the date of the invention, several SERMs had already received FDA approval, opportunities existed to improve the most widely used SERM, tamoxifen, and many promising SERMs were in development.

44. Contrary to Dr. Harris's assertion that some of tamoxifen's agonist

activity that was not beneficial (the rare instances of endometrial cancer) pointed to pure estrogen antagonists, Ex. 1015 at ¶ 85, in reality, at the time of the invention, many scientists and pharmaceutical companies were attempting to develop better SERMs by seeking a superior balance between antiestrogen activity and estrogen agonist activity, instead of entirely eliminating agonist activity. The prior art explained exactly that: "[t]he finding of endometrial cancer resulting from tamoxifen treatment has led researchers to investigate new agents that retain favorable estrogenic properties in specific tissues and display antiestrogen activity on the endometrium. Such research has generated the concept of selective estrogen receptor modulators (SERMs) that mediate either estrogen agonist or estrogen antagonist effects in different tissues." Ex. 2022 (Minton) at 1.

45. In fact, the focus on improving the agonist-antagonist balance of tamoxifen led to an "explosion of research to understand the molecular basis for this specificity and a race to develop these 'designer estrogens' or Selective Estrogen Receptor Modulators (SERMs) as pharmaceutical products." Ex. 2023 (Grese 1998) at 2.

46. As of the date of the invention, other SERMs that had received FDA approval included toremifene, which was found to be as efficacious as tamoxifen in the first-line setting (Ex. 2022 (Minton) at 2), and raloxifene for osteoporosis (Ex. 2024 (Hortobagyi New Eng. J. Med. 1998) at 9). Many promising SERMs were

also known to be in clinical development at the time including idoxifene (in a phase I clinical trial "was well tolerated with only mild toxicities, and the patients had a partial response rate and stable response rate of 14% and 29%, respectively, ranging from 1.4 to 14 months"), droloxifene (multiple phase II trials had been reported, with the largest showing "a 30% response in the 20-mg arm compared to a 47% response in the 40-mg arm and a 44% response in the 100-mg arm" with side effects "similar to that of tamoxifen"), TAT-59 (in a phase I clinical trial "[t]he total response rate was 30% in the TAT-59 arm compared to 26.5% in the tamoxifen arm"), arzoxifene (reported to be "a SERM with improved *in vivo* potency as an oral estrogen antagonist, which maintains tissue-specific estrogen agonist effects on serum cholesterol and bone mineral density at doses as low as 0.01 mg/kg"), CP-336,156 (identified as "a potent tissue selective estrogen agonist"), and LY326315 (known to possess "a fully differentiated agonist/antagonist profile on reproductive vs. non-reproductive tissue"). Ex. 2022 (Minton) at 2; Ex. 2023 (Grese 1998) at 11-12. Dr. Harris neither mentions nor references any of the other SERMs which had been approved or the newer SERMs in development by 2000.

2) Aromatase Inhibitors (AIs)

47. The most promising endocrine therapies at the time of the invention were aromatase inhibitors. Indeed, this class was the primary focus of many

researchers at the time aiming to solve the problem of tamoxifen resistance. Unlike fulvestrant, tamoxifen, and the newer SERMs, aromatase inhibitors had a very different and known mechanism of action. Rather than targeting the estrogen receptor (like all the SERMs and fulvestrant), the aromatase inhibitors targeted the aromatase enzyme[1] and inhibited the formation of estrogen, the ligand for the estrogen receptor. This meant that aromatase inhibitors were less likely than other SERMs and fulvestrant to be "cross-resistant" to tamoxifen. "Cross-resistance" means that a drug's efficacy is significantly reduced when it is administered to a patient following progression on a different drug with a similar mechanism of action. In particular, an advantage of aromatase inhibitors noted at the time was that they are "effective therapy in patients with breast cancer ***even after they relapse*** from responses to antiestrogen or progestin (medroxyprogesterone acetate or megestrol acetate) therapy." Ex. 2025 (Masamura 1994) at 2 (emphasis added). Dr. Harris apparently disagrees that AIs were believed to be less likely than other SERMs and fulvestrant to be "cross-resistant" to tamoxifen but cites nothing to rebut it. Ex. 1015 at ¶ 79.

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[1] Aromatase is the enzyme that catalyzes the rate-limiting step in the formation of estrogen. Ex. 2026 (Kelloff 1998) at 1. Clinical studies had shown that "aromatase inhibitors cause tumor regression in postmenopausal breast cancer patients." Ex. 2026 (Kelloff 1998) at 2.

48. At the time of the invention, anastrozole (Arimidex®) and letrozole (Femara®) had received FDA approval in the second-line endocrine therapy setting. Ex. 2022 (Minton) at 3; Ex. 2139 (Dombernowsky); Ex. 2140 (Buzdar 2001); Ex. 2119 (Buzdar 1996); Ex. 2138 (Jonat 1996). In late 1999, exemestane received similar FDA approval as Aromasin®.

49. AIs that had been in development prior to the invention included vorozole ("[p]otent aromatase inhibition, few side effects, and possibility of influencing estradiol levels in premenopausal women are of interest for chemoprevention"), formestane ("approved in Europe for the treatment of metastatic breast cancer in women who have failed tamoxifen therapy . . . has been shown to have high response rates"), fadrozole (CGS 16949A) ("studies demonstrated that fadrozole is 500-fold more potent than aminoglutethimide"), ORG 33201 ("[a]lthough less potent than fadrozole in the model systems examined, it was more selective and did not demonstrate any additional unwanted hormonal activity"), and CGP 47645 ("a fluorinated derivative of letrozole, which is equipotent with letrozole toward aromatase *in vitro* but is 10 times more active *in vivo*"). Ex. 2022 (Minton) at 4; Ex. 2025 (Masamura 1994) at 4; Ex. 2026 (Kelloff 1998) at 5, 9.

50. At the time of the invention, the skilled artisan would have focused on AIs, as demonstrated by the prior AIs that received FDA approval, the possibility of

improving on existing endocrine therapies with newer AIs, and the reports of promising AIs in development. Further, the known mechanism of action of AIs was important for researchers because researchers are always looking for the most promising path; proven mechanisms are much less risky than unproven mechanisms.

3) Pure Antiestrogens

51. Without even mentioning the class to which it belongs, Dr. Harris vaguely asserts that "fulvestrant was well understood" and "much was known about fulvestrant at the time of the alleged invention." Ex. 1015 at ¶ 84. No pure antiestrogen had been approved at the time of the invention. At the time of the invention, few ***pure*** antiestrogens were in development and, as noted below, fulvestrant was not the most promising candidate.

52. Researchers hoping to find a treatment for tamoxifen-resistant patients would have been hesitant of approaches that focused on the estrogen receptor, as tamoxifen also operated on the estrogen receptor and usually resulted in tumor resistance. Ex. 1039 (Osborne 1995) at 1 ("Most tumors eventually became resistant to [fulvestrant] and grew independently of estrogen."). Researchers also highlighted a potential risk of pure antiestrogens—cross-resistance with tamoxifen—"[o]n the basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with

tamoxifen." *Id.* at 5. In this circumstance, the value of using sequential endocrine agents would be negated. On the other hand, aromatase inhibitors exhibited alternative mechanisms of action that were believed to offer potential solutions to tamoxifen resistance.

53. Moreover, in terms of side effects, it was feared that pure antiestrogens would have deleterious effects on the bone and heart as opposed to the beneficial effects on bone and the heart provided by tamoxifen and other SERMs. Ex. 2027 (Dukes 1994) at 5 ("[A] possible undesirable consequence of pure antioestrogen therapy is an adverse effect on bone mineral metabolism leading to induction or exacerbation of osteoporosis."); Ex. 1039 (Osborne 1995) at 5 ("The estrogenic properties of tamoxifen in bone and on blood lipids may help to reduce bone loss and prevent cardiovascular disease . . . . The effect of [fulvestrant] on these parameters is not yet known, but it might be deleterious given its lack of estrogenic qualities."); Ex. 2023 (Grese 1998) at 4 ("For example, ICI 164,384 and ICI 182,780, exhibited no capacity for lowering serum cholesterol or sparing bone loss in the OVX rat model.").

54. Dr. Harris alleges that "[i]n the early 1990s, it was known that the properties of fulvestrant make it 'a prime candidate with which to evaluate the potential therapeutic benefits of complete oestrogen withdrawal in endocrine-responsive human breast cancer.'" Ex. 1015 at ¶ 87. The sentence Dr. Harris

quotes actually highlights the lack of precedent (and with it the attached risks) for successfully developing a pure antiestrogen—its unproven mechanism of action and the potential disadvantages on bone and lipids would have discouraged a skilled artisan from taking a pure antiestrogen approach. Furthermore, the fact that all SERMs up to this point had shown cross-resistance to tamoxifen meant that there was also no proven success in targeting the ER with two antiestrogens sequentially. These facts are reflected in the relatively few ***pure*** antiestrogens known in the art at the time of the invention.

55. But, even if a skilled artisan were interested in pure antiestrogens, such a person would have focused on the most potent pure antiestrogens and those that could be administered orally. A number of them existed, including EM-652, EM-800, RU 58668, and ZM 189,154. Ex. 2022 (Minton) at 3; Ex. 2032 (Labrie 2004); Ex. 2034 (Labrie 1999); Ex. 2033 (Van de Velde); Ex. 2027 (Dukes 1994). For example, "EM-652 is the active metabolite of the prodrug EM-800 and is available in oral form." Ex. 2022 (Minton) at 3. EM-652 was reported to be "20 times more potent" than fulvestrant. Ex. 2022 (Minton) at 3. "EM-652 has the highest known affinity to the ER when studied in competition receptor assays in animal models." Ex. 2022 (Minton) at 3. In terms of reviewing the whole class of pure antiestrogens, Dr. Harris states that "although there were other pure antiestrogens in development at the time, it was known that fulvestrant, also designated ICI

182780, had greater potency and bioavailability." Ex. 1015 at ¶ 132. As can be noted from the literature referenced above, this is simply incorrect. Among the pure antiestrogens listed above EM-652 had greater potency for the ER and was orally available. Based on oral bioavailability and superior potency, a skilled artisan would have preferred the EM series of compounds over fulvestrant.

56. Additionally, a "small [] phase II trial investigating EM-800 in the metastatic breast cancer setting in women who had progressed on tamoxifen showed encouraging results and thus implie[d] a lack of cross-resistance with tamoxifen." Ex. 2022 (Minton) at 4. These encouraging results which were published in 1999 before the invention of the '680 Patent revealed EM-800 as a promising new agent, with 19 out of the 43 patients (44%) studied reporting positive responses to treatment. Ex. 2034 (Labrie 1999) at 26-28. Prior to 2000, this led to EM-800 being "studied in a large [phase III] trial comparing its efficacy to anastrozole in the second-line treatment setting of metastatic breast cancer" to demonstrate that EM-800 should become a standard of care. Ex. 2022 (Minton) at 4; *see also* Ex. 2034 (Labrie 1999) at 2. On the other hand, as discussed in more detail below, Howell 1996 reports a less potent estrogen receptor antagonist being delivered in a parenteral formulation. Dr. Harris's argument that "fulvestrant dominated the studies, including pre-clinical and clinical trials, at the time" and was known to have "greater potency and bioavailability" than other pure antiestrogens is

thus belied by the literature which he fails to even reference never mind discuss. Ex. 1015 at ¶¶ 86, 132 (citing Exs. 1049 (Anderson), 1061 (Thomas)). Indeed, while Thomas and Anderson discuss ICI 182,780's greater potency over ICI 164,384, another pure antiestrogen in development by AstraZeneca at the time, neither discusses ICI 182,780's activity compared to the more promising EM-800. Ex. 2022 (Minton) at 3 ("EM-652 is 20 times more potent than [fulvestrant and] has the highest known affinity to the ER when studied in competition receptor assays in animal models.").

57. Even if a skilled artisan wanted to develop a pure antiestrogen at the time of the invention of the '680 Patent, such a person would have preferred compounds with oral bioavailability and/or improved potency compared to fulvestrant.

4) Other Endocrine Therapies

58. Progestins, anti-progestins, androgens and luteinizing hormone-releasing hormone agonists (LHRH agonists) were all additional approaches that had been attempted in clinical trials prior to the invention of the '680 Patent, which worked to impact the hormonal-dependent pathway. Each of those classes had individual agents described in the literature as having promise and each had the benefit of having a different mechanism of action than tamoxifen. An example of a progestin that had been developed includes megestrol acetate. Ex. 2035

(Hortobagyi 1998) at 2. Examples of anti-progestins in development at the time include onapristone, ORG 31710, and ORG 31806. Ex. 2036 (Robertson 1999); Ex. 1050 (Buzdar Clin. Cancer Res. 1998) at 7-8. Fluoxymesterone, a synthetic androgen, had been "used in patients with persistently hormone-responsive tumors as fourth-line therapy." Ex. 2035 (Hortobagyi 1998) at 3. Luteinizing hormone-releasing hormone analogs such as goserelin had "proven to be of major efficacy in chemical gonadal ablation in both women and men." Ex. 2035 (Hortobagyi 1998) at 2; Ex. 2037 (Hortobagyi 1997) at 1.

59. As described above, the skilled artisan at the time of the invention would have had numerous approaches to systemic endocrine therapies for breast cancer treatment, each with promising compounds.

C) Fulvestrant Was Less Promising Than The Other Available Endocrine Agents in 2000

60. In my opinion, at the time of the invention, the skilled artisan would not have been motivated to select fulvestrant to develop a treatment of hormonal dependent benign and malignant diseases of the breast and reproductive tract, including breast cancer, and would not have had a reasonable expectation of success in doing so.

61. In my view, fulvestrant was less promising as a potential treatment than other available endocrine agents. Dr. Harris argues that "[m]uch had been written throughout the 1990s regarding fulvestrant's promise as a treatment for

hormone dependent breast cancer that lacked many of the drawbacks to tamoxifen and other SERMs," "by the year 2000, it was known that fulvestrant was effective in treating breast cancer, was low risk, had shown good activity in early-stage research, did not promote uterine cancer[], had no adverse impact on bones, and showed improvements in overcoming cross-resistance," "by the year 2000, not only were the [] efficacy, cross-resistance, tolerance and side-effect profiles established [for fulvestrant], so too were the pharmacokinetics, formula, and route of administration in humans" and "while other potential treatment options existed at the time, fulvestrant looked to be among the most promising." Ex. 1015 at ¶¶ 84, 87-88, 131. In my view, this misrepresents the state of the art in January 2000 in terms of (1) agents and other endocrine classes as development options, (2) other pure antiestrogens, and (3) the information which was known and established about fulvestrant. I will discuss each of these areas below.

62. Of the more than 15 endocrine agents available in 2000, fulvestrant was not the most promising. First, fulvestrant was from a new class that had many risks. While it was known to target the estrogen receptor, it had an unproven (and not fully understood) mechanism of action than the other endocrine agents such as the aromatase inhibitors (i.e., the most promising class at that time) and the designer SERMs, and activities within these other classes were already more advanced in their development at the time. Scientists did not expect that fulvestrant

would be more effective than AIs or SERMs, even after the publication of Howell 1995. "It remains to be seen whether it will be more effective than other non-steroidal anti-oestrogens with less agonist activity than tamoxifen or toremifene, such as idoxifene. Our data suggest that it may not be substantially more effective in terms of response rate than aromatase inhibitors, with which it is conceptually similar in its pure deprivation of the oestrogenic signal." Ex. 2038 (Dowsett 1995) at 1.

63. Second, even within its class, fulvestrant was not the most attractive of the pure antiestrogens. For example, EM-800 was already in phase III trials, thought to be more potent than ICI 182,780, and had shown good activity in phase II trials. Additionally, the oral pure antiestrogen compounds, such as EM-800 or ZM 189,154, were more attractive options for both patients and physicians due to the issues that are associated with parenteral drug administration.

64. Third, it was important that a new endocrine therapy was not associated with cross-resistance to subsequent endocrine therapies–indeed not being cross-resistant was one of the desired features for a new endocrine therapy. Osborne had raised this concern about cross-resistance with tamoxifen—"[o]n the basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with tamoxifen." Ex. 1039 at 5. This was a concern that was further highlighted even after the small non-

randomised study (n=19) by Howell 1996. In the small sub-group of responders from the Howell 1996 study, all failed to show an objective response to subsequent third-line therapy with megestrol acetate and led to the stated concern at the time. Ex. 1043 (Robertson 1997) at 3 ("[T]his early finding raises the hypothesis as to whether acquired resistance to [fulvestrant] may be equivalent to developing an endocrine resistant phenotype.").

65. Dr. Harris's declaration includes a section in which he makes claims regarding the clinical efficacy and safety of fulvestrant, which have no basis, are over-interpretations of available data, or statements about the potential and promise of the compound. Ex. 1015 at ¶¶ 84-101, 130 ("[M]any reports lauded fulvestrant as offering additional benefits over tamoxifen and other conventional anti-estrogens in the treatment of human breast cancer."). Relying on this, I understand that InnoPharma is arguing that it was "already known that fulvestrant is an effective treatment for hormone dependent breast cancer." Petition at 24.

66. However, every reference that Dr. Harris cites uses language like "potential," "maybe," or "might" indicating at most a hope not an expectation and certainly not "knowledge." Ex. 1031 (Wakeling 1991) at 7 ("The data available to date for ICI 182,780 presented here [] indicate that pure antiestrogens ***may*** find a valuable place in the treatment of breast cancer." (emphasis added)); Ex. 1036 (Dukes 1992) at 1 (fulvestrant "***may*** offer advantages in breast cancer treatment

compared with partial agonists like tamoxifen" (emphasis added)); Ex. 1057 (Dukes 1993) at 1 ("ICI 182,780 is a potent specific pure antioestrogen which ***may prove*** superior to conventional partial agonist antioestrogens in the treatment of breast cancer." (emphasis added)); Ex. 1058 (Wakeling 1993) at 8 ("If the greater efficacy of pure versus partial agonist antiestrogens against human breast cancer cell growth described above 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." (emphasis added)); Ex. 1061 (Thomas) at 1 ("ICI 182,780 ***may*** be a useful compound in the treatment of oestrogen-dependent gynaecological disease" (emphasis added)); Ex. 1038 (DeFriend) at 1 ("These properties identify ICI 182780 as a ***candidate agent*** with which to evaluate whether a pure estrogen antagonist offers any additional benefit in the treatment of human breast cancer over conventional nonsteroidal antiestrogens[.]"(emphasis added)); Ex. 1056 (Howell 1995) at 2 (fulvestrant "***may*** improve the rate and duration of response when used as a first-line treatment for advanced breast cancer" (emphasis added)); Ex. 1039 (Osborne 1995) at 1 ("[P]ure steroidal antiestrogens ***may*** be effective in some tamoxifen-resistant patients." (emphasis added)); Ex. 1032 (Nicholson 1995) at 12 ("In clinical breast cancer it is ***too early to judge*** the final value of these compounds." (emphasis added)); Ex. 1007 (Howell 1996) at 7 ("[I]t is ***possible***, therefore, that this new agent ***may***

improve the rate and duration of response in patients with advanced breast cancer." (emphasis added)); Ex. 1051 (Howell Eur. J. Cancer 1996) at 6 ("ICI 182,780 ***may*** be an important new approach to antioestrogen therapy." (emphasis added)); Ex. 1049 (Anderson) at 3 ("[I]t ***appears*** that at least ***some*** of the changes described after ICI 182780 treatment in vitro also occur in human primary breast tumours in vivo." (emphasis added)); Ex. 1009 (O'Regan 1998) at 1 ("ICI 182,780 ***may*** prove useful as an adjuvant agent in early stage endometrial cancer." (emphasis added)). This does not demonstrate that fulvestrant's human clinical efficacy in breast cancer patients was "well known."

67. Dr. Harris further argues that "AstraZeneca ignores the many numerous other details about fulvestrant that a person of skill in the art would have considered positive" from Howell such as its teachings that fulvestrant "[h]ad no 'apparent negative effects on the liver, brain or genital tract'" and "[p]roduced '[n]o serious drug-related adverse events.'" Ex. 1015 at ¶ 140. By the time of the invention, there had only been 19 highly selected patients ever treated in one small, non-randomized, phase II clinical study (Howell 1995/1996), which itself recognized the need for further clinical trials to assess the efficacy of fulvestrant. Howell himself concludes "further studies are required to confirm the response rate." Ex. 1007 at 7. The need for further studies to further assess the adverse events profile was also highlighted. Ex. 1007 at 6 ("The lack of apparent adverse

effects of ICI 182780 seen in the present study would, ***if confirmed in future larger trials***, give the specific anti-oestrogen ***potential*** advantages over currently available second-line endocrine agents." (emphases added)).[2] And with regard to the specific adverse event of uterine cancer, again, Dr. Harris's statement that "by the year 2000, it was known that fulvestrant . . . did not promote uterine cancer" (Ex. 1015 at ¶ 87), is not really accurate. One cannot make a reasonable assessment of the risk of developing endometrial cancer from fulvestrant based on 19 patients treated for a median of 18 months.

68. Turning to efficacy, Dr. Harris states that Howell "confirmed the efficacy of fulvestrant in women for the treatment of breast cancer." Ex. 1015 at ¶ 127. Howell 1996 reported that 13 of 19 patients responded (69%): 7 "partial responders," whose tumors decreased in size; and 6 "no change" patients, whose tumors neither shrank nor grew but remained stable, which was considered by some researchers to be a clinically beneficial outcome. Howell also noted that up to one-third of responses could have been due tamoxifen withdrawal, i.e., shrinkage of the cancer due to coming off tamoxifen and taking away the estrogen

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[2] Dr. Harris ignores this statement in Howell when he states that "Howell reported no adverse side-effects with this dose." Ex. 1015 at ¶ 142; *see also* Ex. 1007 at 4 ("No ***serious*** drug-related adverse events occurred in any of the 19 patients treated with ICI 182780." (emphasis added)).

stimulation that is associated with tamoxifen. Ex. 1007 at 7 ("[W]e and others have demonstrated so-called withdrawal responses in breast cancer patients after stopping treatment with tamoxifen at the time of tumour progression, further suggesting tumour stimulation by tamoxifen as a possible cause of treatment failure [Ex. 2016 (Howell 1992)]. [I]n most studies withdrawal responses occur in only one-third or less of patients[.]"). Accordingly, because all of the patients in Howell 1996 previously progressed while on tamoxifen, the skilled artisan would understand that up to one-third of the responses (2 of 7 partial responders; and 2 of 6 no change) may be attributed to tamoxifen withdrawal rather than treatment with fulvestrant. Thus, the actual number of patients whose tumors showed shrinkage based on treatment with fulvestrant may have been as low as 5 patients. The authors highlighted the need for "further studies . . . to confirm the response rate" (Ex. 1007 at 7) as well as other researchers stating at the time that the results "should be interpreted with care." Ex. 2038 (Dowsett 1995). Thus, Dr. Harris's statement in terms of efficacy that Howell "reported on the only Phase II trial . . . and confirmed the efficacy of fulvestrant in women for the treatment of breast cancer" (Ex. 1015 at ¶ 127) is incorrect.

69. The conclusion at the time was that fulvestrant at best had some promise, but no more than other agents, yet it also held significant disadvantages which pointed away from its development in favor of agents from other less risky

classes or better pure antiestrogens like EM-800.

D) Fulvestrant Formulations, Schedule And Route Of Administration, Optimal Dose and Pharmacokinetics Were Not "Established" In The Prior Art

70. Dr. Harris attempts to compartmentalize the claimed method of treatment into its individual parts, stating that "by the year 2000, it was known that fulvestrant was effective in treating breast cancer" and "formulations were published, pharmacokinetics were established, and it was known that in humans, fulvestrant must be administered by IM injection." Ex. 1015 at ¶¶ 87, 101. To pull each of these factors apart is to fundamentally misunderstand drug delivery. From a clinician's perspective, one cannot divorce any one of these factors from the others. Indeed, clinicians realize that these factors are inextricably intertwined—changing one can radically affect the others.

71. The sweeping generalizations of Dr. Harris's declaration oversimplify the interactions of formulation, dose, route of administration, and scheduling in terms of their impact on drug delivery and efficacy. Indeed, it is the importance of such interactions which requires the method of treatment of drugs (i.e., formulation, dose, route of administration, and scheduling) to be clearly stated on a drug approved by regulatory authorities.

72. Regarding indication, despite claiming that "many researchers" were reporting on human research with fulvestrant, Dr. Harris cites to three such studies,

Howell 1996, Thomas, and DeFriend, and notes that "all three of the studies that tested fulvestrant in humans administered the drug by IM injection." Ex. 1015 at ¶¶ 88, 156. But the administration route is the only commonality across the three studies. These three studies give no consistent data regarding formulation, dose, or delivery schedule. Thomas uses a short-acting fulvestrant formulation delivered as a 12 mg i.m. injection daily for 7 days (Ex. 1061 (Thomas)); DeFriend uses a short-acting propylene glycol fulvestrant formulation delivered as a 6 or 18 mg i.m. injection daily for 7 days (Ex. 1038 (DeFriend)); Howell 1995/1996 uses a long-acting castor oil-based fulvestrant formulation (with no further information regarding ingredients) delivered as a 250 mg i.m. injection every four weeks (Exs. 1007 (Howell 1996), 1056 (Howell 1995)). If Dr. Harris is pointing to commonality, then at most this could suggest daily use was the aim, like tamoxifen and the existing AIs.

73. Moreover, the Howell study explicitly states that the dose used was ***not*** optimal. It says "there was evidence of drug accumulation after multiple dosing, such that after 6 months treatment there was an 80% increase in mean end of month drug levels and a 50% increase in the AUC compared with data from 1 month. These data suggest that lower doses of the drug may be as effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis." Ex. 1007 (Howell 1996) at 6.

74. From a clinician's perspective, route and schedule of administration are critical factors. The various papers cited by Dr. Harris describe subcutaneous administration, oral administration and intramuscular administration as options used in research, with dosing schedules from once a day to once a month. The optimal dosing regimen would be once a day orally like tamoxifen. This regimen is supported by the art generally. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative."). Most of the papers cited by Dr. Harris use subcutaneous administration daily or weekly. Ex. 1031 (Wakeling 1991); Ex. 1040 (Wakeling 1992); Ex. 1058 (Wakeling 1993); Ex. 1039 (Osborne 1995); Ex. 1008 (McLeskey); Ex. 1009 (O'Regan). Only the Howell and Dukes papers disclose intramuscular monthly dosing.

75. Regarding pharmacokinetics, Dr. Harris states that Howell 1996 "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 [intramuscular] injection of the long-acting formulation used." Ex. 1015 at ¶ 97. However, first, this statement needs to be read in context. In the very next paragraph Howell reports that "a direct pharmacokinetic-pharmacodynamic link [was] not proven with the few patients

studied to date" and that "future larger trials" were needed. Ex. 1007 (Howell 1996) at 6. Second, what was predicted from animal experiments was not reflected in humans. For example, Dukes 1992 had stated "[i]nterestingly, in that study the increasing delay of the onset of uterine growth after the second and third doses indicated a cumulative biological effect. However, estimates of concentration of drug in the serum did not indicate that drug accumulation was responsible for this increased efficacy (F. Sutcliffe, unpublished studies)." Ex. 1036 (Dukes 1992) at 8. In contrast, the drug accumulation seen in the first 19 patients reported by Howell was not the pharmacokinetics expected from animal experiments.

76. Therefore, for the reasons described above, Dr. Harris's sweeping statement (Ex. 1015 at ¶ 88) that "[t]he time-line shows that, by the year 2000, not only were the foregoing efficacy, cross-resistance, tolerance and side-effect profiles established, so too were the pharmacokinetics, formula, and route of administration in humans" is simply not true/correct.

XI) REFERENCES CITED IN THE PETITION

77. In InnoPharma's Petition and accompanying clinician declaration, InnoPharma and Dr. Harris select a very specific set of references as showing the scope of prior art at the time of the invention. Petition at 18-26; Ex. 1015 at ¶¶ 102-120. This selection looks backwards from the present day, ignoring the perspective that a skilled clinician would have had at the time of invention. As I

discuss above, the universe of options for therapeutic agents available to a clinician was broad, with many options available for each important consideration, like active, administration method and amount (dosing). In my view, the references in the Petition and declaration are not representative of the full scope or content of the prior art, nor of the knowledge or skill of a POSA at the time of the invention. I address each of the references cited below.

A) Howell 1996 (Ex. 1007)

78. I am an author of Howell 1996. Howell 1996 does not disclose "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." Howell 1996 administered a dose of 250 mg but concluded that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels" so an ordinary researcher would have been motivated to use lower doses. Ex. 1007 (Howell 1996) at 6. Howell 1996 does not disclose the composition of the administered formulation of fulvestrant and the skilled artisan would not be able to use the data in Howell 1996 to obtain the claimed method of treatment.

79. Howell 1996 administered a monthly depot intramuscular injection of fulvestrant "contained in a castor oil-based vehicle" to 19 patients. Ex. 1007 at 2. Serum levels of fulvestrant were measured in 15 patients that were started on 250 mg in the first month and 11 patients in the sixth month. Ex. 1007 at 3. Even at

month 6, the mean end-of-month plasma concentration of 5.6 ng ml^{-1} was below 8.5 $ngml^{-1}$. Based on this data, a skilled artisan would have known that 250 mg monthly fulvestrant would not achieve 8.5 $ngml^{-1}$ "for at least four weeks" in this population in the method described by Howell 1996. Howell states that in his study C_{max} occurred around days 8 and 9. Ex. 1007 at 3 ("In the majority of patients, the measured C_{max} was reached 8 or 9 days after the start of the drug administration."). As can be seen from Figure 2 in Howell 1996, the blood level of fulvestrant then dropped off over the rest of the four week period until it reached its trough level on day 28—which was always below 8.5 $ngml^{-1}$. Ex. 1007 at 4. Therefore, contrary to Dr. Harris's opinion that Howell meets "the therapeutically significant blood plasma fulvestrant concentration limitation[s]" of the claims (Ex. 1015 at ¶ 166), it is clear from the method in Howell 1996 that 250 mg monthly fulvestrant would not achieve 8.5 $ngml^{-1}$ "for at least four weeks."

80. Importantly, Howell 1996 also states that "[t]here was no significant difference in the median C_{max} and AUC between responders and non-responders to treatment." Ex. 1007 at 3. Additionally, "[a]fter 6 months of treatment there was no significant difference between C_{max} and AUC for patients who had a partial response (PR) compared with those with a no change (NC) response." Ex. 1007 at 3. Accordingly, Howell 1996 concluded that "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date." Ex.

1007 at 6. This means that not only were no therapeutic blood levels determined, but also that no correlation between blood levels and clinical activity was found.

81. Howell 1996 encouraged a skilled artisan to seek lower blood levels of fulvestrant than achieved in Howell 1996. Howell 1996 said that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis." Ex. 1007 at 6; *see also id.* at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective."). Indeed, AstraZeneca in its subsequent clinical studies did precisely that including 50 and 125 mg doses. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2030 (Robertson 2001). These statements in Howell 1996 would suggest to the skilled artisan that increasing the blood plasma concentration ***would not result in greater clinical benefit***.

82. Dr. Harris states that "Howell reports that 'it was predicted that serum levels of ICI 182780 in the range of 2-3 ng/ml were consistent with a therapeutic effect in patients with advanced breast cancer.'" Ex. 1015 at ¶ 144. Howell explains that the original dose for this predicted window was selected based on monkey and biological marker studies. Ex. 1007 at 6. But, the Howell 1996 study concluded that based on the clinical data "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date"—that

is, the Howell study did not establish a therapeutic level. *Id.* Furthermore, the Howell paper unexpectedly found drug accumulation. Ex. 1007 at 7 ("At the dose used [250 mg], there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective."). In view of all the Howell data, the researchers determined the 250 mg dose may be too high and suggested further research to decrease the dose and determine therapeutic blood levels. *Id.* at 6 ("These data suggest that lower doses of the drug may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm the hypothesis."). Thus, while Dr. Harris now in 2017 states that he "disagree[s] that Howell teaches to lower the dose" (Ex. 1015 at ¶¶ 141, 143), in the randomized clinical trials following Howell at the time of the invention (Studies 18, 20, 21: over 1,000 patients) the doses assessed were 250, 125, and 50 mg. It is clear therefore that the investigators of these large clinical trials at the time followed Howell's recommendation. In sum, this suggestion by Howell of lowering the dose was not "merely a hypothesis" as suggested by Dr. Harris (Ex. 1015 at ¶ 143) but was based on the pharmacokinetic and clinical results, as described below (¶¶ 124-138), was consistent with the knowledge from prior endocrine therapies and was followed in 3 further clinical studies.

83. Dr. Harris further argues that "a person of ordinary skill in the art reading Howell would have been motivated to achieve [the claimed]

therapeutically significant blood plasma fulvestrant concentrations, including concentrations of at least [8.5 $ngml^{-1}$] for at least 4 weeks." Ex. 1015 at ¶¶ 146-147. From a clinician's perspective, there would be no reason for a POSA to attempt to achieve concentrations at or above 8.5 $ngml^{-1}$ for 4 weeks because Howell 1996 suggested a lower dose. It does not matter that a POSA could do it—there is no reason why a POSA would want to do it here especially in light of Howell 1996 which suggested the opposite. The fact that the clinical investigators of Studies 18, 20, and 21 (involving over 1,000 patients) looked at doses of 250 mg or lower (i.e., 250 mg, 125 mg, 50 mg) confirms that a POSA would not have been motivated to look at higher doses/serum concentrations of fulvestrant.

84. Dr. Harris also mischaracterizes Howell 1996 by stating that it "was considered a success." Ex. 1015 at ¶ 106. Howell 1996 actually concluded that fulvestrant "warrants further evaluation" and "further studies are required to confirm the response rate and also to determine the long-term effects of this agent on bone, plasma lipids and the endometrium." Ex. 1007 at 1, 7.

85. Both Drs. Harris and Bergstrom state/imply that Howell was looking to reach steady state with 250 mg IM monthly and then use this suggestion of steady state to lead on to using a loading dose to reach steady state quicker (Ex. 1013 at ¶¶ 16, 124, 148-155; Ex. 1015 at ¶¶ 143-145, 218-228) or looking for higher doses. The latter they try to justify on two grounds—i.e., that DeFriend

showed a dose response effect to ER downregulation (Ex. 1013 at ¶¶ 16, 97, 123, 136, 138-139, 142; Ex. 1015 at ¶¶ 176, 178, 182, 217) or that increasing dose was a standard approach to developing new drugs (Ex. 1015 at ¶¶ 145, 225-228). The claim that DeFriend showed dose response is simply incorrect and will be addressed in Section XII.D.1. The idea as described by Dr. Harris that "when it is observed that the drug is well-tolerated, dosing will scale up to achieve a maximum therapeutic effect" (Ex. 1015 at ¶ 200) is a principle which has been applied to developing non-endocrine therapy drugs (e.g., with chemotherapy seeking maximum kill of dividing cells or as Dr. Harris notes with trastuzumab (Ex. 1015 at ¶ 227)). Again, this maximum tolerated dose concept was not the approach taken for developing endocrine therapies in all major classes. As will be described in detail below (¶¶ 124-138), the history of endocrine therapy has been to seek the lowest efficacious dose of an endocrine agent. Thus, Drs. Harris and Bergstrom's statements that Howell was looking to reach steady state with 250 mg IM monthly and then use this suggestion of steady state to lead on to using a loading dose to reach steady state quicker or looking for higher doses does not reflect the reality of what Howell stated in 1996 or what Howell and other researchers were practicing at the time of the '680 Patent. Furthermore, the two grounds Drs. Harris and Bergstrom then try to use to justify this re-interpretation of history—i.e., DeFriend showed a dose response and the maximum tolerated dose

concept should be applied to endocrine therapies—will also be shown to be not a true representation of the literature or state of the art at the time of the invention.

86. The evidence that Howell was looking to reach a predicted therapeutic window as opposed to pursuing steady state at 250 mg as a goal is shown clearly within the Howell 1996 manuscript. Ex. 1007 at 6 ("From studies on inhibition of endometrial proliferation in the monkey and inhibition of tumour proliferation in a previous phase I study, it was predicted that serum levels of ICI 182780 in the range of 2-3 $ngml^{-1}$ were consistent with a therapeutic effect in patients with advanced breast cancer."). Having noted the originally predicted 2-3 $ngml^{-1}$ window, Howell concluded from the data that "a direct pharmacokinetic-pharmacodynamic link [was] not proven with the few patients studied to date"—i.e., a therapeutic level was not established. Ex. 1007 at 6. Howell went on to suggest a lower dose and lower blood levels, stating that "lowering the dose may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this." Ex. 1007 at 6. It is thus clear that Howell was not per se trying to reach a steady state at 250 mg or higher as advocated by Dr. Harris, but rather sought the lowest efficacious dose of fulvestrant.

87. Understanding the distinction between reaching steady state and seeking the lowest efficacious dose highlights a number of inaccurate statements by Drs. Harris and Bergstrom. Dr. Bergstrom tries to refute that Howell is

"teaching away" towards a lower dose by stating "Howell teaches potentially lowering the dose to achieve the ***same 'therapeutic serum drug levels.'*** Indeed, the sentences immediately preceding . . . teach that drug accumulation had occurred. Because this drug accumulation was occurring, a lower dose could potentially be used to achieve the ***same*** 'therapeutic serum drug ***levels***.' Thus, AstraZeneca's assertion that this passage teaches lowering blood concentrations is inaccurate." Ex. 1013 at ¶ 159 (emphases in original); *see also id.* at ¶¶ 156-158. In other words, he argues that Howell proposed lowering the dose but not lowering blood concentration levels. Dr. Bergstrom misinterprets Howell on this point for the following reasons. First, and simply, Howell does not use the word "same." Second, by inserting the word "same" Dr. Bergstrom is proposing an interpretation of Howell which goes against a basic understanding of pharmacokinetics—i.e., that one can change the dose but not the serum concentration. Third, what Howell actually states is that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels." Ex. 1007 at 6. Howell noted that no pharmacokinetic-pharmacodynamic link had been proven and thus points to lower doses to achieve and maintain "therapeutic serum drug levels," i.e., levels not yet established. Howell thus teaches to lower the dose and, as a result, the serum drug levels, and teaches away from the claims. This also addresses Dr. Bergstrom's comment "that teaching away cannot be premised on unclaimed elements . . . and

[] dose is not claimed." Ex. 1013 at ¶ 160. In fact, Howell in his statement of lowering the dose is fundamentally linking it to serum concentration. And, as addressed in detail below (¶¶ 124-138), this teaching away is based on the prior art as a whole—both for endocrine therapy and for fulvestrant in particular—and would "discourage" a POSA "or lead them in a direction divergent from the invention." Ex. 1013 at ¶¶ 161-162.

88. Understanding Howell's reason for suggesting lowering the dose also makes clear that Dr. Bergstrom's argument that someone in the population receiving 250 mg IM monthly could potentially reach 8.5 $ngml^{-1}$ at month 5 (Ex. 1013 at ¶ 112, n.5) is based on contorted statistics and a number of unsupported assumptions which I understand Dr. Sawchuck will address. As regards Drs. Bergstrom and Harris's similar argument for 2.5 $ngml^{-1}$ dose (Ex. 1013 at ¶¶ 101-105, 164-166; Ex. 1015 at ¶¶ 210-211) they miss the goal of Howell 1996 which was a window of 2-3 $ngml^{-1}$. From the perspective of a clinician, the claims to at least 2.5 $ngml^{-1}$ are clearly different from the original predicted 2-3 $ngml^{-1}$ window in that the claims raise the floor (from 2 $ngml^{-1}$ to 2.5 $ngml^{-1}$) and take off the cap (of 3 $ngml^{-1}$). Further, Howell explains that this level was not established as the therapeutic level and, as I stated above, Howell noted that no pharmacokinetic-pharmacodynamic link had been proven and thus pointed to lower doses to achieve and maintain "therapeutic serum drug levels," i.e., levels not yet established.

89. Moreover, a skilled artisan would have interpreted the results reported in Howell 1996 with caution, because the study used only 19 patients, administered a first dose of 100 mg to the first four patients for "appraisal of drug safety," did not have a control group, and was not blinded. Ex. 1007 at 2. Howell further explained that tamoxifen was known to stimulate tumor growth and that the withdrawal of tamoxifen from patients in this study could account for some of the responses seen in the study. Ex. 1007 at 7. Finally, Howell noted that (i) the results needed to be confirmed in "future larger trials" and (ii) in terms of lowering the dose "further clinical studies are required to confirm this hypothesis." Ex. 1007 at 6. Dr. Howell reiterated his note of caution when he wrote that "phase II studies are notoriously unreliable in predicting superiority over old agents." Ex. 2040 (Howell 1997) at 3-4. This trial is an early stage research trial with a limited number of patients with advanced disease and lack of controls. The skilled artisan would know that drug candidates with encouraging phase II clinical results more often than not fail to reach market, especially in the area of treatment for breast cancer.

B) McLeskey (Ex. 1008)

90. McLeskey does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract." Further, McLeskey does not disclose "administering intramuscularly to a human in need of such treatment." Additionally, McLeskey does not disclose the limitations: "a

therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (i.e., individual).

91. McLeskey is a basic science research paper designed to investigate an artificial hormone independent mouse tumor model related to growth factor signaling pathways.

92. McLeskey states that model systems using FGF-transfected MCF-7 cells "have been described previously." Ex. 1008 at 2. McLeskey explains that these cell lines "allow[] effects of FGF overexpression on metastatic capability to be assessed by X-gal staining of organs and tissues of tumor-bearing mice." Ex. 1008 at 2. Based on the use in McLeskey of FGF-transfected MCF-7 cells, the skilled artisan would know that McLeskey continues a line of research into hormone independent pathways of tamoxifen resistance. The authors injected the cells into mice and used this model to evaluate whether tamoxifen resistance is related to FGF signaling pathways.

93. Dr. Harris states that "McLeskey discloses that the fulvestrant used in its experiment was formulated to a 50 mg/ml concentration, and further discloses the same formulation of fulvestrant as claimed" and that "the formulation 'was supplied by B.M. Vose (Zeneca Pharmaceuticals)" and "administered to mice at a

dose of 5 mg delivered subcutaneously every week." Ex. 1015 at ¶¶ 112-114. Dr. Harris's statement is misleading in that, in fact, McLeskey describes ***two*** formulations of fulvestrant. First, "powdered drug was [] dissolved in 100% ethanol and spiked into warmed peanut oil." Ex. 1008 at 2. Second, "50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil was supplied by B.M. Vose (Zeneca Pharmaceuticals)." Ex. 1008 at 2. Furthermore, these formulations were treated as interchangeable for the purposes of the research study. The paper does not specify which of the two formulations, if any, was used for the *in vivo* experiments—for example, in none of the figures is it clearly stated which fulvestrant formulation, if any, was used. In the *in vitro* experiments it is clear that fulvestrant (the compound) was administered.

94. The studies in McLeskey were not designed to evaluate the treatment of any disease with fulvestrant; instead, four different actives, tamoxifen, 4-OHA, letrozole, and ICI 182,780 (fulvestrant) were used as a research tool to assess a model of FGF-mediated tumor growth. The animal formulations administered in McLeskey included sustained-release tamoxifen pellets, letrozole in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage, 4-OHA (formestane) in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection, and two fulvestrant formulations—50 mg/ml preformulated drug in a vehicle of 10%

ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil, and powdered drug dissolved in 100% ethanol and spiked into warmed peanut oil to give a final concentration of 50 mg/ml—by subcutaneous injection.

95. McLeskey provides no data related to safe or effective treatment of humans or animals—indeed, McLeskey indicates that none of the test drugs slowed tumor growth. Ex. 1008 at 1. McLeskey calls the inability of fulvestrant to affect the estrogen-independent *in vivo* growth of FGF-transfected MCF-7 cells a "treatment failure." Ex. 1008 at 10. "[T]he insensitivity of the estrogen-independent *in vivo* growth of the FGF transfectants to [fulvestrant] or the aromatase inhibitors implies that clinical tamoxifen resistance due to FGF receptor-mediated signaling ***may not respond*** to a second hormonal therapy." Ex. 1008 at 11 (emphasis added). Because fulvestrant was ineffective, McLeskey proposes that "[t]herapy . . . with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1008 at 12-13.

96. McLeskey provides no blood plasma concentration levels in mice after subcutaneous administration of any of the experimental drug formulations used—not for fulvestrant or the aromatase inhibitors or tamoxifen, nor did McLeskey administer an "intramuscular injection" to "a human in need." For the experiment in mice, fulvestrant was administered "5 mg s.c. [subcutaneous] every week." Ex. 1008 at 5. Thus, from a clinician's perspective, it does not teach treatment of

humans or minimum plasma levels.

97. McLeskey also provides no solubility or other data for any of the formulations used.

C) O'Regan (Ex. 1009)

98. O'Regan does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." O'Regan does not disclose "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." Further, O'Regan does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (i.e., individual).

99. O'Regan describes a study in ovariectomized mice with implanted endometrial tumors, evaluating the risks of promoting endometrial cancer after treatment with toremifene or fulvestrant. The only fulvestrant formulation used in O'Regan was dissolved in ethanol and administered in peanut oil (following the evaporation of the ethanol under N_2) to mice by subcutaneous injection. Ex. 1009 at 2.

100. O'Regan cites to Howell 1996 as an early stage study and states that

"there are not the same stringent requirements for a drug that is used as a palliative therapy in advanced disease compared with drugs that are used for long-term adjuvant therapy." Ex. 1009 at 2. And, O'Regan observes that "[c]learly, a woman should not be led to believe that no risks exist because inadequate and early clinical studies are being reported." *Id.* at 5.

D) DeFriend (Ex. 1038)

101. DeFriend does not disclose "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." Further, DeFriend does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

102. Dr. Harris's statement that "DeFriend describes the first Phase I studies using fulvestrant to treat breast cancer" is incorrect. Ex. 1015 at ¶ 118. DeFriend is not a treatment study. It is a first-in-humans study to evaluate the biological activity of fulvestrant as an estrogen antagonist in primary breast tumors *in vivo*. DeFriend studied pharmacodynamic indicators of antiestrogen activity in fifty-six patients with primary breast cancer that were administered fulvestrant prior to receiving primary breast surgery. Ex. 1038 at 1. The DeFriend study administered 7 daily doses of 6 mg or 18 mg i.m. injection of "a short-acting

formulation, containing 20 mg/ml drug in a propylene glycol-based vehicle." Ex. 1038 at 2.

103. DeFriend reports that "[a]nimal studies have demonstrated considerable interspecies variability in the elimination half-life of [fulvestrant], with a half-life of about 4 h in rats and 2 days in dogs after i.m. administration." Ex. 1038 at 5. In other words, the translation of pharmacokinetic information from one species to another would be very different. Dr. Harris argues that the DeFriend study "was reported as a success." Ex. 1015 at ¶ 93. DeFriend concluded that "[t]his small study has shown [fulvestrant] to be well tolerated after short term administration and has produced preliminary evidence to suggest that this novel agent does exhibit biological activity as an estrogen antagonist in primary breast tumors, without producing demonstrable agonist effects." Ex. 1038 at 6. The study does not investigate whether fulvestrant is an effective treatment for breast cancer, and the authors conclude only that fulvestrant should be further evaluated to determine "whether a pure estrogen receptor antagonist offers any additional benefit in the treatment of human breast cancer" over traditional treatments such as tamoxifen. Ex. 1038 at 1. In particular, the authors caution that "the pure [estrogen] antagonist profile of activity of ICI 182780 in human subjects will need to be confirmed in future clinical studies." Ex. 1038 at 5. In other words, DeFriend concludes that, while fulvestrant had potential, its efficacy on disease

was unknown.

104. DeFriend provides some pharmacokinetic data in Figure 1, however that figure does not teach therapeutically significant fulvestrant blood plasma concentrations over 4 weeks from one dose. Figure 1 merely shows that there is some accumulation of fulvestrant in the blood stream after repeated injections. Dr. Harris states that DeFriend found that "[t]he serum concentration of ICI 182,780 [fulvestrant] was dose dependent." Ex. 1015 at ¶ 119. However, Dr. Harris fails to recognize that DeFriend did not show a dose effect on estrogen and progesterone receptor expression, as there was no significant difference between the 6 and 18 mg doses, i.e., there was no correlation between the level of fulvestrant in the blood and the activity seen in the tumors. In any case, Dr. Harris's citation to serum concentration as "dose dependent" relates to the propylene glycol-based formulation used in DeFriend. The paper does not teach the ordinary researcher anything about any other formulation.

105. The planned study using a long-acting castor oil-based fulvestrant formulation, mentioned in DeFriend (Ex. 1038 at 5), was intended to seek early evidence of inhibitory activity of the compound on human breast cancer and to address the question of whether the adverse effects seen in the present studies were due to the drug itself or to the propylene glycol based formulation, as noted in the reference itself: "It is possible, therefore, that these adverse events were related

either to the drug itself or to the propylene glycol-based vehicle used in the short-acting formulation. This question will be addressed in future studies which are planned with a different, long-acting, formulation of ICI 182780 contained in a castor-oil based vehicle." *Id.* at 5. DeFriend does not provide any further information regarding the components of this long-acting castor oil-based fulvestrant formulation.

XII) THE CLAIMS OF THE '680 PATENT ARE NOT OBVIOUS

A) Ground One: Howell 1996

1) Howell 1996 Would Not Have Been A Logical Starting Point: It Left Many Questions Unanswered And Was Questioned By Researchers At The Time

106. Dr. Harris argues that "[a]s a starting point, a person of ordinary skill in the art would have read the existing literature and known about the positive results that were reported in Howell regarding the first Phase II clinical trial" which "provide[d] the most robust clinical data on fulvestrant at the time of the invention" and "was a recognized success." Ex. 1015 at ¶¶ 127-129. Furthermore, he argues "[t]he clinical results of Howell would have been of key interest to those of skill in the art because they reported on the only Phase II trial of a drug that proved to show tremendous promise and confirmed the efficacy of fulvestrant in women for the treatment of breast cancer." Ex. 1015 at ¶ 127. In my opinion, as I stated in my previous declaration, a skilled artisan would interpret the limited data in

Howell 1996 with caution, and would not rely on these data to choose fulvestrant from the many other treatment candidates available at the time of the invention as Howell left many questions unanswered regarding active ingredient, amount, and route of administration.

107. Regarding active ingredient, Howell 1996 uses data from a study of 19 "highly selected" patients (i.e., patients most likely to respond to hormone treatment were selected for the study) by the same investigators, myself included. A skilled artisan would realize that the underlying study reported in these references was not from a large, randomized, double-blind phase III clinical trial. It was a small, highly selected group of patients with hormone sensitive tumors and there was no control group comparing the results to the standard therapy at that time. And, indeed, we noted in Howell 1996 that the results needed to be confirmed in "future larger trials." Ex. 1007 at 6. A skilled artisan would interpret the results reported from this small non-randomized study with caution. In particular, the underlying study treated only 19 patients, administered a first dose of 100 mg to the first four patients for "appraisal of drug safety," did not have a placebo control, and was not blinded. Ex. 1007 at 2.

108. As noted in paragraph 68 above, up to one-third of responses could have been due to tamoxifen withdrawal. Therefore, the actual number of patients whose tumors showed shrinkage based on treatment with fulvestrant may have

been as low as 5 patients.

109. The skilled artisan would also be concerned about the possibility of fulvestrant resistance precluding further endocrine treatment and whether fulvestrant would have deleterious effects on other tissues and bone given its lack of estrogenic qualities. Ex. 1039 (Osborne 1995) at 5. For example, in Robertson 1997, which described the same 19-patient study of Howell 1996, we stated that "[n]one of the 10 patients who developed acquired resistance to [fulvestrant] subsequently showed an objective response to megestrol acetate as third-line therapy." Ex. 1043 (Robertson 1997) at 3. For this reason, we cautioned that "this early finding raises the hypothesis as to whether acquired resistance to [fulvestrant] may be equivalent to developing an endocrine resistant phenotype." Ex. 1043 (Robertson 1997) at 3. Dr. Harris is silent on this point.

110. Dr. Bergstrom opines that Howell 1996 "provides significant detail concerning the formulation . . . for fulvestrant." Ex. 1013 at ¶ 86. There are no details provided in Howell 1996 regarding the fulvestrant formulation used in that study other than that it was a monthly depot intramuscular injection of fulvestrant "contained in a castor oil-based vehicle" to 19 patients. Ex. 1007 at 2. I understand that InnoPharma argues that "[a] POSA would have been motivated to develop a fulvestrant formulation that would achieve the positive results reported in Howell." Petition at 35. I understand that other AstraZeneca experts have

concurrently submitted declarations that address this issue. However, as a clinician, I do understand that different formulations, whether or not they contain castor oil, will give different physiological results.

111. Dr. Harris disagrees with my characterization of the patient population in Howell 1996 as "'highly selected' and not blinded" instead arguing (without literature support) that "[t]his is exactly the population in which one should test new endocrine therapies developed to overcome tamoxifen resistance." Ex. 1015 at ¶ 137; *see also* Petition at 21. But "highly selected" literally means that the patients selected for the study were those most likely to respond to treatment, i.e., there is a bias towards response. This was done for two reasons: (1) to give us (the researchers) the best chance of understanding whether fulvestrant could work to treat breast cancer and (2) to give the patients the best chance of actually benefitting from treatment. Indeed, in Howell 1996 we indicated the nature of the disease in these "highly selected" patients (i.e., all had slow growing metastatic tumors) and the ethical responsibility we had to give these patients the best chance to respond because they were foregoing other treatment options to be in the study. Ex. 1007 at 1-2 ("Since tamoxifen-resistant breast cancer cell lines have been shown to retain sensitivity to specific anti-oestrogens . . . the effects of ICI 182780 were evaluated in a group of post-menopausal patients with tamoxifen-resistant breast cancer. . . . The study was approved by the ethics committee of each clinical

centre. . . . Patients were included if they had been treated with tamoxifen as an adjuvant to surgery for more than 2 years and then relapsed, or if they had been treated with tamoxifen for advanced disease, had a complete or partial remission or disease stabilization ('no change') for at least 6 months, and subsequently progressed while taking tamoxifen."), 3 (Table I summarizing patient characteristics and tumour receptor status), 7 ("the highly selected group of patients reported here").

112. Moreover, the very reference InnoPharma's experts cite in their declarations (e.g., Ex. 1013 at ¶ 143), Howell Breast, further explains the reasoning behind our selection, i.e., that "[i]t was not clear that the compound should continue in development and a trial was required which would give the indication of maximal compound potency whilst requiring as few patients in trial as possible. . . . Because there was no guarantee of response, and it was an unusual study of sequential use of two antioestrogens, we selected patients likely to respond to therapy." Ex. 1041 (Howell Breast) at 2.

113. The highly selective nature of the study is important to note because the results may be representative only of this favorable subgroup of patients, not the population of postmenopausal women with metastatic breast cancer as a whole—this concern was raised by other researchers in the field at the time (1995/1996) who, unlike Dr. Harris (in 2017), were very aware of the importance

of this particular point. Ex. 2038 (Dowsett 1995) at 1 ("[T]he group of patients that they selected for treatment [in Howell] would generally be regarded as favourable in relation to treatment with a second-line agent such as an aromatase inhibitor.").

114. In fact, Dowsett reanalyzed two clinical studies with letrozole and vorozole to support his concern regarding the highly selected patient population and the inclusion of the no change category in Howell. Following reanalysis, the response rates for letrozole and vorozole jumped from 33% to 83% and 75%, respectively, for a combined response rate of 78%. Ex. 2038 (Dowsett 1995) at 1 ("We have reanalysed the response rate of our two phase I/II studies of two new triazole aromatase inhibitors (vorozole and letrozole). . . . In this reanalysis we have included only patients who fitted Howell and co-workers' entry criteria. Thus, patients were excluded if they had received chemotherapy in addition to tamoxifen, failed on adjuvant tamoxifen after less than 2 years treatment, or showed intrinsic resistance to tamoxifen in the metastatic setting. We have also included patients with no change for 6 months in the group of responders. 6 of 21 and 12 of 24 patients were acceptable for this reanalysis from the letrozole and vorozole studies, respectively. There were 5 of 9 responders, respectively, giving a combined response rate of 78% (14/18), which is clearly not significantly different from that with the new antioestrogen. The response rate cited in each of the

original papers without this selection was 33% (7/21 and 8/24, respectively).").

115. Dr. Bergstrom's comment that "the lack of blinding in Howell, [] is irrelevant" (Ex. 1013 at ¶ 163) simply underscores the unreliability of phase II studies. By definition, when a trial is blinded, it must be a randomized comparison because one cannot blind a non-randomized trial. The fact that a trial is not blinded is certainly a limitation for understanding how a new drug would compare to standard of care.

116. InnoPharma also criticizes my characterization of Howell as "too 'small' of a study to assess whether fulvestrant was efficacious." Petition at 20. Notably, InnoPharma's own expert, Dr. Bergstrom, and the very publications InnoPharma cites acknowledge the limitations of small studies. Ex. 1013 at ¶¶ 37-38, 176 ("[I]nter-subject variability in a pharmacological response to any particular drug is often very high. Due to this variability, in order to determine the precise PK/PD relationship, large sample sizes of patients are used."; "[T]ypically a very large patient population is required before a formal PK/PD link can be established."); Ex. 1032 (Nicholson 1995) at 12 ("[A]lthough these results [in Howell] are better than would have been expected following tamoxifen withdrawal or second line endocrine therapy, the study numbers were small and no direct randomized comparisons were made with other endocrine measures.").

117. And, Dr. Howell, himself, sounded a further note of caution based on

the composition of the open label, phase II trial of 19 patients reported in Howell 1996. Referring to the Howell 1996 data, Dr. Howell wrote that "phase II studies are notoriously unreliable in predicting superiority over old agents." Ex. 2040 (Howell 1997) at 3-4. Thus, the authors of the phase II study of 19 patients highlight the limitations of the data and describe such data as "notoriously unreliable" in predicting whether a drug will successfully survive the clinical development process.

118. Contrary to InnoPharma's argument (Petition at 20), it was not I nor AstraZeneca that cautioned that Howell "should be interpreted with care in relation to other published data"—it was, indeed, other skilled researchers in the field. Ex. 2038 (Dowsett 1995) at 1 ("[T]he cited response rate of 13/9 (69%), albeit striking, should be interpreted with care in relation to other published data."). As stated above, those researchers also noted the highly selective nature of the patients studied in Howell 1996 and that the approach taken in Howell 1996 to include "no change" responses with objective responders is uncommon. Ex. 2038 (Dowsett 1995) at 1 ("First, although there are biological and clinical arguments to include patients with 6 months of no change with objective responders, this approach is uncommon. Second, the group of patients that they selected for treatment would generally be regarded as favourable in relation to treatment with a second-line agent such as an aromatase inhibitor."). Dr. Harris argues that "it is routine

practice to include the 'no change' category in reporting results" and quotes the Howell 1995 paper wherein we indicated that "it is important to recognise the no-change category of response since it is clinically relevant" as if that is in some way contradictory to my opinions now. Ex. 1015 at ¶¶ 134-136. It is not. The point is that from an objective view of the literature, at the time of the invention, it was far from settled. Other skilled researchers in the field criticized our inclusion of the no-change category in the response rate—this is a noted limitation of the study.

119. As an aside, I note that InnoPharma misinterprets Howell 1995 (Petition at 20). Our statement that the hypothesis as to whether "[t]he ability of ICI 182,780 to bind tightly to the oestrogen receptor [] and to downregulate the receptor might afford the specific antiestrogen a therapeutic advantage over other forms of endocrine therapy" was "worth pursuing" was in response to Dowsett's "suggest[ion] that treatment with ICI 182780 is conceptually similar to that with aromatase inhibitors" not in response to his argument that "the high response rate we reported. . . should be interpreted with care." Ex. 1045 (Howell 1995) at 1-2.

120. Regarding the amount of fulvestrant to deliver, a skilled artisan would need further experiments to determine the relationship between the responses observed in Howell 1996 and the reported blood plasma levels. In particular, the Howell 1996 paper stated that "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date." Ex. 1007 at 6. In fact, as

discussed above (Section XI.A.), Howell goes on to state that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels" but notes that "further clinical studies are required to confirm this hypothesis." Ex. 1007 at 6; *see also id.* at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective."). These are not "isolated snippet[s] divorced from all context" (Petition at 29-30)—these are verbatim conclusions reported in Howell 1996 in both the discussion section of the paper and *again* in the conclusion based on the pharmacokinetics observed in the study, conclusions that were acted upon by the research community.

121. In other words, while Howell 1996 initially targeted a blood plasma level between 2-3 $ngml^{-1}$ with 3 $ngml^{-1}$ set as a maximum blood plasma level, when analyzing the research results, Howell found that no therapeutic level had been established and encouraged that further studies look to lower doses. Howell 1996 ***did not*** set a minimum blood plasma concentration of at least 2.5 $ngml^{-1}$. And, because Howell 1996 suggested to go down in dose compared to the initial target window, Howell 1996 taught even further away from targeting at least 8.5 $ngml^{-1}$ as required by the claims.

122. Dr. Harris disagrees with the plain language of Howell 1996. According to Dr. Harris, "Howell's comment [regarding lower doses] is merely a

hypothesis," "a person of skill in the art would not have wanted to lower the dose used in Howell, which directly correlated with efficacious results and showed no adverse side effects," and "[r]educing the dose in such a situation would be against the basic principles of practice in my opinion." Ex. 1015 at ¶¶ 143-145. Not surprisingly, Dr. Harris cites not a single endocrine therapy reference for support.

123. Dr. Harris's comment that Howell's statement regarding "lower doses" was "merely a hypothesis" has already been addressed. *See* Section XI.A. (detailing the internal consistency and argument by Howell within the paper (Howell 1996) and the fact that the subsequent clinical trials (Studies 18, 20, 21) then included doses of 250 mg, 125 mg, and 50 mg).

124. As regards Dr. Harris's statement that decreasing the dose would be against basic principles of practice, lowering the dose was consistent with the knowledge from previous endocrine drugs at the time (e.g., SERMs, aromatase inhibitors, progestins, antiprogestins). I discussed this concept extensively in my previous IPR declaration (*see* Ex. 2136 (Robertson Mylan Decl.) at ¶¶ 179-183). However, neither InnoPharma nor Dr. Harris address this consistent teaching in the field. I thus reiterate the examples from my previous declaration as well as include many other examples herein.

125. For the SERMs, tamoxifen was studied in randomized clinical trials at doses of 40 mg and 20 mg, and it was determined that the higher dose did not

confer any significant advantages over the lower 20 mg dose. Ex. 2050 (Bratherton) at 6 ("[N]o statistically significant advantage for 40mg daily over 20mg daily [tamoxifen] has been found[.]"); Ex. 2010 (Fornier) at 4 ("Several randomized studies demonstrated that tamoxifen doses higher than 20 mg/d do not confer further advantages."); Ex. 2014 (Pritchard 1997) at 7, 13 ("Several large randomized or dose-finding studies have shown no major dose-response effect for doses of tamoxifen ranging from 2 to 100 mg/m^2 body surface area given twice daily. . . . Loading doses of tamoxifen had been suggested as being most consistent with its pharmacology but the lack of dose-response with the drug suggests that this approach is unlikely to be clinically useful."). Consequently, it is the lower dose of tamoxifen that is used in clinical practice.

126. Toremifene is another example of a SERM that showed no further clinical benefit with higher doses. Toremifene was investigated at doses of 200 mg and 60 mg and it was concluded that the higher dose provided no benefit over the lower dose and, in fact, may be associated with increased toxicity. Ex. 2010 (Fornier) at 4 ("Toremifene doses higher than 60 mg/d did not offer any advantages over lower doses."); Ex. 1050 (Buzdar Clin. Cancer Res. 1998) at 3 ("In a comparative trial involving women with advanced breast cancer, toremifene (60 and 200 mg) showed similar efficacy and safety to tamoxifen (20 mg). The higher dose of toremifene had no benefit over the lower dose and was associated

with an excess of liver function abnormalities; thus, 60 mg/day toremifene was approved for advanced breast cancer."); Ex. 2022 (Minton) at 2 ("To date, these phase III trials have not demonstrated greater benefit from higher doses of toremifene."). Median survival for patients who received 60 mg/day toremifene was 38 months and 200 mg/day toremifene was 30 months (compared to tamoxifen 20 mg/day which was 32 months). Ex. 2039 (Hayes 1995) at 3. Toremifene was approved by the FDA at the lower 60 mg dose.

127. Phase II trials evaluating different doses of droloxifene were found to have not convincingly demonstrated a dose effect. The first phase II trial reported on the 100 mg dose of droloxifene only but referenced two other large phase II dose-finding studies under way that were looking down to lower doses, i.e., 20 mg and 40 mg doses per day. Ex. 2041 (Haarstad 1992) at 3. There were 369 patients included in one large phase II trial (268 evaluable) which compared 20 mg versus 40 mg versus 100 mg per day of droloxifene. Ex. 2047 (Rauschning 1994) at 1. The results indicated that 20 mg droloxifene was inferior in terms of response rates to 40 mg, 100 mg and combining 40+100 mg. *Id.* For example, the response rates (CR+PR) were 30% in the 20 mg group, 47% in the 40 mg group, and 44% in the 100 mg group. *Id.* The other large phase II trial included 196 patients and again compared 20 mg versus 40 mg versus 100 mg per day of droloxifene. Ex. 2061 (Bellmunt 1991) at 1. The results indicated that 17% of patients treated with

20 mg/day responded to treatment, compared to 30% in the 40 mg/day group and 31% in the 100 mg/day group. *Id.* at 2. In the phase III trials comparing droloxifene to tamoxifen as first-line endocrine treatment, the 40 mg/day dose of droloxifene was used (i.e., the lowest dose which seemed efficacious), not the 100 mg/day dose. Ex. 2083 (Buzdar 2002) at 1-2; *see also* Ex. 2085 (Buzdar 1994) at 3 ("In a phase I-II European trial, the drug showed significant antitumor activity when given at 20, 40, and 100 mg on a once-a-day schedule. In this study there was suggestive evidence that a higher response rate occurred at 40 and 100 mg/day than at 20 mg/day, but this suggestion was inconsistent with the experience with tamoxifen, which had no dose-dependent antitumor activity.").

128. This concept similarly applied to SERMs after the invention date. For example, clinical efficacy of another SERM, arzoxifene, was evaluated at 20 mg and 50 mg per day doses in phase II studies in hormone-sensitive advanced breast cancer patients. The first phase II study evaluated 92 patients and found no difference between doses although response rates for 20 mg were numerically higher than for 50 mg (40.5% versus 36.4%), as was clinical benefit rate, which included stable disease (64.3% versus 61.4%). Ex. 2088 (Baselga 2003) at 1. The second phase II study evaluated the same two doses in 63 tamoxifen-resistant patients, and separately in 49 patients with hormone-sensitive disease. Ex. 2108 (Buzdar ASCO 2001) at 3 ("There were no significant differences in response

rates, time-to-progression, or toxicity, between the 20 and 50 mg subgroups."); *see also* Ex. 2111 (Buzdar 2003) at 1 ("The 20-mg dose seems to be at least as effective as the 50-mg dose. Accordingly, arzoxifene 20 mg/d was selected for further study in patients with breast cancer."). Response rates were the same in the tamoxifen-resistant patients for both doses (10%). *Id.* In contrast, a response rate of 26% was seen with 20 mg arzoxifene in the hormone-sensitive group with an overall median TTP of 8.3 months. *Id.* The response rate for the 50 mg dose was somewhat lower (8%) and the TTP was shorter (3.2 months). *Id.* Based on this data, 20 mg arzoxifene was taken forward into phase III trials against tamoxifen as first-line therapy.

129. The teaching of lower doses for endocrine agents similarly applied to aromatase inhibitors. For example, anastrozole was studied clinically at two doses, 10 mg and 1 mg, and researchers concluded that there was no difference between the doses. Ex. 2119 (Buzdar 1996); Ex. 2137 (Buzdar 1997) at 1 ("[T]here was no statistical evidence of a difference between either 1 or 10 mg doses of anastrozole and megestrol acetate for any efficacy endpoint."); Ex. 2138 (Jonat 1996) at 1 ("There were no statistically significant differences between either dose of anastrozole and megestrol acetate in terms of objective response rate, time to objective progression of disease or time to treatment failure."); Ex. 2010 (Fornier) at 4 ("No difference was found between the two doses of anastrozole."); Ex. 2022

(Minton) at 3 ("The group using 10 mg/day [of anastrozole] showed no advantage in response rate or survival over the group using 1 mg/day."). Anastrozole was approved at the lower 1 mg dose.

130. For letrozole, like anastrozole, there were two pivotal phase III trials comparing two doses of letrozole (2.5 mg, 0.5 mg) versus megestrol acetate. These gave slightly differing results but again confirmed overall no dose response. In the first of these trials, 551 postmenopausal women with metastatic breast cancer progressing after treatment with tamoxifen were randomized to receive letrozole 2.5 mg daily, letrozole 0.5 mg daily, or standard doses of megestrol acetate. The letrozole 2.5 mg dose yielded an overall response rate of 35% compared with 27% for letrozole 0.5 mg and 32% for megestrol acetate. The TTP was 5.6 for letrozole 2.5 mg, 5.1 for letrozole 0.5 mg, and 5.5 for megestrol acetate. The OR and TTP showed a significant difference between letrozole 2.5 mg and letrozole 0.5 mg in favor of the 2.5 mg dose. Ex. 2139 (Dombernowsky) at 1, 3-5. In the second study, carried out in 120 centers in the U.S. and Canada involving 602 patients with advanced breast cancer progressing on tamoxifen, patients were randomized to letrozole 2.5 mg daily, letrozole 0.5 mg daily, or a standard dosage of megestrol acetate. While the study design was similar to the first trial, the results were different. In this trial, the objective response rates were 16%, 21%, and 15%, respectively. The median TTP was 3 months for letrozole

2.5 mg, 6 months for letrozole 0.5 mg, and 3 months for megestrol acetate. Patients with letrozole 0.5 mg had a significantly longer TTP than megestrol acetate whereas patients on letrozole 2.5 mg did not show a significant improvement compared to megestrol acetate. The results between letrozole 2.5 mg and 0.5 mg were numerically in favor of the lower dose but not statistically different. Ex. 2140 (Buzdar 2001) at 1, 5-7. As noted by the authors of this study "there was no dose-dependent effect noted between letrozole 0.5 mg and letrozole 2.5 mg." *Id.* at 9. Both the Dombernowsky and Buzdar papers noted that a previous study (Ex. 2141 (Dowsett Clin. Cancer Res. 1995 at 1)) had reported that "[t]here were no significant differences between the doses in aromatase inhibition." The reason the company, Novartis, selected to proceed with the letrozole 2.5 mg dose was not disclosed and referenced as "(data on file, Novartis Pharmaceuticals Corporation, East Hanover, NJ)." Ex. 2140 (Buzdar 2001) at 9.

131. In a review article on vorozole (Ex. 2142 (Goss 1998)), three studies reporting on the degree of aromatase inhibition by different doses of vorozole (1 mg, 2.5 mg, 5 mg) were described. In the first two, Goss noted "[n]o statistical differences between the doses were seen, thus a minimally effective dose could not be identified" and "[n]o dose response relationship could be established," respectively. *Id.* at 3-4. In the third study, a trend for one of a number of measures of aromatase inhibition performed in that study suggested the 1 mg dose might

have lower potency. *Id.* at 5. Goss reports that the difference in this single measurement between 1 mg and 2.5 mg was the reason for supporting selection of the 2.5 mg dose for clinical development. There was no difference in any of the studies for any parameter between the 2.5 mg and 5 mg doses.

132. Fadrozole, a potent oral nonsteroidal aromatase inhibitor, was investigated in a large multicenter double-blind randomized trial of 423 postmenopausal women with advanced breast cancer after failure on tamoxifen. The doses tested were 1 mg, 2 mg, and 4 mg. The authors concluded that the objective response rate was no different between the three doses. Ex. 2143 (Hoffken) at 2.

133. Aminoglutethimide, the first generation aromatase inhibitor which had been reported to be as effective as tamoxifen but had more side effects, was assessed at varying doses and no dose response identified. This was initially looked at as far back as 1985 when Bonneterre reported on a multicenter randomized trial comparing 500 mg with 1000 mg per day of aminoglutethimide. One hundred seventy patients were randomized to the study. As Bonneterre notes "[r]esponse rates were similar in both groups," "[d]uration of response was the same in both groups[], as was mean time to response" and "[s]urvival[] was similar in both groups." Ex. 2144 (Bonneterre 1985) at 1. Importantly, in consideration of the potential value of increasing dose, Bonneterre reports "[n]o response could be

obtained with 1 g after relapse or failure with 500 mg" confirming not only that the clinical outcomes were the same in each group but there was no benefit in moving to a higher dose after using a lower dose, which is further evidence of the lack of a dose response. *Id.*

134. The teaching of lower doses for endocrine agents also applied to progestins. For example, medroxyprogesterone acetate was evaluated at 400 mg/day p.o. (10 patients) and 800 mg/day p.o. (29 patients) doses and the CR + PR rate was 67% in the 400 mg/day patients and 37% in the 800 mg/day patients. Ex. 2145 (Hortobagyi 1985) at 2. Another trial randomly assigned 201 patients with advanced breast cancer to receive 300 mg/day versus 900 mg/day of oral medroxyprogesterone acetate. The overall response rates were 23% and 16%, respectively. There was also no difference in the response duration and survival. The TTP was reported as significantly longer in patients treated with 900 mg/day. Ex. 2146 (Rose 1985) at 3. In a randomized trial of medroxyprogesterone acetate 1200 mg/day p.o. and 600 mg/day p.o. in 80 patients, there was no significant differences between the two treatment arms in terms of response rate, duration of response, overall survival, or toxicity. Ex. 2147 (Koyama) at 1.

135. Similarly, for the progestin, megestrol acetate, there was a series of studies conducted but ultimately no benefits were identified with using higher doses. The first study randomly assigned 172 patients with advanced breast cancer

to receive megestrol acetate 160 mg/day or high-dose megestrol acetate 800 mg/day. The higher dose resulted in a superior complete plus partial response rate (27% versus 10%), TTF (median 8.0 months versus 3.2 months), and survival (median 22.4 months versus 16.5 months) when compared to the lower dose. However, weight gain was noted as a distressing side effect with "43% of high-dose patients gaining more than 20 lbs" (compared to 13% for the lower dose). Ex. 2148 (Muss) at 1, 8 ("Although high-dose therapy was significantly more efficacious than standard-dose treatment in this trial, we believe that it is premature to recommend it as standard treatment. The substantial weight gain associated with this regimen is likely to be psychologically deleterious to many women."). The second trial was a phase I/II trial of 57 patients using doses of megestrol acetate ranging from 480 to 1600 mg/day. Substantial weight gain again occurred in patients treated at the 1600 mg dose level. Ex. 2149 (Abrams 1990) at 3. Results from these two trials justified the development of a large definitive phase III trial of 368 women with metastatic breast cancer treated with either 160 mg/day, 800 mg/day, or 1600 mg/day of megestrol acetate. The response rates were 23%, 27%, and 27%, respectively. The authors noted that "[r]esponse duration correlated inversely with dose." Ex. 2150 (Abrams 1999) at 1. For TTP and overall survival there was no significant differences between the three dose treatment arms. As with the two previous studies, toxicity (i.e., weight gain) was

clearly dose related with 20% of patients on the two higher doses arms reporting weight gain of 20% compared with only 2% in the lower 160 mg/day dose group. This led the authors to conclude that "[w]ith a median follow-up of 8 years, these results demonstrate no advantage for dose escalation of MA in the treatment of metastatic breast cancer." *Id.*

136. This prevailing wisdom continues to be true for endocrine therapies today with Faslodex® (fulvestrant) intramuscular injection being the exception. For example, the teaching of lower doses for endocrine agents also applies to antiprogestins. In a phase II trial evaluating a 100 mg/day dose of onapristone in 118 postmenopausal patients with advanced breast cancer who had progressed on tamoxifen, the response rate was 10% and clinical benefit rate was 49%. In 1995, a phase II trial looked down in dose, evaluating both 50 mg and 100 mg/day doses of onapristone. The trial was halted not because of efficacy but because of side effects, i.e., liver function abnormalities that were observed for both doses. Similarly, for lonaprisan, 68 patients were evaluated in a phase II study comparing doses of 25 mg and 100 mg/day. Stable disease rates for the 25 mg/day dose was 21% and for the 100 mg/day was 7%. Ex. 2151 (Jonat 2013) at 1.

137. Thus, it was known at the time (and continues to hold true today) that for nearly all prior art endocrine therapies higher tolerated doses do not improve efficacy. In fact, in another related case, in trial testimony, the clinical expert for

the patent challengers admitted exactly this concept. Ex. 2049 (July 14 Trial Tr.) at 216:4-11 ("Q. Dr. Mehta, you are familiar with the experience with endocrine therapies that greater doses even without toxicity did not lead to increased efficacy, right? A. I'm familiar with that. Q. And, for example, anastrozole was tolerated at 10 mg and 1 mg, but there is no additional clinical benefit for the higher dose, right? A. That is correct."), 219:15-20 ("Q. And, Dr. Mehta, you would agree that in fact anastrozole, aminoglutethimide and fadrozole studies all showed that higher tolerated doses did not provide greater efficacy? A. That is correct. Q. And all of that was known prior to 2000, correct? A. That is correct."). Dr. Bergstrom argues that Howell's teaching to lower the dose cannot teach away from the claims because "teaching away must be based on the prior art as a whole." Ex. 1013 at ¶ 161. Indeed, as illustrated above, here it is.

138. In the phase III clinical trials of fulvestrant versus anastrozole, AstraZeneca included a lower dose of 125 mg, which confirms that the skilled artisan would have sought lower blood plasma fulvestrant concentrations based on Howell 1996. In fact, the skilled artisans did so. This lower 125 mg dose of fulvestrant was subsequently not found to be effective and was therefore dropped from both of these phase III trials of fulvestrant versus anastrozole. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002).

139. Dr. Bergstrom's argument that "[t]he fact that Howell could not

formally determine a PK/PD link as a statistical matter does not alter its teaching that a PK/PD link was predicted and achieved" is, first, logically inconsistent. Ex. 1013 at ¶ 176. Second, there is no "teaching" in Howell that a PK/PD link was "predicted and achieved," only that it was not. Ex. 1007 at 6 ("[A] direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date."). And, Dr. Bergstrom's attempt to downplay Howell's findings as not "discredit[ing] or criticiz]ing] the 250 mg dosing regimen in any way" (Ex. 1013 at ¶ 162) contradicts his opinion that a PK/PD link is needed "to develop the optimal dose of a drug that is effective in the majority of patients representing a population" because "inter-subject variability in a pharmacological response to any particular drug is often very high." Ex. 1013 at ¶¶ 35, 37. Indeed, in Howell 1996, "wide variation between individual patients were observed." Ex. 1007 at 4.

140. Both InnoPharma and Dr. Bergstrom argue that "Howell's discussion of lower doses cannot teach away from the '680 patent because dosage is ***not*** a limitation in any challenged claim" and "[t]hus, a PK/PD link is not required by the claims" and nonobviousness cannot be based on dose. Petition at 30 (emphasis in original); Ex. 1013 at ¶ 173. I disagree for three reasons. First, I find this argument entirely inconsistent with InnoPharma and its experts' reasonable expectation of success arguments regarding the blood plasma level limitations, and, in particular, their DeFriend arguments (discussed below) which are solely

based on dose. Second, as noted in paragraphs 33 and 87, dose is not divorced from the claims. Third, and importantly, the limitations of the claims dictate both the administration duration and dose of the formulation, i.e., an amount sufficient to provide a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 or 8.5 $ngml^{-1}$ for at least two or four weeks.

141. Regarding route of administration, Howell 1996 would be recognized to be a preliminary study of safety and efficacy of the molecule in few patients. A skilled artisan would not conclude that even the method of administration used in Howell was optimal. Indeed, it is not unusual that the method of administration used in early phase clinical trials (first in man, or early phase I or II studies) is not intended to be, or is discovered not to be, the best method of administration for clinical use. Ex. 2051 (Cohen) at 14; Ex. 2052 (Sweetana) at 9 ("'Heroic' approaches describe efforts to solubilize drugs for early clinical studies [] using additives that probably are not acceptable for commercial formulations."). In particular, often early studies use parenteral routes of administration as a way to simply get the drug into the body in order to evaluate basic safety and toxicity questions and development work on the optimal formulation or route of administration proceeds thereafter if further clinical research is warranted.

142. For example, after close of the clinical trial reported in Howell 1996, AstraZeneca conducted clinical trials using ICI 182,780 in different

formulations for a route of administration, as well as different dosages. Starting in 1994, AstraZeneca began clinical study of ICI 182,780 in an oral formulation. After an early clinical study with the oral formulation demonstrated ICI 182,780 was safe to administer to humans, AstraZeneca conducted three phase I clinical trials with oral formulations in 1995, 1996, and 1998.

143. Indeed, an oral formulation was preferable to an intramuscular injection for a number of reasons, including patient tolerability and convenience. The leading SERM (tamoxifen) and aromatase inhibitor (anastrozole) were both administered orally. Then and even since, patients receiving endocrine therapy prefer to receive oral administration instead of injections. Ex. 2053 (Fallowfield 2006) at 1 ("Sixty-three per cent of patients preferred tablets, 24.5% preferred the injection and 12.5% had no preference."). Dr. Harris states (once again without literature support) that "IM injections are also favored because they ensure compliance for patients because, in contrast to oral doses that are typically taken by patients at home, injections must be administered by nursing staff. This ensures that the dose is administered correctly." Ex. 1015 at ¶ 160. In fact, "health-care professionals consider that patients dislike injections, and consequently they are more likely to prescribe oral treatments." Ex. 2053 (Fallowfield 2006) at 1.

144. Thus, the '680 Patent claims are not obvious based on Howell 1996.

B) Ground Two: Howell 1996 In Combination With McLeskey

145. InnoPharma argues that its "Petition changes the obviousness analysis by arguing that Howell—and not McLeskey—is the appropriate starting point." Petition at 9. However, Ground 2 of Mylan's Petition was obviousness over "Howell 1996 in view of McLeskey" (Ex. 1078 at 62) which the Board expressly considered and rejected. Ex. 1011 (PTAB Decision) at 22 ("Petitioner further argues that, in light of Howell 1996's teaching that intramuscular administration of fulvestrant in a castor oil-based depot injection for the treatment of breast cancer provides continuous drug release over a one-month dosing interval . . . a 'POSA looking to treat a patient suffering from breast cancer . . . . would then look to the prior art to determine an appropriate formulation'" and "would have been immediately drawn to McLeskey."). Similar to Mylan, Dr. Harris asserts a POSA "would have been motivated to develop a formulation of fulvestrant for the treatment of hormone-dependent breast cancer" based on Howell, "would have searched the existing literature for information regarding a suitable formulation for using fulvestrant in breast cancer treatment" and "would [have] been led to McLeskey, which also used a castor oil formulation." Ex. 1015 at ¶¶ 148-150. Moreover, he argues that "Howell and McLeskey are fully and logically combinable" and a POSA "would have been motivated to combine Howell and McLeskey and would have been able to modify the dose and route of

administration disclosed in McLeskey to the methodology disclosed in Howell with a reasonable expectation of success." Ex. 1015 at ¶¶ 53, 125; *see also id.* at ¶¶ 124, 231. I reiterate the opinions in my prior declaration on this ground below.

1) No Reason To Select McLeskey

(i) McLeskey Fails To Disclose Nearly All Of The Limitations Of The '680 Patent Claims

146. Dr. Harris argues that "McLeskey discloses that the AstraZeneca formulation it used is a fulvestrant composition that is 50 mg/ml fulvestrant 'in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil,' which is ***precisely*** the formulation recited in one of the claim elements of AstraZeneca's '680 Patent" and "a person of skill in the art would quite simply apply the McLeskey AstraZeneca formulation with the methodology shown in Howell (also using an AstraZeneca formulation) to reach the patented result." Ex. 1015 at ¶¶ 165, 167 (emphasis added). First, McLeskey does not disclose *precisely* the concentrations of excipients. It is clear to a skilled person that there are no units disclosed in McLeskey therefore these cannot be the *precise* concentrations disclosed in the claims. Second, there are two fulvestrant formulations disclosed in McLeskey and the paper does not specify which of the two formulations, if any, was used in the experiments. Ex. 1011 (PTAB Decision) at 9 ("McLeskey does not specify whether the peanut oil-based or the castor oil-based fulvestrant composition was used for this experiment."). Dr. Harris does not

address this point. Third, the claims are to a method of treatment. As shown in the table that follows and as was acknowledged by the Board, "McLeskey fails to teach critical elements of the claimed invention, which impacts the obviousness analysis." Ex. 1011 at 23; *see also id.* a 29 ("It is not enough for Petitioner to establish that castor oil-based intramuscular injections of fulvestrant were known; the evidence must provide a reason for one of skill in the art to administer McLeskey's disclosed fulvestrant formulation 'intramuscularly' to 'achieve[] a therapeutically significant blood plasma concentration' for 'treating a hormonal dependent benign or malignant disease of the breast or reproductive tract,' as recited in the challenged claims."). Again, Dr. Harris does not address this point.[3]

'680 Patent Claim Limitations	**McLeskey**
A method for treating a hormonal dependent benign or malignant disease of the breast or	NOT hormonal dependent . . . "hormone independent" NOT treatment . . . "treatment

[3] Dr. Harris's attempt to separate the formulation from both the route and schedule of administration is improper. As discussed below, one cannot simply take a formulation using one route of administration and schedule and expect to achieve the same results when using it with another route of administration and schedule.

reproductive tract comprising	failure" NOT malignant disease of the breast . . . genetically engineered model
administering intramuscularly	NOT intramuscular . . . "subcutaneous"
to a human in need of such treatment a formulation comprising	NOT human . . . mice
wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 ngml^{-1} [8.5 ngml^{-1}] for at least four weeks.	NO blood plasma levels NOT therapeutically significant . . . "treatment failure" NOT once every four weeks . . . "once weekly"

147. These missing limitations from McLeskey were also acknowledged by the Examiner during the prosecution of the '680 Patent. Ex. 1042 at 313 ("Mc[L]eskey et al. teaches a studies employing subcutaneous injection of fulvestrant to nude mice. . . . Mc[L]eskey et al. does not expressly teach the use of fulvestrant in treating hormonal dependent diseases of the breast. It does not expressly teach the dosing regimen to be once a month, intramuscular administration, or the volume administered. Mc[L]eskey et al. does not expressly teach the herein claimed serum concentration of fulvestrant.").

(ii) A Skilled Artisan Would Not Have Considered McLeskey Relevant

148. A skilled artisan looking for a treatment for hormonal dependent disease[4] would not look to McLeskey. The skilled artisan, and, in particular, such a person engaged in the clinical treatment of hormonal dependent diseases of the breast and/or reproductive tract and hoping to develop a treatment for such diseases, would not have considered McLeskey relevant. The title of McLeskey teaches that fulvestrant was ***unsuccessful*** in the McLeskey model: "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are ***Cross-Resistant*** *in Vivo* to the Antiestrogen ICI 182,780 [fulvestrant] and Two Aromatase Inhibitors." Ex. 1008 at 1 (emphasis added). McLeskey repeatedly indicates that the mouse model being studied is "hormonal independent." Ex. 1008 at 12 ("[T]hese data provide evidence for a mechanism by which FGF-stimulated estrogen-independent growth bypasses the ER signal transduction pathway. . . . [O]ur studies implicate direct action by FGFs in the estrogen-independent growth produced by transfection of either FGF-4 or FGF-1 into MCF-7 cells."). This was acknowledged by the Board. Ex. 1011 (PTAB Decision) at 24 ("McLeskey is not directed to the

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[4] All of the patent claims of the '680 Patent are directed to a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract." Ex. 1001 ('680 Patent).

treatment of a 'hormonal dependent benign or malignant disease.'"). Even if the skilled artisan had read the full publication, McLeskey would have encouraged the skilled artisan to study growth factor inhibitors to solve tamoxifen resistance—not endocrine therapies, such as fulvestrant, which failed to inhibit tumor growth or metastases in the animal model studied.

149. I disagree with InnoPharma that "a POSA would necessarily have looked to McLeskey to find" a castor oil-based formulation or that the POSA "would [have] been led to McLeskey." Petition at 9; Ex. 1015 at ¶ 150. According to the publisher, the full text of the issue of the journal in which McLeskey appeared was not searchable online prior to the invention of the '680 Patent. Ex. 2042 (AACR Journals Online); Ex. 2125 (Affidavit of Internet Archive).

150. The challenged patent claims all relate to a method of treating hormone-dependent breast cancer in humans. Nevertheless, Dr. El-Ashry argues (without literature support) that McLeskey would be relevant to a clinician treating "both hormone-dependent and hormone-independent breast cancer" because "***a patient with hormone-independent*** cancer will likely be resistant to anti-estrogen therapy, and mechanisms leading to tamoxifen-resistance could cause cross-resistance to additional anti-estrogens like fulvestrant," thus, "[a] skilled researcher would need to understand both mechanisms to effectively treat ***such a patient***." Ex. 1014 at ¶ 16 (emphases added); *see also* Petition at 22. Dr. El-Ashry further

argues that "[t]o better understand" and "more effectively treat breast cancer," "a skilled researcher would have to study both hormone-independent and hormone-dependent pathways." Ex. 1014 at ¶¶ 65-66; *see also* Petition at 25. As a clinician specializing in the treatment of breast cancer for over 30 years, I disagree with Dr. El-Ashry, who is not a clinician. The question here is not whether a clinician would consider a patient's hormone status to determine whether ***fulvestrant treatment*** was appropriate but whether a clinician seeking to ***develop*** a treatment for hormone-dependent breast cancer would turn to a reference on a purely hormone-independent model for guidance. In other words, we are not treating a patient whose status is unknown. By definition in the claims, the status of the patient is hormone-dependent. Dr. El-Ashry provides no explanation as for why treating a hormone-independent patient would be relevant to treating a hormone-dependent patient with a hormone-dependent treatment, such as fulvestrant, nor can she. Tellingly, InnoPharma's clinician, Dr. Harris, is silent on this issue.

151. Dr. El-Ashry further argues (again without literature support) that understanding the mechanism of hormone-independent breast cancer is particularly important for second-line therapies such as fulvestrant. Ex. 1014 at ¶¶ 65-66; *see also* Petition at 25, 52. But, as she herself admits, fulvestrant "is typically used after resistance to tamoxifen has developed," which is another hormone-dependent treatment. Ex. 1014 at ¶ 65. Dr. El-Ashry has not cited any reference suggesting

that knowledge of hormone-independent mechanisms are needed to develop hormone-dependent treatments. As both a matter of logic and a historic fact, hormone-dependent treatments were used long before scientists understood the mechanism of resistance to such treatments. Dr. El-Ashry does not dispute this. Ex. 1014 at ¶ 66 ("Various studies have shown that the development of a hormone-independent phenotype may be a mechanism of antiestrogen resistance."); Ex. 1066 (Johnston 1995) at 7 ("The results from the adjuvant group provide the best evidence that acquisition of a true ER [negative] phenotype may be one mechanism for tamoxifen resistance."). She also admits that hormone independent patients require different treatments. Ex. 1014 at ¶ 16 ("[A] patient with hormone-independent cancer will likely be resistant to anti-estrogen therapy."). Either the two pathways are analogous (as Dr. Harris also argues (Ex. 1015 at ¶ 126)) and fulvestrant is a "treatment failure" for both based on the plain text of McLeskey or they are not analogous and McLeskey would not be considered relevant to the skilled artisan. Regardless, Dr. El-Ashry's argument that the skilled artisan would not exclude McLeskey does not provide any motivation to select McLeskey.

152. Dr. El-Ashry's statement that "fulvestrant was and is known to be a second-line therapy for the treatment of breast cancer, and is typically used after failure with tamoxifen" (Ex. 1014 at ¶¶ 16, 37) is factually incorrect. Fulvestrant was not approved by the FDA as a second-line therapy until 2002. For this reason,

her statement that fulvestrant "was known as an effective, if not superior, alternative to tamoxifen, especially as second-line therapy following tamoxifen resistance" (Ex. 1014 at ¶ 31) is also incorrect (and internally inconsistent). There was no direct comparative data of fulvestrant to tamoxifen by 2000, so "superiority" had never been shown and no patient had ever been given fulvestrant ***unless*** it was after tamoxifen. Similarly, her statement (Ex. 1014 at ¶ 24) that SERDs were one of "the main types of hormone therapy" by 2000 is incorrect. Indeed, fulvestrant was the first SERD to be approved by the FDA in 2002 and the only one to this day.

153. McLeskey says nothing about the use of fulvestrant for the treatment of breast cancer and, instead, encourages that "[t]herapy of such tumors with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1008 at 12-13. And, as discussed below, even if hormone independent cancers were somehow relevant to the skilled researcher (which I dispute), McLeskey unequivocally indicates that fulvestrant was a "treatment failure." Ex. 1008 at 10.

(iii) McLeskey Is A Study Of Basic Biology Unrelated To Treatment

154. McLeskey is a basic science research paper designed to investigate an artificially modified (transfected to overexpress FGFs) hormone independent mouse tumor model related to growth factor signaling pathways. Dr. McLeskey

herself stated that the research "was not designed to look at the treatment of any disease with fulvestrant." Ex. 2043 (McLeskey Declaration) at 2. The text of the paper makes that clear.

155. It is undisputed that Dr. McLeskey herself stated that "[t]he paper is clear that the formulations of these drugs were for research purposes for subcutaneous administration to mice—not treatment of humans." Ex. 2043 (McLeskey Declaration) at 2. Indeed, one of ordinary skill would recognize the formulations used for the McLeskey research to be those for use in animal research, not for human therapy. InnoPharma agrees that because of the constraints of animal biology and animal research, for basic biology research like this, special animal research formulations are used. Petition at 23-24. A skilled researcher would understand that the formulations used for endocrine therapy in McLeskey are all specific for the constraints of working in a mouse model. For example, the tamoxifen pellets used in McLeskey were purchased from Innovative Research of America, a company that specializes in only animal formulations. Ex. 2044 (Innovative Research) at 9 ("All products in this catalog are sold for investigational use in laboratory animals only and are not intended for diagnostic or drug use."). In contrast, for humans, tamoxifen was administered orally in 20 mg tablets. Ex. 2045 (PDR 1999 Nolvadex®) at 4. Similarly, letrozole was administered in McLeskey in a liquid vehicle of 0.3% hydroxypropyl cellulose via

gavage—for humans, letrozole was approved and sold as oral tablets, with excipients including ferric oxide, microcrystalline cellulose, and magnesium stearate. Ex. 2046 (PDR 1999 Femara®) at 12. The McLeskey authors administered 4-OHA, also known as formestane, in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection once daily, six days a week—for humans, a different formulation was approved in Europe, i.e., 4-OHA powder suspended in physiological saline for intramuscular injection every two weeks. Ex. 1054 (Santen) at 8; Ex. 2152 (Goss 1986) at 1; Ex. 2153 (Dowsett 1989) at 1.[5]

156. InnoPharma and its expert, Dr. El-Ashry, attempt to distinguish the tamoxifen pellet and letrozole gavage formulations in McLeskey from the fulvestrant injections, stating that "these are formulations of drugs that are typically administered orally in the clinical setting and necessarily need to be specially formulated for administration to mice." Petition at 23-24; Ex. 1014 at ¶¶

[5] Even if one accepts InnoPharma's argument regarding the constraints of i.m. administration to mice due to muscle size, 4-OHA could actually have been administered orally or by i.m. injection because formestane had been given both ways clinically but McLeskey instead chose an entirely different route (i.e., subcutaneous) and formulation than that used in humans. Ex. 2153 (Dowsett 1989) at 1 ("[4-OHA] is a clinically effective treatment for advanced postmenopausal breast cancer by both the parenteral and p.o. routes.").

16, 59-60 ("[O]ral dosage forms must generally be given to mice via different routes of administration.").[6] In other words, InnoPharma and Dr. El-Ashry admit that the tamoxifen and letrozole formulations were plainly not for human use. But, they attempt to distinguish the tamoxifen and letrozole formulations from the fulvestrant formulations based on McLeskey's description of the castor oil-based fulvestrant formulation as "preformulated." Petition at 24; Ex. 1014 at ¶¶ 16, 61. This same fact was noted by Mylan at least ***five times*** in its IPR Petition and rejected by the Board. Ex. 1078 at 20, 32 (twice), 50, 55. In any event, preformulated formulations are not necessarily appropriate for human use, as the preformulated letrozole and tamoxifen examples show. Further, by InnoPharma and Dr. El-Ashry's own admission, a "POSA would recognize that depot formulations are administered to mice subcutaneously because mice generally do not have adequate muscle mass for IM injections." Petition at 51; Ex. 1014 at n.2 ("[A] person of skill in the art would use the subcutaneous route of administration in mice, even for drugs that are known to be administered intramuscularly in humans."). This confirms that the fulvestrant formulations are indistinguishable

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[6] Letrozole was administered via gavage in McLeskey which is still an oral route of administration but a different formulation. This further supports that McLeskey's formulations were specifically formulated for administration to animals.

from the other specially made formulations for this animal research study. A POSA would have no reason to select the animal research castor oil-based formulation of McLeskey.

157. Given the difference in formulation and mode and schedule of administration of the other three endocrine agents used in McLeskey (tamoxifen, letrozole, 4-OHA) between this animal research experiment and human treatment, a POSA would not expect that s/he could simply transfer either of the fulvestrant formulations used in mice and deliver them by a different route and schedule of administration to humans and achieve successful results. Dr. Harris notes only that a POSA would have known to administer the fulvestrant formulations intramuscularly in humans. Ex. 1015 at ¶¶ 155, 170-171, 186-187, 199. But, not surprisingly, he does not answer the question of how a POSA would know that using the McLeskey formulations and route and schedule of administration for fulvestrant in mice would successfully translate to humans. This is especially true given that the mode and schedule of administration and formulations for fulvestrant used by McLeskey were a "treatment failure."

158. In fact, InnoPharma states that "[a] POSA would appreciate these differences [between the two routes] and would not seek to 'extrapolate' the results of SC and IM administration." Petition at 51. This acknowledges that InnoPharma cannot account for the differences.

159. McLeskey does not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of any of the experimental drug formulations used. Ex. 1011 (PTAB Decision) at 9, 24 ("McLeskey [does not] address fulvestrant blood plasma levels, or otherwise provide pharmacokinetic data, for any experiment."; "McLeskey is silent with respect to 'achiev[ing] a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [8.5 $ngml^{-1}$] for at least four weeks.'"). A skilled researcher would not find the lack of pharmacokinetic data surprising given that the study was designed to look at issues relating to basic science and not drug formulation.

(iv) McLeskey Does Not Teach A Successful Fulvestrant Formulation

160. InnoPharma's expert, Dr. El-Ashry, argues that "Dr. McLeskey and AstraZeneca misinterpret the McLeskey Reference when they characterize its use of fulvestrant as a 'treatment failure.'" Ex. 1014 at ¶¶ 16, 53-54. Dr. El-Ashry argues that a POSA would understand that "fulvestrant worked exactly as it was intended in the McLeskey Reference—by inhibiting the estrogen receptor" because "[t]he outcome of McLeskey was not due to the performance of fulvestrant, but rather was a consequence of FGF overexpression." Ex. 1014 at ¶¶ 16, 44, 50, 58; *see also* Petition at 21, 23. Specifically, Dr. El-Ashry states "we directly confirmed that fulvestrant was blocking the estrogen receptors in the FGF cells," "that fulvestrant 'retained activity' and inhibited endometrial growth in intact mice," and

"that no growth occurred in the presence of fulvestrant" and, therefore, "the results of the McLeskey study show that fulvestrant ***successfully*** inhibits ER activity in wild-type breast cancer cells and in those that have been transfected with FGF" because "if fulvestrant had not worked as anticipated by blocking the estrogen receptors, we could not have drawn the conclusion that FGF cell growth was *bypassing* the estrogen receptors." Ex. 1014 at ¶¶ 45-49, 58 (first emphasis added); *see also id.* at ¶¶ 16, 44-52, 54-58. Dr. El-Ashry's reference to the effect of fulvestrant on estrogen receptors (whether this be EREs (Figure 8) or any of the cell line experiments (Figures 4, 5, 6)) all relate to use of the ***compound***, fulvestrant, dissolved in cell culture media (or estrogen-depleted medium)—not either of the fulvestrant formulations used for the *in vivo* experiments. This further supports McLeskey's description of the fulvestrant formulations used in the *in vivo* experiments as a "treatment failure." Nonetheless, Dr. El-Ashry's explanation now in 2017 is inexplicably at odds with her statement as a co-author in 1998 when she described fulvestrant as a "treatment failure" at least 10 times in the McLeskey paper. Even if accepted at face value (which I reject), this new view of Dr. El-Ashry was not available to a POSA in 2000.[7]

[7] Similarly, Dr. El-Ashry's citation to "subsequent clinical studies performed on human breast cancer patients" that "cite the McLeskey Reference to explain their experimental results" dated 2008 and 2003, years after the invention date,

161. As I discussed in my previous IPR declaration, the plain text of McLeskey characterizes the fulvestrant animal formulations used as "**treatment failure[s]**." Ex. 1008 at 10 (emphasis added). Indeed, the very text of McLeskey repeatedly emphasizes the failure of these fulvestrant (ICI 182,780) animal formulations to arrest the cancer:

- "Treatment with ICI 182,780 ***did not inhibit*** tumor growth" (Ex. 1008 at 4 (emphasis added));
- "***[F]ailure of ICI 182,780 to inhibit*** the estrogen-independent growth exhibited by this cell line" (*Id.* (emphasis added));
- "Fig. 1 Growth of FGF-transfected MCF-7 cells in ovariectomized nude mice is ***not inhibited by treatment with ICI 182,780***" (*Id.* at 5 (emphasis added));
- "ICI 182,780 ***did not decrease tumor growth***" (*Id.* (emphasis added));
- "ICI 182,780 ***did not inhibit*** estrogen-independent tumor growth" (*Id.* (emphasis added));
- "Administration of ICI 182,780 to animals . . . ***produced no effect***" (*Id.* (emphasis added));

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were not available to a POSA in 2000 and are likewise irrelevant. Ex. 1014 at ¶ 64.

- "[T]he continued ***progressive in vivo growth***" (*Id.* (emphasis added));
- "Table 1 Metastasis of FGF-transfected MCF-7 cells is ***not inhibited by treatment with ICI 182,780*** or aromatase inhibitors" (*Id.* at 6 (emphasis added));
- "Metastatic Frequency of Tumors Produced by FGF-transfected MCF-7 Cells in Mice Treated with ICI 182,780 or Aromatase Inhibitors Is ***Not Affected by Treatment***" (*Id.* (emphasis added));
- "FGF-transfected MCF-7 cells is ***not affected by ICI 182,780*** or by either of two aromatase inhibitors . . . treatment failure" (*Id.* at 10 (emphasis added)).

162. Even the title of McLeskey informs the skilled artisan that "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are ***Cross-Resistant in Vivo to the Antiestrogen ICI 182,780 [fulvestrant]*** and Two Aromatase Inhibitors." Ex. 1008 at 1 (emphasis added). In other words, the cells are resistant to treatment with tamoxifen and additionally resistant to treatment by fulvestrant.

163. For this reason, McLeskey encourages the skilled artisan to seek alternatives to fulvestrant for breast cancer treatment. McLeskey explains that tamoxifen resistance is an "important therapeutic dilemma." Ex. 1008 at 1. The fact that the FGF-transfected cells were "cross-resistant" to the subsequent exposure to endocrine agents indicates that none of the drugs (aromatase

inhibitors or fulvestrant) used in the animal studies worked to suppress tumor growth in this artificial model. For this reason alone a POSA would not recommend this formulation for human testing based on this study. Further, McLeskey cites the preliminary results in Howell 1995 and Howell 1996 for the proposition that many tamoxifen-resistant patients ***do not respond*** to fulvestrant. Ex. 1008 at 2. McLeskey proposed that the failure of tamoxifen-resistant patients to respond to further hormone therapy like fulvestrant suggests a hormone-independent mechanism of such resistance. Ex. 1008 at 2. McLeskey suggests that additional research should look to whether the growth factor, FGF, could provide such a hormone-independent mechanism.

164. McLeskey found that "[fulvestrant] did not affect the estrogen-independent growth of the FGF-transfected MCF-7 cells *in vivo*." Ex. 1008 at 6. McLeskey explained that "[t]hese studies indicate that estrogen independence may be achieved through FGF signaling pathways independent of ER pathways." Ex. 1008 at 1. McLeskey encouraged that, instead of using antiestrogen therapy, like fulvestrant, "[t]herapy of such tumors with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects." Ex. 1008 at 12-13. McLeskey concluded that "[t]he persistence of estrogen-independent growth despite pharmacological strategies to abrogate all estrogenic activity supports the hypothesis that the effect of FGF transfection in promoting such growth is due to a

direct effect of the transfected FGF." Ex. 1008 at 10. Thus, McLeskey notes a clinical problem of tamoxifen resistance, proposes a mechanism to explain that problem, and reports experiments on the basic biology supporting a hormone-independent mechanism.

(v) The Skilled Artisan Would Not Expect The Administration Method Of McLeskey To Succeed

165. Given that the fulvestrant formulations used in McLeskey were deemed a "treatment failure" when administered to mice, the ordinary researcher would certainly have no basis to expect success in administering those same formulations to humans using a different route and schedule of administration. Ex. 1011 (PTAB Decision) at 28, 30 (Petitioner "fail[s] to address the differences between injection methodologies. . . . '[R]esults from subcutaneous administration in general, and including those included in McLeskey, cannot be extrapolated to intramuscular administration,' either with respect to side effects or efficacy.").

166. Dr. Harris argues that "[i]n spite of the significant prior art teaching the efficacy of fulvestrant, Dr. Sawchuk asserted that 'one of ordinary skill in the art would not have been informed about the usefulness of either fulvestrant formulation when administered subcutaneously to a mouse for the treatment of cancerous tumors.'" Ex. 1015 at ¶ 52. The possible "efficacy" of a ***compound*** is different than the success of a particular formulation. McLeskey lacks any data from which an ordinary researcher could draw conclusions regarding drug

absorption and metabolism, much less safety and efficacy, of any formulation.

167. For this reason, as noted above, Dr. El-Ashry's declaration wherein she focuses on the alleged activity of the ***compound*** fulvestrant does not add anything with regard to the formulations. Ex. 1014 at ¶¶ 16, 47, 55-57 ("the McLeskey Reference would convey to the skilled researcher that ***fulvestrant*** effectively inhibits the estrogen receptor"; "we injected ***fulvestrant*** into reproductively intact female mice for two weeks"; "we administered ***fulvestrant*** and two AIs to block the effect of estrogen"; "we treated wild-type ML-20 breast cancer cells with ***fulvestrant*** and found that growth did not occur"; "when we injected ***fulvestrant*** into reproductively intact female mice . . . we found that ***fulvestrant*** 'retained activity' and successfully prevented growth of endometrial cells"; "when the cells are treated with ***fulvestrant*** . . . ER activity was blocked as would be expected"). In all of the above quotes by Dr. El-Ashry which refer to *in vitro* studies not only does she only reference the compound, but, indeed, neither of the fulvestrant formulations reported in the *in vivo* studies were used in the *in vitro* experiments. The only reference above involving *in vivo* experiments relates to the report on the effects of the four actives (letrozole, 4-OHA, tamoxifen, fulvestrant) on the endometrium. Once again, Dr. El-Ashry does not specifically attribute any of the "Results Reported" and "Conclusions That A Skilled Researcher Would Draw" from McLeskey (Ex. 1014 at ¶¶ 38-58) to either one of the two disclosed

fulvestrant formulations and, indeed, she cannot because it is not disclosed in the publication which, if any, was used in the study.

168. The text of McLeskey itself characterizes the results with ICI 182,780 as a "failure." Ex. 1008 at 10. There are no fulvestrant blood concentrations reported for any of the *in vivo* experiments in McLeskey and therefore there is no evidence that fulvestrant was even delivered to the tissues of interest. A skilled researcher would not find the McLeskey reference description of any formulation to be helpful in looking to find a formulation to safely and effectively treat hormonal dependent diseases, such as breast cancer, in humans. Instead, the skilled researcher reading McLeskey would conclude that it raised doubts about the usefulness of anti-hormone treatments for breast cancer.

169. Dr. Harris opines that "[a] person of skill in the art would not be deterred by the fact that McLeskey administered fulvestrant subcutaneously in mice" and "would have known that mice would not usually be treated via IM injection because they do not have sufficient muscle and therefore are at risk of tissue damage." Ex. 1015 at ¶ 154. But McLeskey expressly states that the fulvestrant formulations used in the study were administered subcutaneously, not intramuscularly. There is no suggestion in McLeskey to administer the formulations intramuscularly. And, in fact, physicians consider intramuscular and subcutaneous administration to be very different because their environments for

injection are entirely different. InnoPharma's expert, Dr. Bergstrom, admits that intramuscular administration can lead to different pharmacokinetic results than subcutaneous administration. Ex. 1013 at ¶ 18 ("When a drug is administered to a subject, there are various factors that affect the manner in which the drug moves through and is processed by the body [including] the anatomical or physiological environment in which the drug is placed, and the distribution of the drug into the peripheral tissues of the subject."). One could not extrapolate subcutaneous administration in mice to intramuscular administration in humans with any reasonable expectation of success, especially since the fulvestrant formulations in McLeskey "***did not inhibit tumor growth***." Ex. 1008 at 4 (emphasis added).

170. I disagree with Dr. Harris's unqualified statement that "animal studies are predictive of clinical effects in humans" and "[i]t was reported that the human studies were bearing out the early predictions of the animal studies" so a POSA would be "motivated to look to pre-clinical animal studies." Ex. 1015 at ¶¶ 151-154, 191; *see also* Ex. 1014 at ¶¶ 16, 40, 63. The references Dr. Harris cites for support are Thomas which is a phase I study in humans and Derendorf which is a study relating to antibiotics, not cancer treatment, with no mention of fulvestrant. Simply because live animals were used for the research does not make the methodologies applicable for humans in the clinic. Much of basic biology research, being done on animals that will be sacrificed, is done using techniques and formulations not

applicable to human treatment. For instance, as discussed above, the formulations used in McLeskey were laboratory formulations for use in basic biology research in animals: "[l]etrozole . . . was administered via gavage"; and "[s]ustained-release (60 day) pellets containing 5 mg of tamoxifen were obtained from Innovative Research of America." Ex. 1008 at 2. As noted above, a POSA would not look to a formulation such as that disclosed in McLeskey—which was identified as a "treatment failure"—and expect success in administering it to humans.

2) No Reason To Combine McLeskey With Howell 1996

171. In addition to there being no reason to select either McLeskey or Howell 1996, as discussed above, one of ordinary skill would not have reasonably expected that animal research investigating a basic biological mechanism or creating a disease model for one biological (hormone independent, growth factor mediated) pathway (i.e., FGF) could provide any relevant information regarding the usefulness of a specific pharmaceutical formulation for treating a disease in humans via a different biological pathway (i.e., ER). In my opinion, one of ordinary skill in the art would have had no reason to combine the basic biology rodent model research reported in McLeskey with the early stage clinical study reported in Howell 1996 and, he or she would not have had a reasonable expectation of success in doing so.

172. Dr. Harris argues that "a person of skill in the art would quite simply

apply the McLeskey AstraZeneca formulation with the methodology shown in Howell (also using an AstraZeneca formulation) to reach the patented result." Ex. 1015 at ¶ 167. In other words, Dr. Harris suggests that McLeskey and Howell "match." They do not.[8]

173. As demonstrated in the table below, a researcher would have no motivation to combine the McLeskey formulation with the method described in Howell 1996 because the two simply do not match on nearly every significant parameter (other than active ingredient and vehicle).

Howell 1996	**McLeskey**
Intramuscular administration	Subcutaneous administration
To humans	To mice
Once monthly	Once weekly

[8] This statement highlights Dr. Harris's retrospective analysis. By choosing McLeskey, which fails to teach nearly all of the limitations of the claims and itself describes the fulvestrant formulations used in the study as "treatment failure(s)," to combine with Howell 1996, Dr. Harris ignores the clear teachings of the art. Indeed, if a POSA were to look to any fulvestrant formulation based on Howell 1996, it would not look to a failed animal formulation such as the one disclosed in McLeskey. Ex. 1015 at ¶ 193.

Antitumor effects	Treatment failure
Not cross resistant	Cross resistant

174. McLeskey studied a model of estrogen-independent growth, and not the claimed hormonal dependent breast cancer. Ex. 1008 at 2 ("We therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to [fulvestrant]."). McLeskey administered the castor oil-based formulation to cell cultures and mice, not humans. Ex. 1008 at 2. McLeskey administered the formulation subcutaneously, not by the claimed intramuscular route. Ex. 1008 at 2 ("ICI 182,780 . . . was administered s.c."). McLeskey administered the formulation weekly, not monthly or biweekly. Ex. 1008 at 2 ("ICI, 182,780 . . . was administered . . . every week."). The title of McLeskey declares that the tumors studied were "Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780." Ex. 1008 at 1. The abstract explains that the fulvestrant formulations "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." Ex. 1008 at 1. And, McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1008 at 10.

175. Dr. Harris argues that Howell and McLeskey are combinable because McLeskey had "a purpose similar to Howell" in that both used fulvestrant due to "its proven success as a pure antiestrogen that blocks estrogen by binding to ER." Ex.

1015 at ¶¶ 162-163. First, as discussed above, Howell and McLeskey are directed to investigations of different biological pathways (hormone dependent versus hormone independent (FGF)) in different species (humans versus mice) for different reasons (treatment for breast cancer in humans versus animal research investigating a basic biological mechanism)—I disagree that their purposes were similar. Second, Howell was the first phase II clinical trial to administer fulvestrant to humans so to state that Howell used fulvestrant due to its "proven success" is misleading.

176. Moreover, in describing the rationale for the research, McLeskey cites to a range of eight papers reporting clinical study of fulvestrant and aromatase inhibitors and Howell 1996 is an author on four of the eight papers cited in that range, including one on aromatase inhibitors and one on endocrine therapies generally—there is no reason to pick out Howell 1996 as having a connection. If anything, McLeskey criticizes Howell 1996—as a rationale for the significance of her research relating to an alternative pathway, McLeskey interprets Howell 1996 as having a low percentage of positive responses to fulvestrant and aromatase inhibitors as support that a different, hormone-independent pathway exists. Ex. 1008 at 2 ("[E]arly results for small numbers of tamoxifen-resistant patients have shown that only about 30-40% of such patients have a positive response to subsequent ICI 182,780 or aromatase inhibitor therapy."). Further, the reasoning that McLeskey is somehow connected to

AstraZeneca and that connects the animal research formulation to the Howell 1996 study is also attenuated. Other papers cited by Dr. Harris include the work of the AstraZeneca team, however, McLeskey has no AstraZeneca authors.

3) No Expectation That This Combination Would Successfully Treat Hormone Dependent Breast Cancer In Humans

177. A skilled artisan would have no expectation that combining the formulation in McLeskey with the method in Howell 1996 would successfully treat postmenopausal women with hormone dependent breast cancer. First, as noted above, the publications do not match on many significant parameters, each difference raising uncertainty. Second, each publication independently teaches away from the parameters of the claims. For example, Howell 1996 teaches a POSA to go down in dose (which turned out to be a failure). McLeskey refers to fulvestrant repeatedly as a treatment failure, cites to Howell 1996 as showing the low response rate of fulvestrant, and uses weekly subcutaneous administration. Third, as discussed in more detail below, many other promising drugs failed even after reaching late-stage clinical development so the limitations of both Howell 1996 and McLeskey noted above would provide no expectation of success to a clinician that the combination of the two could successfully treat hormone dependent breast cancer in postmenopausal women.

178. Dr. Harris argues that a POSA "would have reasonably turned to McLeskey to combine the disclosed formula with the method taught by Howell to

administer the claimed fulvestrant formulation via IM injection once or twice a month to humans and would have achieved the claimed therapeutically significant blood plasma fulvestrant concentrations." Ex. 1015 at ¶ 169. Importantly, Dr. Harris provides no reason why a POSA would possibly expect the McLeskey fulvestrant formulations, which failed in animal experiments, to achieve success in humans using Howell 1996's method.

179. Dr. Harris simply states that "a skilled artisan would have had a reasonable expectation that the formulation in McLeskey would be therapeutically effective in IM injections in humans even though it was used subcutaneously on mice in that case" and "would have expected to see the same pharmacokinetics as Howell if given intramuscularly in humans." Ex. 1015 at ¶¶ 189, 195. While he comments that "[t]here were numerous studies reporting on successful results using fulvestrant both in animals and humans as a treatment of hormone-dependent cancer" he fails to reference any of these studies. Ex. 1015 at ¶ 190. Indeed, there was only one study using fulvestrant in humans as a treatment for hormone dependent breast cancer by 2000, i.e., Howell 1996. Dr. Harris then continues that a POSA "would have known that formulations used in the various tests can be comparatively effective used in humans" but fails to reference or even state the basis for his opinion. *Id.* He further states his opinion that "it is routine practice to look to early animal studies to determine formulations for new drugs" and a POSA

"would know that he or she could apply teachings regarding the fulvestrant formulation used in animals, such as McLeskey, to that used in humans." Ex. 1015 at ¶ 192. If this was indeed routine practice, he fails to address why the other three actives in McLeskey (tamoxifen, 4-OHA, letrozole) all used different formulations in humans. Indeed, Dr. Harris cherry picks fulvestrant but even then doesn't comment on the fact that there were two fulvestrant formulations reported in McLeskey. McLeskey would have informed the skilled artisan that the reported fulvestrant formulations would be ineffective.

180. Dr. Harris then proceeds to selectively quote (out of context) from a report published in 1994 of which I am a co-author, Nicholson, which he claims "explained that the efficacy and toxicity reports shown in vitro can be predictive of and compared to results shown in vivo to achieve successful results." Ex. 1015 at ¶ 194. In fact, what Nicholson stated clearly at the outset was that "[s]ince pure antioestrogens are now entering clinical development, the current paper seeks to outline some of their basic cellular and antitumour properties on human breast cancer cells in vitro primarily using the lead compound ICI 164,384, and to compare this information with data derived from a phase I study of ICI 182,780 in primary breast cancer patients." Ex. 1053 (Nicholson 1994) at 3-4. This statement alone at the beginning of the paper would tell the skilled artisan that the *in vitro* results could not be predictive of clinical efficacy since the authors are comparing

results on two entirely different compounds. The Nicholson paper was not about using the *in vitro* results for one drug (ICI 164,384) to predict the clinical results of another (ICI 182,780). Rather, the paper is a review of information about pure anti-estrogens that notes that "clinical trials with pure antioestrogens are in their infancy" and "consequently little is known about their clinical properties." Ex. 1053 (Nicholson 1994) at 12. Indeed, in a publication a year later (1995), Nicholson, the same author, also compares these compounds and concludes that "[i]n clinical breast cancer it is ***too early to judge*** the final value of these compounds." Ex. 1032 (Nicholson 1995) at 12 (emphasis added).

181. InnoPharma additionally argues that "Howell teaches that IM injections of fulvestrant are successful." Petition at 56. But, Howell nowhere says this as a universal rule for any formulation, which would be scientifically improper. And, Howell gives no information on the composition of the formulation aside from castor oil. InnoPharma is relying on McLeskey for that. Thus, InnoPharma must show that the skilled artisan would expect the McLeskey castor oil fulvestrant formulation to be successful, despite McLeskey's own characterization of the work as a "treatment failure" and its absence of pharmacokinetic data. That it cannot do.

182. Dr. Harris's rationale for "how to account the differences between administering a drug subcutaneously in mice versus by IM injection in humans"

further supports my opinion that one could not predict how a failed subcutaneous formulation tested in mice would work in humans intramuscularly. Ex. 1015 at ¶ 196. For example, he argues that a skilled artisan would know that: "mice have a much higher and faster metabolism and rate of clearance than humans" and "a weekly subcutaneous injection in a mouse would be released more rapidly." Ex. 1015 at ¶ 199. Despite admitting these differences in release rates between species he argues that "more frequent subcutaneous injections in mice would understandably and predictably be replaced by longer acting IM injections in women" and "more frequent subcutaneous injections would be expected to be replicated by less frequent longer acting injections." Ex. 1015 at ¶¶ 199, 209. It is not surprising that Dr. Harris does not cite to a single reference for support. Indeed, as the Board noted, "the composition of a formulation can have significant and unpredictable effects on the pharmacokinetics, efficacy, and side effects (including post-administration precipitation reactions) when administered intramuscularly." Ex. 1011 (PTAB Decision) at 27. Thus, the Board concluded, "given the unpredictability in the art, we are not persuaded that [a POSA] would have reasonably expected that the castor oil-based formulation of McLeskey would provide the claimed pharmacokinetic profile." Ex. 1011 (PTAB Decision) at 28.

183. Without support, Dr. Harris states that a POSA "looking at the McLeskey formulation—which, like the product used in Howell, is also a castor

oil-based composition supplied by AstraZeneca with the same concentration (50 mg/ml) of fulvestrant—would have expected to see the same pharmacokinetics as Howell if given intramuscularly in humans." Ex. 1015 at ¶ 189. But, there is no reason the skilled artisan would have believed that the McLeskey formulation would result in the Howell pharmacokinetics given that McLeskey does not address fulvestrant blood plasma levels, or otherwise provide pharmacokinetic data, for any experiment. Essentially, Dr. Harris is arguing that any castor oil-based formulation would give the same pharmacokinetics.

184. To try to support his argument that the pharmacokinetics would be expected, Dr. Harris attempts to suggest (without basis) that the McLeskey formulation and the Howell formulation are the same. For example, he argues that "[h]aving seen the positive results of Howell, a person of ordinary skill in the art would be drawn to other experiments using the same formulation, including McLeskey, and would have combined McLeskey with Howell." Ex. 1015 at ¶ 164. He also provides the unsupported "opinion" that "a pharmaceutical company providing a formulated agent for testing purposes would provide the same product to investigators." Ex. 1015 at ¶ 164. These suggestions are baseless. In a related litigation, the defendants made the same allegations submitted by InnoPharma here, including just such an unsupported suggestion. The clinical expert testifying for those defendants, when questioned by the Court, admitted that a skilled artisan

at the time of the invention would have no idea what formulation was used in Howell 1996. He stated that his guess that the McLeskey formulation was used in that study was "speculating," and that "[t]here is nothing in the literature to confirm [this] speculation." Ex. 2049 (July 14 Trial Tr.) at 213:10-17.

185. Indeed, it is not unusual that the method of administration used in early phase clinical trials (first in man, or early phase I or II studies) is not intended to be, or is discovered not to be, the best method of administration for clinical use. Ex. 2051 (Cohen) at 14; Ex. 2052 (Sweetana) at 9 ("'Heroic' approaches describe efforts to solubilize drugs for early clinical studies [] using additives that probably are not acceptable for commercial formulations.").

186. Dr. Harris argues that a POSA "would have been motivated by the many positive reports on fulvestrant to research a long-acting formulation of fulvestrant for long-term use as a therapeutic agent." Ex. 1015 at ¶ 159. But, at the time of the invention leading to the '680 Patent, only a small number of innovator companies were pursuing pure antiestrogens. And, to date, no compound with the same mechanism of action as fulvestrant has ever received FDA approval. Simply because a compound shows promise in early clinical work does not provide a reasonable expectation that any method of treatment using that compound would be successful. Indeed, of the "promising" compounds described above (Section X.B.), not one of the new compounds in development at the time reached the

market except fulvestrant.

187. For example, the second-generation aromatase inhibitor formestane produced a 24% objective tumor response rate in a large clinical trial. Ex. 2025 (Masamura 1994) at 4. However, its intramuscular route of administration was considered an "[o]bstacle[] to the use of formestane." Ex. 2026 (Kelloff 1998) at 8. In particular, "studies reported sterile abscesses due to the intramuscular injection required for administration of this compound." Ex. 2025 (Masamura 1994) at 4. Formestane has not received FDA approval.

188. Therefore, a POSA would not have been motivated to apply the teachings of McLeskey to Howell 1996 and would not have had a reasonable expectation of success that the combination could be used for treating hormone dependent breast cancer in humans.[9]

C) Ground Three: Howell 1996 In Combination With McLeskey And O'Regan

1) O'Regan Adds Nothing And Further Supports That One Would Not Use The Formulation In McLeskey

189. O'Regan describes a study in ovariectomized mice with implanted endometrial tumors "to evaluate the effects of toremifene and ICI 182,780 on the growth of human endometrial cancer." Ex. 1009 at 1. O'Regan discloses that

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[9] I am not a formulator or a pharmacokineticist and I understand that experts in those areas will be providing their opinions in support of AstraZeneca.

"[t]amoxifen and toremifene were each suspended in a solution of 90% CMC (1% carboxymethlycellulose in double-distilled water) and 10% PEG 400/Tween 80 (99.5% polyethyleneglycol 400 and 0.5% Tween 80)" and that "[t]amoxifen was administered orally, i.e., by mouth, at a dose of 0.5 mg per mouse daily for 5 days each week" and "[t]oremifene was administered orally at a dose of 0.5, 1.5, or 5 mg per animal." Ex. 1009 at 2. The ICI 182,780 (fulvestrant) formulation used in O'Regan "was dissolved in ethanol and administered in peanut oil (following the evaporation of ethanol under N_2) to a final concentration of 50 mg/mL" and "injected subcutaneously at a dose of 5 mg (0.1 mL peanut oil) per animal each week." Ex. 1009 at 2.

190. O'Regan cites to Howell 1996 as an early stage study and states that "there are not the same stringent requirements for a drug that is used as a palliative therapy in advanced disease compared with drugs that are used for long-term adjuvant therapy" and "[c]learly, a woman should not be led to believe that no risks exist because inadequate and early clinical studies are being reported." Ex. 1009 at 2, 5. O'Regan further warns (citing to Howell 1996) that "[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Ex. 1009 at 2.

191. O'Regan does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or

"administering intramuscularly to a human in need of such treatment." O'Regan does not disclose "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." Further, O'Regan does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (i.e., individual).

192. InnoPharma argues that the POSA would "have been motivated by Howell to look up the follow-up study in O'Regan," because "O'Regan specifically cites Howell as confirming that fulvestrant 'has shown promising results clinically in Europe, with high response rates of almost 70%'" and because "O'Regan tests the same compound." Petition at 60. But, at the time of the invention, hundreds of publications reported tests on "the same compound." InnoPharma provides no basis for selecting O'Regan. Moreover, O'Regan cites 38 references, and InnoPharma does not explain how a citation to Howell would teach the POSA to combine O'Regan with Howell specifically to achieve the claimed invention. Further, InnoPharma mischaracterizes O'Regan as a "follow-up" study to Howell. *Id.* In fact, O'Regan was conducted by a completely different group of researchers and was conducted "[a]s a result of claims that *toremifene* is safer than tamoxifen because it does not produce liver tumors in rats." Ex. 1009 at 2

(emphasis added). In other words, the focus of O'Regan is toremifene and not fulvestrant. On the other hand, Howell 1996 is an early stage clinical study, seeking to investigate fulvestrant's biological activity.

193. Dr. Harris argues that a POSA "would have been both motivated to apply the teachings of [] McLeskey and O'Regan to Howell [] and further would have had a reasonable expectation of success that the combination could be used for using the claimed formulation in the claimed amounts as taught in the challenged claims to treat hormone dependent breast cancer in humans." Ex. 1015 at ¶¶ 124, 231. Specifically, Dr. Harris argues that a POSA "would have known that Howell administered an IM formulation to humans and would have searched the existing literature for additional information regarding using fulvestrant in breast cancer treatment in humans and would have been led to O'Regan, which explains that, in humans, fulvestrant should be administered by IM injection due to low oral potency." Ex. 1015 at ¶ 170. O'Regan does not describe the treatment of breast cancer in humans with fulvestrant. O'Regan describes a study in ovariectomized mice evaluating the risks of promoting endometrial cancer after treatment with toremifene or fulvestrant. Ex. 1009 at 1. The only fulvestrant formulation used in O'Regan is a peanut oil formulation administered subcutaneously to mice once-a-week. O'Regan does not use intramuscular administration.

194. Dr. Harris opines that "the reason O'Regan is using fulvestrant subcutaneously in the experiment is because she was using it in mice and it was known at the time that mice have low muscle mass, often making them unsuitable for IM injections." Ex. 1015 at ¶ 116. O'Regan never says that. Rather, like the McLeskey reference, this is a basic science experiment—not an evaluation of a potential clinical formulation. It uses animal formulations.

195. InnoPharma's experts admit that the different injection routes affect the rate of release, and that the results are not predictable. Ex. 1013 at ¶ 18 ("When a drug is administered to a subject, there are various factors that affect the manner in which the drug moves through and is processed by the body [including] the anatomical or physiological environment in which the drug is placed, and the distribution of the drug into the peripheral tissues of the subject."); Ex. 1012 at ¶ 149 ("[S]ubcutaneous administration generally provides a *slower release profile*." (emphasis added) (citing Ex. 1111 at 2 ("Absorption of drugs which are given subcutaneously [in humans] is generally slower than after intramuscular administration because of less efficient regional circulation.")); Ex. 1015 at ¶ 199 ("[A] weekly subcutaneous injection in a mouse would be *released more rapidly*. . . . [F]ulvestrant must be administered via IM injection in humans and [] IM injections of fulvestrant enable prolonged release." (emphasis added)).

196. InnoPharma adds O'Regan to the analysis for Ground 3 solely

because of its statement that "[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Petition at 60-61; Ex. 1015 at ¶ 171. Based on this statement, InnoPharma argues that "O'Regan is strong evidence that a POSA would expect success in using the McLeskey formulation intramuscularly in humans." Petition at 60. But, O'Regan does not add any research on route of administration—O'Regan cites to Howell 1996 for support for this statement (Ex. 1009 at 2). O'Regan adds nothing to Howell's disclosure of intramuscular administration. And, O'Regan says nothing about the McLeskey formulation.

197. This statement actually supports the conclusion that the skilled artisan would be discouraged from using either the subcutaneous formulation in McLeskey or the O'Regan subcutaneous peanut oil formulation—making it clear that such formulations were for animal experiments and differed from how fulvestrant had been administered in early clinical studies.

198. Dr. Harris argues (yet once again without literature support) that a POSA "would have reasonably turned to O'Regan, which used fulvestrant subcutaneously in mice like McLeskey, and would learn that it could use the formula taught by McLeskey in a sustained release IM injection in humans." Ex. 1015 at ¶ 173. Dr. Harris cites nothing in O'Regan to suggest that McLeskey's formulations would be effective when used intramuscularly. Nor can he, given

that O'Regan itself uses subcutaneous administration once-a-week of a peanut oil formulation in mice. Instead, what this argument appears to be suggesting is that if fulvestrant was administered intramuscularly in clinical use so far, ***every*** formulation of fulvestrant, including animal pre-clinical formulations, would therefore be appropriate for intramuscular use in humans and give the same results as Howell. This is scientifically untenable and assumes that formulation excipients are irrelevant, which is entirely belied by basic literature. Ex. 1091 (Ansel Ch. 4) at 21 ("[T]wo seemingly 'identical' or 'equivalent' products, of the same drug, in the same dosage strength and in the same dosage form type, but differing in formulative materials or method of manufacture, may vary widely in bioavailability and thus in clinical effectiveness."). O'Regan, thus, fails to add anything to InnoPharma's other grounds, and AstraZeneca's arguments apply with even greater force to Ground 3.

199. Dr. Harris concludes that "a reasonable expectation of success is strongly supported by the prior art, including (1) McLeskey[], which demonstrated a complete block of fulvestrant on the stimulatory effects of endogenous estrogen on the endometrium of female mice; (2) Dukes 1992[], which proved anti-uterotrophic effects of ICI 182,780 (fulvestrant) in ovarectomized monkeys; (3) O'Regan 1998[], which demonstrated the specific inhibition of tamoxifen-stimulated endometrial cancer growth in mice; and [(4)] DeFriend[], which

demonstrated a reduction in ER indices of ER-positive tumors from 0.73 to 0.01." Ex. 1015 at ¶ 201. Therefore, he concludes "it is reasonable to expect that combining Howell and McLeskey or Howell, McLeskey and O'Regan would yield a successful result." Ex. 1015 at ¶ 202. But, none of these references suggest that administering the castor oil formulation in McLeskey by a different method (intramuscular versus subcutaneous) and different frequency (once monthly versus once weekly) would yield a successful result. McLeskey concludes that the fulvestrant formulation(s) administered (it is unknown whether it is the castor oil-based or peanut oil-based formulation) subcutaneously once weekly to mice in that study is a "treatment failure"; Dukes 1992 discloses i.m. administration of propylene glycol and castor oil-based formulations (with no other formulation components disclosed) and discusses two other fulvestrant formulations for subcutaneous administration: an arachis oil suspension and a propylene glycol solution; the only fulvestrant formulation used in O'Regan is dissolved in ethanol and administered in peanut oil to mice by subcutaneous injection; and DeFriend discloses administration of 7 daily doses of a short-acting formulation, containing 20 mg/ml fulvestrant in a propylene glycol-based vehicle by i.m. injection. All four references disclose different fulvestrant formulations and none discloses the claimed method of treatment.

200. Thus, a POSA would not have been motivated to apply the teachings

of McLeskey and O'Regan to Howell 1996 and would not have had a reasonable expectation of success that the combination could be used for treating hormone dependent breast cancer in humans.

D) Ground Four: Howell 1996 In Combination With McLeskey, O'Regan, And DeFriend

1) DeFriend Adds Nothing And Indeed Was Already Considered And Referenced By Howell 1996

201. DeFriend is a first-in-humans study "to investigate the tolerance, pharmacokinetics, and short term biological effects of seven daily doses of a short-acting formulation of ICI 182,780 in [fifty-six] postmenopausal women prior to surgery for primary breast cancer." Ex. 1038 at 1. Importantly DeFriend is not a therapeutic study of the treatment of breast cancer. In the DeFriend study, patients in each group administered fulvestrant "received daily i.m. injections of ICI 182,780 at doses of 6 mg (n = 21) or 18 mg (n = 16) for 7 days prior to surgery." Ex. 1038 at 2. Furthermore, "ICI 182,780 was administered . . . as a short-acting formulation, containing 20 mg/ml drug in a propylene glycol-based vehicle." Ex. 1038 at 2.

202. With respect to ER expression, in DeFriend, it reported no difference between doses with regard to ER expression. Both doses reduced ER significantly and there is no evidence that there is any significant difference between the doses in terms of ER expression. PR is a functional readout (or measure) of ER activity.

When considering ER and PgR biomarkers it is important that they be considered together. PgR is downstream of the ER, and because of this, reduction in PgR expression can be a valuable indicator of biological activity in addition to reduction in ER expression. Important to that point, DeFriend reports that "the reduction in PgR expression did not achieve statistical significance when the effects of individual dose levels of ICI 182780 were analyzed separately." Ex. 1038 at 4. So in terms of PgR, a biomarker that is a known indicator of biological activity on the ER, there was no difference in reduction of expression between the 6 mg dose and the 18 mg dose. There is no evidence in DeFriend that there is any significant difference between the two doses of fulvestrant in terms of PgR expression.[10]

203. DeFriend notes that the adverse events reported in the study "were related either to the drug itself or to the propylene glycol-based vehicle used in the short-acting formulation" and that "[t]his question will be addressed in future studies

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[10] For Ki67, the 18 mg dose decreased Ki67 significantly whereas the 6 mg dose did not reach statistical significance: the authors offered an explanation that this could be due to relatively small numbers in each sub-group and also an imbalance in the number who had ER+ tumors in each sub-group. As with ER and PgR there was again no significant difference reported for reduction in Ki67 comparing the two doses of fulvestrant. Ex. 1038 at 6.

which are planned with a different, long-acting, formulation of ICI 182780 contained in a castor-oil based vehicle." Ex. 1038 at 5. Further, it states that "[a]nimal studies have demonstrated considerable interspecies variability in the elimination half-life of [fulvestrant], with a half-life of about 4 h in rats and 2 days in dogs after i.m. administration." Ex. 1038 at 5. And "[m]easurement of serum drug levels in this study showed that there was some interpatient variation in the serum concentration of ICI 182780 achieved." Ex. 1038 at 5.

204. DeFriend does not disclose "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." Further, DeFriend does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

205. InnoPharma argues the skilled artisan would add DeFriend to the combination, because "DeFriend tests the same compound for the treatment of breast cancer, and shows greater inhibition of the ER at higher doses with good tolerance." Petition at 63. There are several problems with this proposed motivation that are exacerbated by the very little explanation provided by InnoPharma. If InnoPharma means that the POSA would combine every publication that "tests the same compound," then the POSA would be left to sift

through hundreds of fulvestrant publications at the time of the invention. If InnoPharma limits the publications that "test[] the same compounds" based on "treatment of breast cancer" and a showing of "greater inhibition of the ER," then the skilled formulator would not look to McLeskey. Indeed, McLeskey describes the experiments as demonstrating a "treatment failure" with fulvestrant. Thus, InnoPharma's motivation for selecting DeFriend appears directly contrary to its motivation for selecting McLeskey, suggesting that hindsight alone explains this particular combination.

206. Dr. Harris argues that a POSA "would have been both motivated to apply the teachings of [] McLeskey, O'Regan, and DeFriend to Howell and further would have had a reasonable expectation of success that the combination could be used for using the claimed formulation in the claimed amounts as taught in the challenged claims to treat hormone dependent breast cancer in humans." Ex. 1015 at ¶¶ 124, 231. Despite arguing earlier in his declaration that "the response duration [] is extraordinary in Howell," "[t]he remarkable response rate shown in Howell [] suggests that an effective formulation and dosage regimen is being used," a POSA "would not have wanted to lower the dose used in Howell, which directly correlated with efficacious results and showed no adverse side effects," and Howell "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 [intramuscular] injection of the long-acting formulation used" (Ex. 1015 at ¶¶ 97, 138-139, 144-145), Dr. Harris argues for Ground 4 that a POSA "would have searched the existing literature for information regarding how to ***increase the response rate*** shown in Howell and ***improve upon the efficacy*** of fulvestrant for the treatment of breast cancer" and "[s]uch a person would have been led to DeFriend, which teaches that doses of 18 mg per day (or roughly 500 mg per 4 weeks) was highly effective in ER reduction." Ex. 1015 at ¶¶ 174-175 (emphases added).

207. As a clinician, I disagree that an ordinary clinician reading Howell would be left with the questions of "how to ***increase the response rate*** shown in Howell and ***improve upon the efficacy*** of fulvestrant for the treatment of breast cancer" as Dr. Harris opines. Ex. 1015 at ¶¶ 174-175 (emphases added). Rather, as explained above, the person of ordinary skill would be seeking to understand what the response rate and efficacy using fulvestrant actually would be—the very questions raised by Howell itself. Ex. 1007 at 6-7.

208. As a clinician and investigator on the DeFriend phase I study, I also disagree that DeFriend provided any disclosure that can be associated with the 500 mg dose of Faslodex® (fulvestrant) intramuscular injection. Ex. 1015 at ¶¶ 174, 176, 183-184, 186, 188. Furthermore, I disagree that DeFriend provides any evidence of exposure to fulvestrant for more than 7 days. The study in DeFriend

administered 7 daily doses of 6 mg or 18 mg intramuscular injection of "a short-acting formulation, containing 20 mg/ml drug in a propylene glycol-based vehicle." Ex. 1038 at 2. DeFriend concluded that "[t]his small study has shown [fulvestrant] to be well tolerated after short term administration and has produced preliminary evidence to suggest that this novel agent does exhibit biological activity as an estrogen antagonist in primary breast tumors, without producing demonstrable agonist effects." *Id.* at 6. First, the formulation reported by DeFriend is known not to be the same formulation as reported in the invention since it was propylene glycol-based with a short duration of action. Second, DeFriend is not even related to the clinical treatment of patients, much less successful treatment. This study was designed to evaluate underlying biological mechanisms. Third, DeFriend is not a randomized comparison of two different doses of fulvestrant which therefore makes any comparison between the doses an indirect comparison. Fourth, nowhere in DeFriend does it state there was a significant dose response seen for any of the biomarkers between the 6mg and 18mg doses. Fifth, Dr. Howell is an author on the DeFriend paper and DeFriend came before Howell 1996. In fact, Howell 1996 cites to DeFriend and as in DeFriend makes no claims of a dose response effect between the 6 mg and 18 mg doses. Indeed, Howell 1996 concludes the opposite of what Dr. Harris alleges DeFriend discloses, i.e., Howell states that lower doses of fulvestrant should be pursued.

209. With regards to the results reported in DeFriend, compared to the invention method (including the invention method delivering 500 mg), in my experience, the blood plasma profiles arising from the two formulations would be very different. And, it would be near impossible to extrapolate the serum concentrations achieved from a short-acting daily formulation with the levels (particularly the trough levels) of a long-acting formulation for 28 days. Furthermore, since DeFriend was a non-therapeutic study, there is no link between any pharmacokinetic or pharmacodynamic effects and therapeutic outcome. In addition, a non-randomized comparison introduces other potential causes for any difference in pharmacodynamic effects of different doses—although again I would emphasize no significant difference between the two doses was reported. Given the above, DeFriend alone could not predict improved therapeutic outcome with the invention method (involving a long-acting formulation) at a 500 mg dose. Moreover, the comparison that Dr. Harris attempts to make between the limited duration of exposure to fulvestrant in DeFriend (7 days) which uses a completely different formulation of fulvestrant (propylene glycol-based and short-acting) as well as a different dose and concentration than the Falsodex® (fulvestrant) intramuscular injection 500 mg formulation (castor oil-based and long-acting) is, in my opinion as a clinician, inappropriate. It also does not provide a meaningful assessment of side effects and safety profile or measureable therapeutic outcome of

the invention method (including as delivering 500 mg). For at least all of these reasons, it is my opinion that DeFriend did not disclose any relevant information related to the blood plasma levels achieved by the invention method or how such blood levels relate to safety and efficacy.

210. Dr. Harris admits that phase I studies such as DeFriend are "exploratory," "generally started at low doses for a short duration," and that "the means of administering the drug during Phase I studies is not always clinically applicable." Ex. 1015 at ¶ 158. For example, he disagrees that DeFriend "might suggest daily use was the aim" because "daily IM treatment of patients is simply not feasible over a longer period of time." Ex. 1015 at ¶¶ 157-158. I find it surprising that in light of this admission, Dr. Harris believes he can confidently translate the findings in DeFriend to the clinic.

211. InnoPharma's and Dr. Bergstrom's argument that a "POSA would look to DeFriend for its teachings on the effect of dose on ER inhibition, ***not*** for the formulation used or the method of administration" and "would consider DeFriend relevant for its disclosure of information concerning dose-dependent ER downregulation, not for any particular information on the formulation" is a red herring. Petition at n. 11 (emphasis added); Ex. 1013 at ¶ 147. First, as discussed above, DeFriend does not teach a dose effect on the ER but instead reports that "significant reductions in the median ER indices of ER-positive tumors were evident at

both the 6-mg and 18-mg dose levels" and that there was no difference in reduction of PgR expression (i.e., the indicator of biological activity on the ER) between the 6 and 18 mg doses. Ex. 1038 at 4 (emphasis added). Second, a skilled artisan would review DeFriend in its entirety—s/he would not separate the dose from the formulation and route and schedule of administration. As discussed previously, one cannot simply take a formulation using one route of administration and schedule and expect to achieve the same results when using it with another route of administration and schedule. Third, these arguments by InnoPharma and Dr. Bergstrom contradict Dr. Harris's assertion that "the purpose of Phase I studies is to evaluate toxicity, ***formulation*** and dosing." Ex. 1015 at ¶ 186 (emphasis added). The only explanation for InnoPharma's skewed analysis is that it cannot explain why a skilled artisan would be motivated to combine DeFriend with Howell, McLeskey, and O'Regan and reasonably expect success given its entirely different formulation and administration schedule.

212. Moreover, Dr. Harris states a number of times that "Howell showed that the ER expression in patients treated with fulvestrant at 250 mg per month was not completely suppressed (i.e., Howell only shows approximately 70% reduction from baseline)," "in Howell, it was shown that ER downregulation was incomplete (approximately 70%) following a single 250 mg dose of fulvestrant compared with levels achieved in earlier studies, including DeFriend," and "a person of skill in the

art would have expected that higher dose levels of fulvestrant would be better than Howell's 250 mg per month dose, which only achieved 70% inhibition of the ER." Ex. 1015 at ¶¶ 175, 179, 218. These statements regarding "approximately 70%" ER inhibition are not found anywhere in the Howell publication and, in fact, there is no biopsy data reported in Howell from which such a conclusion could be made, so Dr. Harris's assumption for incomplete inhibition is unsupported.

213. Dr. Harris cites what he refers to as "[c]ontemporaneous other prior art," i.e., Robertson 2007 and Howell 2011, to argue that the "dose-dependent nature of fulvestrant" was known, "[e]vidence that increasing the dose of fulvestrant may improve efficacy was available from biological data in early clinical trials," and "Dr. Robertson and Dr. Howell admit [this] was in the prior art." Ex. 1015 at ¶¶ 176, 178-181. Thus, he concludes "knowing that fulvestrant was dose dependent," a POSA "would have been motivated to increase the dose of fulvestrant in order to increase fulvestrant steady-state plasma concentrations and improve upon the efficacy shown in the Howell Phase II study." Ex. 1015 at ¶ 181. Neither Robertson 2007 nor Howell 2011 is "contemporaneous" with the claimed invention in 2000 and neither is "prior art."

214. Howell 2011 (Ex. 1060) is a review paper published long after the positive results using the claimed method of treatment were known. Howell 2011, in my opinion, retrospectively interprets the data that was available at the time (i.e.,

2000) in the context of a decade of further research including Faslodex® (fulvestrant) intramuscular injection (at different doses), multiple other new endocrine therapies, and many scientific papers which had reported on mechanisms of response and resistance of the ER and PgR pathway to endocrine and growth factor therapies. Dr. Harris's allegation that dose dependency for fulvestrant was known in 2000 (Ex. 1015 at ¶¶ 176-182) directly contradicts Dr. Howell's opinions much closer in time to the inventions. In 1996 and 1997, Dr. Howell warned that in his experiments with fulvestrant in an undisclosed formulation, "a direct pharmacokinetic-pharmacodynamic link [had not been] proven with the few patients studied to date . . . [and] further clinical studies [were] required" (Ex. 1007 at 6), and also that "phase II studies are notoriously unreliable in predicting superiority over old agents" (Ex. 2040 (Howell 1997) at 3-4). Furthermore, between 1997 and 2000 (the latter being at the time of filing of the '680 Patent) Howell was the Chief Investigator of a phase III trial looking at 250 mg and a lower 125 mg dose—looking to achieve efficacy with the lower dose and with less toxicity. It is therefore without foundation for Dr. Harris to state that Howell's writing in 2011 somehow indicates that dose dependence was known in 2000. The warning by Howell noted above was further supported by subsequent studies even between 1997 and the time of the invention which compared new antiestrogens with tamoxifen. Despite the fact that these new antiestrogens had shown "initial

promise" in terms of either improved efficacy over tamoxifen or non-cross resistance, subsequent definitive studies had shown these drugs had failed to deliver on their initial promise which had been portrayed positively by each of the clinical investigators. Dr. Howell's 2011 paper demonstrates the unpredictability of the work involved in new drug development (in this case, the invention) and subsequent success in treatment. The portion of Dr. Howell's paper cited by Dr. Harris highlights that a researcher cannot predict success in treatment from biological activity of the active ingredient alone. Despite all of this information on biological activity, as Dr. Howell explained, improved clinical outcome was not proven in randomized clinical trials.

215. Howell 2011 further describes the unpredictability of this area in its description of the work leading to the 250 mg dose. As discussed above (Section XI.A.), in 1996, Howell suggested ***lowering*** the dose of the formulation used in that study (from 250 mg) because of drug accumulation—in other words, bringing the blood plasma levels down, not up. Ex. 1007 at 6-7. Study 18 (fulvestrant 50, 125, 250 mg doses) and Studies 20 and 21 (fulvestrant 125, 250 mg doses) took a parallel approach. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2030 (Robertson 2001); Ex. 2031 (Robertson Clin. Ther. 2003). In 2011, Howell subsequently explains that it was only after the results of those trials (for which Howell 2011 cites Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2030

(Robertson 2001); Ex. 1044 (Robertson Cancer 2003)) when the 125 mg fulvestrant arm "was withdrawn from these studies due to lack of clinical benefit" that the efficacy and tolerability of the 250 mg dose was "established" and 250 mg dose was chosen over the lower doses. Ex. 1060 (Howell 2011) at 2.

216. Howell 2011 further describes the unpredictability of this area in its description of the work leading to the 500 mg dose. Howell 1996 advocated using ***lower*** doses of the formulation used in that study (i.e., lower than 250 mg) and three clinical studies (i.e., Study 18 and Studies 20 and 21), one of which Howell himself was chief investigator (Study 20), applied parallel reasoning. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2030 (Robertson 2001); Ex. 2031 (Robertson Clin. Ther. 2003). Howell 2011 explains that ***after*** all three studies (i.e., Studies 18, 20, and 21) results (publications in 2001 and 2002—i.e., after the invention), the selected dose was not lower than 250 mg but actually was 250 mg. Howell 2011 states that only after fulvestrant 250 mg had demonstrated similar efficacy to tamoxifen but "failed to meet the non-inferiority endpoint" with patients "progress[ing] quicker on fulvestrant than tamoxifen during the first 3 months of therapy" that "authors hypothesized that the inclusion of a loading dose may also contribute to improve efficacy." Ex. 1060 (Howell 2011) at 2. Howell 2011 views DeFriend in the light of the clinical trials published in 2002, the latter of which Howell states was the reason for going to a higher dose. DeFriend did not

suggest the higher dose hypothesis—Howell was an author on DeFriend. DeFriend was cited in Howell 1996 which reached the opposite hypothesis—i.e., that one should go for a lower dose. DeFriend itself did not and could not suggest that the invention method (involving an entirely different long-acting formulation at that point unpublished) would be expected to have the clinical benefit later trials demonstrated. As noted above, Howell 2011 states that it was only once the phase III clinical studies had been analyzed (these results were not published until 2002) that these results, with the interpretation of the biological data from the randomized clinical presurgical trial (published in 2001) which compared three separate doses (250, 125, 50 mg), led to the exploration of a higher dose. Howell in 2011 (as I will also note below regarding Robertson 2007) when he comments on dose dependency in DeFriend does not state this was a statistically significant finding, nor could he, as that was not reported in DeFriend. Moreover, in his own publication (Howell 1996) when he referenced the DeFriend paper, Howell made no mention of dose dependency. Indeed, the first time a dose dependent effect of fulvestrant on the ER was reported in human breast cancer was in the publication by me in 2001 where we compared three doses of fulvestrant (250, 125, 50 mg). Ex. 2030 (Robertson 2001).

217. Regarding Robertson 2007 (Ex. 1090), again, this is not contemporaneous prior art—it was published 7 years after the invention date. Dr.

Harris argues that I "explained that the Howell study and the DeFriend study both showed the dose-dependent nature of fulvestrant." Ex. 1015 at ¶ 179. First, Robertson 2007 cites to Study 18 (i.e., Robertson 2001 (Ex. 2030) which was published after the invention date) as demonstrating "[d]ose-dependent effects of fulvestrant on ER downregulation," ***not*** Howell 1996, as alleged by Dr. Harris. Ex. 1090 at 5. Study 18 (Ex. 2030 (Robertson 2001)) was the first time this effect had been shown in human breast cancer. Second, the comment in Robertson 2007 regarding "[d]ose-dependent effects on ER levels" in DeFriend is clearly retrospective in that it views the "Correlation of ER Downregulation with Fulvestrant Dose" through the lens of all of the data post-2000 including Study 18. Ex. 1090 at 5-6. From this perspective, I note the numerical difference in ER downregulation with the 18 mg versus 6 mg dose but nowhere do I state that this difference was statistically significant. Indeed, in the subsequent paragraph, I state cautiously that "[b]ecause ER downregulation ***appears to be*** **a** ***dose-dependent*** process, it ***may be possible*** to enhance ER downregulation by further increasing fulvestrant steady-state plasma concentrations." Ex. 1090 at 5 (emphases added). I then compare the pharmacokinetics from the short-acting propylene glycol formulation of the DeFriend study with the pharmacokinetic data from the long-acting castor oil-based formulation studies and state that "[i]ndirect comparison across these two studies suggests that higher mean plasma concentrations ***may*** lead

to greater ER downregulation." *Id.* at 6 (emphasis added). Therefore, I conclude that "there would ***appear*** to be an ***opportunity*** to improve the activity of fulvestrant [] which in turn would increase downregulation of ER." *Id.* (emphases added). Thus, even in 2007, I noted only the "possibility" (not confirmation) of a dose dependent effect on the ER with fulvestrant and my analysis of DeFriend was 7 years after the invention date in the context of significant new data. Like Dr. Howell, I too, was an investigator on clinical studies that looked down in dose following the direction of Howell 1996. It is clear therefore that at the time I conducted those clinical studies, in 1998-2000, DeFriend was not seen by me or others as teaching a benefit in increasing dose.

218. Dr. Harris's (unsupported) statements that a POSA would know that "increasing the dose above the 250 mg dose used in Howell would lead to a successful result owing to the dose-dependent nature of fulvestrant," "would expect that, if they increased the dose of fulvestrant, it would increase fulvestrant steady-state plasma concentrations," "would expect that the absorption of the drug into the body would be at a similar rate in each of the muscles, which, in turn, means that a doubling of absorption from the drug depo would be achieved," "would expect that doubling the dose that was used in Howell, as taught by DeFriend, would necessarily result in significantly higher blood plasma concentrations of fulvestrant" and "would reasonably have expected that increasing

the dose of fulvestrant as taught by DeFriend, either by increasing each monthly dose and/or by using a loading dose, would have led to a successful result in that patients would have higher blood plasma levels of fulvestrant, including blood plasma fulvestrant concentrations of at least 8.5 $ngml^{-1}$ for at least four weeks which, in turn, would increase reduction of the ER indices" (Ex. 1015 at ¶¶ 217-228; *see also* Ex. 1013 at ¶¶ 16, 122-155, 164-171), are entirely hindsight driven and undercut by the consistent teaching in the field at the time to look to lower doses. Indeed, as discussed above, Howell 1996's phase II study came after DeFriend and, in that study, the same researchers suggested lowering the dose. This concept of lowering the dose was consistent with nearly every other prior art endocrine therapy at the time and is, in fact, what AstraZeneca and its clinical investigators did following the Howell study (*see* ¶¶ 124-138). Tellingly, Dr. Harris does not cite a single reference to support his concept that a POSA would ignore Howell's instruction to lower the dose and instead look to an earlier study and double the dose, because he cannot. The prior art consistently did the opposite.

219. Dr. Harris's citations to Exs. 1090 (Robertson 2007), 1082 (Adam 1988), and 1086 (Wilkinson 1982) regarding the exploration of "loading dose and high dose regimens of oral tamoxifen in patients with advanced breast cancer" in the 1980s and 1990s actually supports this point. Ex. 1015 at ¶ 226. Indeed, as Dr.

Harris admits in the very next paragraph, "in current practice, tamoxifen is generally not administered with a loading dose because the daily doses have been proven to be sufficient" and "under certain circumstances, a loading dose or increased dose may not be advantageous because the doses being administered were known to be sufficient or the side effects were too severe." Ex. 1015 at ¶ 227. Nonetheless, following this acknowledgement, he provides the conclusory opinion (without support) that "such was not the case with fulvestrant." *Id.*

220. Moreover, Dr. Harris argues that "[o]ther prior art confirms that fulvestrant doses of 500 mg per month are efficacious and preferred" and cites to the '122 Patent file history which cites to Dukes 1989. Ex. 1015 at ¶ 185 (citing Ex. 1006 at 537 (citing Ex. 1047 (Dukes 1989))). Dukes 1989 relates to therapeutic products comprising an estrogen and a pure antiestrogen for use in treating perimenopausal and postmenopausal conditions. Specifically, "for example, vasomotor disturbances (hot flashes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and osteoporosis." Ex. 1047 at 6. Dukes 1989 does not disclose the use of a pure antiestrogen for the treatment of breast cancer and thus does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering . . . to a human in need of such treatment." Dukes 1989 does not teach that "a therapeutically significant

blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

221. Dukes 1989 states that "[p]referably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antiestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antiestrogen is employed." Ex. 1047 at 6. "Such an injection provides a depot of the pure antiestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks." Ex. 1047 at 6.[11] Thus, Dukes 1989 discloses a wide dosage range of 50-500 mg of a pure antiestrogen for weekly, biweekly, or monthly i.m. administration in an aqueous suspension or oily solution or suspension in arachis or castor oil. Dukes

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[11] Similar to its approach to DeFriend, InnoPharma, through its experts, argues that a POSA would look to Dukes 1989 for its teaching on dose but "would have rejected the Dukes '814 [castor oil-based] formulation due to its high benzyl alcohol content." Petition at 48. This analysis is improper. A skilled artisan would review Dukes 1989 in its entirety—s/he would not separate the dose from the formulation and route and schedule of administration.

1989 does not disclose "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." Further, Howell's phase II study which suggested lowering the dose came after Dukes 1989. A POSA starting with Howell 1996's instruction to lower the dose would not then look to an earlier study and double the dose.

222. A POSA would not have been motivated to apply the teachings of McLeskey, O'Regan, and DeFriend to Howell 1996 and would not have had a reasonable expectation of success that the combination could be used for treating hormone dependent breast cancer in humans.

XIII) OBJECTIVE INDICIA DEMONSTRATE THAT THE CLAIMED INVENTION IS NONOBVIOUS

A) Long-Felt Unmet Need

223. The invention method of treatment filled a long-felt need–i.e., the need to improve on the current standard of care and also extend the sequence of endocrine therapies.

224. The invention method met a treatment need by improving clinical outcomes (i.e., clinical benefit, time to progression, and overall survival benefits versus current standard of care). Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex. 2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015); Ex. 2154 (Robertson 2016).

225. From my clinical perspective, extending the period during which

endocrine therapy can be used as an effective and viable treatment option for hormone dependent breast cancer is an important goal. While prior endocrine therapies had shown evidence of non-cross resistance, patients eventually became resistant to subsequent endocrine treatment. Endocrine agents, which show lack of cross-resistance with known endocrine agents and thereby can be used sequentially ***before and after*** other available therapies, are extremely valuable in extending the life of patients suffering with the disease. Ex. 2059 (Vergote 2003) at 4.

226. The invention method met a need for a new treatment that was not associated with cross-resistance to currently used endocrine therapies such as tamoxifen or AIs or to subsequent endocrine therapies. Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002); Ex. 2060 (Robertson 2004); Ex. 1044 (Robertson Cancer 2003); Ex. 2062 (Chia 2008); Ex. 2063 (Johnston 2013); Ex. 2064 (Robertson 2005) at 1, 5 ("[P]ostmenopausal women with advanced breast cancer who respond to first-line fulvestrant or tamoxifen retain sensitivity to subsequent endocrine therapy. . . . [F]ulvestrant appears to offer an opportunity to prolong the time in which well-tolerated endocrine therapies are used before reliance upon cytotoxic chemotherapy is necessary."); Ex. 2065 (Johnston 2004) at 2 ("These results suggest that in addition to producing responses after prior tamoxifen, disease progression after anastrozole may not preclude subsequent treatment with fulvestrant.").

227. In addition to having sequential options, the FIRST and CONFIRM

studies showed that putting Faslodex® (fulvestrant) intramuscular injection 500 mg into the sequence of treatment (whether in the first-line setting or second-line setting) provided not only an option in terms of cross-resistance but resulted in improved disease control and overall survival which satisfied an unmet need. In contrast, the introduction of nonsteroidal AIs, such as letrozole and anastrozole, into the sequence of endocrine therapies had not shown an overall improved disease control in the second-line setting (which fulvestrant did) nor improved overall survival in the first-line setting (which fulvestrant did). Anastrozole and letrozole were initially introduced in second-line based not on improved time to progression (i.e., disease control) but on reduced side effects (particularly weight gain) versus megestrol acetate. In the first-line both anastrozole and letrozole showed improved disease control (i.e., improved time to progression) but no significant difference in overall survival.

228. Indeed, it has been acknowledged in the literature that Faslodex® (fulvestrant) intramuscular injection met an unmet need. Ex. 2066 (Pharma Marketletter 2004) at 1-2 ("There has been an unmet need for an effective endocrine therapy which works in women who have become resistant to other hormonal treatments including tamoxifen and [AIs]. . . . [Faslodex® (fulvestrant) intramuscular injection] is a better treatment than other endocrine therapies and could be used in preference to [AIs] after tamoxifen or, eventually, even before

tamoxifen."); Ex. 2067 (Cancer Weekly April 2004) at 2 (Faslodex® (fulvestrant) intramuscular injection was a new type of therapy which offered women with advanced breast cancer ("ABC") a method to "extend[] the sequence of 'patient-friendly' hormonal therapies that can be used to control the disease." The invention method "therefore [met] a key unmet need . . . since it c[ould] be added in to the sequence of well-tolerated hormonal therapies and may [have] delay[ed] the need to resort to cytotoxic chemotherapies with their well-recognized side effects.").

B) Unexpected Results

229. Based on the properties of the available hormone therapies, as well as the properties of fulvestrant itself, scientists and clinicians would not have expected the invention method to have its beneficial clinical results. The balance of side effects and adverse events with efficacy (net clinical benefit) for the invention method would have been predicted to be similar or worse than the SERMs or AIs because fulvestrant, the active ingredient, acted, as those agents also do, on the estrogen pathway, and because it had no "balancing" agonist activity. For example, after the initial publication of the phase II trial of fulvestrant following progression on tamoxifen, scientists did not expect that a method of treatment using fulvestrant would be more effective than AIs or SERMs, noting that "[i]t remains to be seen whether it will be more effective than other non-steroidal anti-oestrogens with less agonist activity than tamoxifen or toremifene, such as idoxifene. Our data suggest

that it may not be substantially more effective in terms of response rate than aromatase inhibitors, with which it is conceptually similar in its pure deprivation of the oestrogenic signal." Ex. 2038 (Dowsett 1995) at 1. A person of skill in the art would have expected the invention method to be cross-resistant with tamoxifen because both drugs prevent estrogen from binding to the ER (i.e., ER antagonists). Ex. 2010 (Fornier) at 4; Ex. 1044 (Robertson Cancer 2003) at 2. At the time of the invention, it was known that other SERMs, which act on the ER, were cross-resistant with tamoxifen. Ex. 2010 (Fornier) at 4; Ex. 2013 (Johnston 1997) at 1; Ex. 2068 (Baumann 1998) at 1-2, 9; Ex. 2017 (Jordan 1995) at 1, 6-10; Ex. 2011 (Jordan Supp. 1995) at 2; Ex. 2069 (Pyrhönen 1994); Ex. 2070 (Stenbygaard 1993). And, indeed, I highlighted this point in my 1997 paper.

230. However, because of the unique combination of the active ingredient and delivery system as well as the specific blood levels and profile achieved, the invention method surprisingly and unexpectedly showed improved clinical outcomes compared to AIs; and had an improved side effect profile compared to other hormone therapies (e.g., antiestrogens, progestins).

1) Improved Clinical Outcomes

231. First, it was unexpected that the invention method would have improved clinical outcomes compared to AIs. AIs, "which block production of estrogen through their interaction with the estrogen-producing enzyme aromatase, []

demonstrated increased efficacy compared with the ER antagonist tamoxifen in postmenopausal women as first line endocrine treatment for ER+ advanced breast cancer and as adjuvant therapy for postmenopausal women with early breast cancer." Ex. 2071 (Robertson 2014) at 1.

232. Because fulvestrant, like tamoxifen, acts as an ER antagonist, a person of skill in the art would not have expected fulvestrant to be more efficacious than AIs. However, the invention method was unexpectedly more efficacious compared to AIs—particularly, a third-generation, gold standard AI, such as anastrozole.

233. For example, the 500 mg dose of the invention method displayed significantly longer time to progression (TTP) and treatment failure (TTF) and better overall survival (OS) compared with anastrozole 1 mg in the phase II FIRST trial. Ex. 2058 (Ellis 2015) at 3-6 ("This study reports improved OS with fulvestrant 500 mg treatment compared with anastrozole in the first-line setting for ER-positive [ABC], with an approximately 30% reduction in mortality risk. . . . To our knowledge, this represents the first time an endocrine monotherapy has demonstrated improved efficacy compared with a third-generation AI."); Ex. 2057 (Robertson SABCS 2014) at 1 ("HR+ [patients] receiving first-line fulvestrant 500 mg lived significantly longer than [patients] on anastrozole . . . . FIRST is therefore the second randomized trial to show an OS advantage for fulvestrant 500 mg over another endocrine therapy."); Ex. 2071 (Robertson 2014) at 5 ("This was the first

trial to indicate that an alternative endocrine therapy may be more effective than an AI in the first-line setting for [ABC.]"); Ex. 2072 (Barrios 2012) at 3 ("TTP was significantly prolonged with fulvestrant 500 mg [and d]ata from the FIRST study showed that the significant difference in TTP had persisted with longer follow-up[.]");Ex. 2056 (Robertson 2012) at 6 ("Fulvestrant 500 mg as first-line endocrine treatment was associated with a significantly longer TTP compared with anastrozole 1 mg . . . . [and] an improved TTF compared with anastrozole. . . . [M]edian TTF was significantly longer for fulvestrant versus anastrozole."); Ex. 2055 (Robertson 2009) at 4 ("[M]ost notably[,] median TTP [] was estimated to be 60% longer in patients treated with fulvestrant [high-dose (HD)] compared with TTP for those treated with anastrozole, a statistically significant difference."). In that same study, duration of response (DOR) and clinical benefit (DoCB) data favored the 500 mg dose of the invention method versus anastrozole 1 mg, which supported "observations in previous fulvestrant studies suggesting that prolonged response may be a consistent benefit of fulvestrant treatment." Ex. 2055 (Robertson 2009) at 5.

234. With respect to the 250 mg dose of the invention method, "DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group" in phase III trials comparing the 250 mg dose of the invention method and anastrozole 1 mg. Ex. 1044 (Robertson Cancer 2003) at 1, 7;

Ex. 2073 (Robertson Eur. J. Cancer 2005) at 4 ("A combined analysis of all patients included in both second-line Phase III trials demonstrated a significant 30% increase in mean DOR in patients treated with fulvestrant."); Ex. 2074 (Clinical Practice Guidelines 2003) at 47 ("Fulvestrant [250 mg] appears to be at least as effective as anastrozole in patients whose disease progressed on previous endocrine therapy, and a recent reanalysis of these studies suggests a longer [DOR] favoring fulvestrant.").

2) Improved Side Effect Profile

235. The invention method had an unexpectedly better side-effect profile as compared with other hormonal agents. For example, as compared to AIs, the invention method was not associated with bone loss. Ex. 2075 (Vergote 2006) at 3 ("The AIs inhibit endogenous oestrogen synthesis via aromatase, which in postmenopausal women results in very low plasma levels of oestrogen, and these agents may therefore be associated with some deleterious effects on bone."). A person of skill in the art would have "predicted undesirable action of pure antiestrogens in therapeutic use [due to a] tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis." Ex. 1058 (Wakeling 1993) at 7. Faslodex® (fulvestrant) intramuscular injection is a pure antiestrogen but is not associated with bone loss (i.e., there are no changes in serum markers of bone resorption or formation). Agrawal 2009 (Ex. 2076) reported on bone formation

markers, bone alkaline phosphatase (BAP) and N- terminal propeptide of procollogen type 1 (PINP), and the bone resorption marker C-terminal telopeptide (CTX). Ex. 2076 (Agrawal 2009) at 3 ("[T]here was a lack of change in markers equating to long-term stability of bone turnover markers in postmenopausal women with [locally advanced primary breast cancer] treated with fulvestrant for over a period of 18 months. This is in contrast to the increase in bone markers (serum BAP, PINP and CTX) at 12 months compared to the baseline seen in 58 patients who received anastrozole in a sub-protocol study of patients in ATAC trial."). The absence of an effect of the invention method on these bone markers of resorption or formation was irrespective of dose for the 250 mg and 500 mg dose of the invention methods. Ex. 2077 (Kuter 2012) at 5 ("Serum bone marker levels were similar within and between the two groups throughout the study, with neither dose producing substantial changes in any of the three bone markers assessed (ALP, CTX, and PINP)."). The use of the invention method avoids the bone loss which occurs with AI treatment. This was surprising because AIs have been known to cause bone loss and other skeletal-related events. Ex. 2078 (Buzdar 2006) at 5 ("Clinical trials including postmenopausal women with [early breast cancer] have confirmed that [AIs] have detrimental effects on bone, which may give rise to an increased risk of osteopenia, osteoporosis, and an increased susceptibility to fractures."). Moreover, "both steroidal and nonsteroidal [AIs have been] shown to

increase markers of bone turnover." Ex. 2078 (Buzdar 2006) at 5 ("Anastrozole increased markers of bone resorption and formation in clinical studies, whereas letrozole increased bone resorption markers, but without a compensatory increase in bone formation markers. . . . [E]xemestane appears to increase both markers of formation and resorption to a greater extent than does either of the nonsteroidal agents.").

236. Surprisingly, the injections of the invention method are well tolerated locally, with a low incidence of injection-site reactions. Ex. 2075 (Vergote 2006) at 2 ("Fulvestrant i.m. injection was well tolerated locally; in most cases injection-site reactions were non-serious, mild and transient: only 4.6% and 1.1% of fulvestrant i.m. injections in trials 0021 and 0020, respectively resulted in injection-site events."); Ex. 1044 (Robertson Cancer 2003) at 9 ("The incidence of injection-site reactions and withdrawals due to such reactions was low, indicating that administration of fulvestrant by injection is well tolerated and is not disadvantageous compared with oral administration."); Ex. 2028 (Howell 2002) at 6 ("Only 20 [fulvestrant] injections out of the total of 1,898 (1.1%) resulted in an injection site event."); Ex. 2029 (Osborne 2002) at 6 (finding that "86 fulvestrant courses (4.6%) of the total of 1,879 and 71 placebo courses (4.4%) of the total 1,624 resulted in an injection site event" which shows that fulvestrant doesn't cause injection site pain by itself and that the placebo (which used the same delivery

system as that used for delivering fulvestrant) caused little injection-site reaction). This was surprising in and of itself because other injectable anticancer agents, such as the steroidal AI, formestane, were not well tolerated locally. Ex. 2075 (Vergote 2006) at 2 ("[F]ulvestrant i.m. injection is well tolerated [locally] in contrast to some other injectable anticancer agents such as the steroidal AI formestane."); Ex. 2025 (Masamura 1994) at 4 ("[S]tudies reported sterile abscesses due to the intramuscular injection required for administration of this compound [formestane]."). The local tolerance of the invention method permits divided dosing with two injections, allowing delivery of a 500 mg dose and the local tolerance of the injections permits long-term care.

237. The invention method therefore not only delivers fulvestrant in a manner that allows reproducible, prolonged release of fulvestrant which gives stable drug exposure with blood concentrations maintained within a narrow range over 4 weeks but also produces very little injection-site reactions. Both were unexpected and the combination of the favorable absorption characteristics and the lack of local site reaction was even more unexpected.

C) The Invention Method Is The Reason For These Surprising Results

238. Treatment is a balance between side or adverse effects and beneficial efficacy effects. However, the pharmacodynamics for side or adverse effects may or may not be linearly linked. The blood plasma level profile of the drug impacts

the correlation between side effects and beneficial effects.

239. The invention methods of the '680 Patent include concepts of a particular combination of ingredients to be administered in a particular way to achieve specific blood levels for treating a specific disease. The choice of active ingredient is but one part of treatment. An active ingredient alone cannot treat the disease—it must be delivered in an effective, safe, and tolerable manner to the human body. Here, the entire invention method, including its delivery system leads to unexpected results of enhanced clinical benefit. The invention method can provide a sustained release of fulvestrant over one month, surprisingly achieving what had never been possible before (or since) with multiple dosing regimens of conventional dosage forms – the ability to attain higher blood levels and a reproducible blood plasma level profile and dose response, resulting in improved efficacy and no associated increase in side effects. As I noted after the large scale clinical testing of the invention method, it "offers the assurance of stable drug exposure, with plasma fulvestrant concentrations maintained within a narrow range throughout the administration interval," which minimizes the risk of drug-associated tolerance problems and "obviates patient compliance issues during long-term treatment." Ex. 2060 (Robertson 2004) at 10. The direct result of the invention method of treatment is an unexpectedly improved patient treatment.

240. The relationship between the invention method and its resulting steady

blood plasma levels leading to the unexpected results of increased efficacy is demonstrated by the comparisons of results with two doses of Faslodex® (fulvestrant) intramuscular injection – 500 mg and 250 mg. The CONFIRM study (Faslodex® (fulvestrant) intramuscular injection 500 mg versus 250 mg) was carried out in the same advanced breast cancer population (i.e., second-line endocrine therapy) as Studies 20 and 21 (Faslodex® (fulvestrant) intramuscular injection 250 mg versus anastrozole). Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014); Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002). Studies 20 and 21 both individually (Ex. 2028 (Howell 2002); Ex. 2029 (Osborne 2002)) and when combined (Ex. 2031 (Robertson Clin. Ther. 2003)) showed that 250 mg Faslodex® (fulvestrant) intramuscular injection in this patient population was equivalent to the third-generation aromatase inhibitor, anastrozole. The CONFIRM study carried out in a similar patient population then showed in a direct, double-blind randomized comparison that Faslodex® (fulvestrant) intramuscular injection 500 mg was superior to 250 mg both in terms of time-to-progression and in terms of overall survival. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014). An indirect comparison in the second-line setting (i.e., Studies 20 and 21 combined versus CONFIRM) indicates a benefit of the Faslodex® (fulvestrant) intramuscular injection 500 mg over anastrozole; these findings are consistent with the results of the direct comparison of Faslodex® (fulvestrant) intramuscular injection 500 mg versus

anastrozole in the first-line setting reported in the FIRST study. Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex. 2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015). Furthermore, the CONFIRM study shows that the higher dose of Faslodex® (fulvestrant) intramuscular injection (500 mg) with its increased concentration of fulvestrant compared to the 250 mg dose resulted in improved disease control on treatment, as shown by the improved progression-free-survival, and also improved overall survival. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014). CONFIRM was a double-blind clinical trial comparing the same drug (Faslodex® (fulvestrant) intramuscular injection) at two different doses. There was therefore no need for the clinician or the patient to know which arm of the study the patient was in when they had disease progression in terms of selecting subsequent therapy. Indeed, ~90% of patients in the CONFIRM trial were never unblinded in terms of what dose of Faslodex® (fulvestrant) intramuscular injection they had received. Since treatment options were therefore the same for patients in both arms of the trial following progression, the survival advantage seen in CONFIRM cannot be deemed to be due to differences in the treatment post-progression on fulvestrant. The improvement in disease control on treatment with the Faslodex® (fulvestrant) intramuscular injection 500 mg dose therefore appears to have carried through to result in an overall improvement in survival. The higher dose of Faslodex® (fulvestrant) intramuscular injection (500 mg) is linked to the higher serum

concentration which, in turn, is linked directly to the formulation and method of treatment of the invention.

241. A person of skill in the art would have expected the 500 mg dose invention method to result in proportionally increased toxicity and adverse events as compared to the 250 mg dose invention method. However, the 500 mg dose invention method did not increase toxicity or safety concerns in what again should be noted was a double-blind trial—i.e., neither physician nor patient knew what dose they were on. Ex. 2004 (Di Leo 2010) at 1, 5; Ex. 2005 (Di Leo 2014) at 5; Ex. 2057 (Robertson SABCS 2014) at 1; Ex. 2071 (Robertson 2014) at 4; Ex. 2056 (Robertson 2012) at 2.

242. Compared to the 250 mg dose invention method, the 500 mg dose invention method results in increased down regulation in ER levels. The clinical trial, NEWEST, found that "fulvestrant 500 mg is associated with significantly greater early reduction in tumor biomarker Ki67 and ER expression versus fulvestrant 250 mg." Ex. 2077 (Kuter 2012) at 8.

243. Additionally, two studies looking at the three dose regimes (approved dose ("AD"), loading dose ("LD"), high dose ("HD")) which, between them, were used in all of the clinical trials of Faslodex® (fulvestrant) intramuscular injection, were investigated in both an Asian population (Ex. 2006 (FINDER 1)) and a western population (Ex. 2007 (FINDER 2)) in 2010. Other

than ethnicity, the demographics of the patients in both studies were similar. Plasma fulvestrant concentration level measurements including C_{max}, C_{min}, and AUC were in both studies approximately double for the Faslodex® (fulvestrant) intramuscular injection 500 mg dose compared to the 250 mg dose. Ex. 2006 (FINDER 1) at 2 ("[P]harmacokinetic (PK) analysis demonstrated that fulvestrant HD achieved plasma levels approximately double those seen with fulvestrant AD."); Ex. 2007 (FINDER 2) at 5, 7-8 ("At month 3, C_{min} and the AUC were similar for the AD and LD regimens, whereas these parameters were approximately doubled with the HD regimen. . . . While fulvestrant HD did not show superior efficacy versus fulvestrant AD in these two small Phase II studies, the CONFIRM study, which was a much larger, Phase III trial has clearly demonstrated the clinical benefits of fulvestrant HD over AD in the management of postmenopausal women with advanced breast cancer."). Furthermore, FINDER 2 reports that "[r]ecent data from the large Phase III [CONFIRM] study, which compared the clinical benefit of fulvestrant HD versus AD in postmenopausal women with ER+ advanced breast cancer have shown that TTP was significantly longer for fulvestrant HD (n=362) than AD (n=374) (hazard ratio 0.80; 95% CI, 0.68, 0.94; P=0.006), corresponding to a 20% reduction in the risk of progression. Fulvestrant HD also showed numerical advantages in other secondary efficacy endpoints while keeping a similar tolerability profile to

fulvestrant AD. Overall, these results suggest that the risk:benefit profile for fulvestrant HD is better than that of AD." Ex. 2007 (FINDER 2) at 7. The authors of FINDER 1 make a similar connection to the CONFIRM trial and conclude "[t]ogether with a favourable tolerability profile and no evidence of dose-related AEs, this equated to an improved benefit-risk profile for HD compared with AD." Ex. 2006 (FINDER 1) at 5. The patient demographics in the CONFIRM trial were similar to FINDERS 1 and 2, which all looked at second-line hormone therapy in patients with hormone receptor-positive metastatic breast cancer.

244. In contrast, increases in dose of other endocrine agents showed no corresponding increase in net clinical benefit, as discussed above at paragraphs 124-138.

245. The '680 Patent specification explicitly teaches the "therapeutically significant levels," i.e., the blood plasma levels that provide a therapeutic effect in a patient over the course of a month. Ex. 1001 at 9:24-28. Furthermore, the specification teaches that the claimed method results in a "particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." Ex. 1001 at 10:49-51. The unique characteristics of the method of the invention, as described above, have resulted in the improved clinical outcomes reported, for example, in the CONFIRM and the FIRST studies. Ex. 2004 (Di Leo 2010); Ex. 2005 (Di Leo 2014); Ex. 2055 (Robertson 2009); Ex. 2056 (Robertson 2012); Ex.

2057 (Robertson SABCS 2014); Ex. 2058 (Ellis 2015).

246. The PFS benefit found in the FIRST study has recently been shown through a phase III study. The purpose of the study was to demonstrate sufficient evidence that would change the standard of care in the first-line setting in patients with hormone dependent breast cancer. Following the open label phase II FIRST trial, a phase III randomized double-blind trial (FALCON) was set up to compare fulvestrant 500 mg versus anastrozole 1 mg in postmenopausal patients with hormone receptor positive advanced breast cancer. The population of patients studied were hormone naïve (i.e., they had never received an anti-hormonal therapy for breast cancer—a clinically meaningful patient population). Ex. 2154 (Robertson 2016). This allowed a direct unbiased comparison of the efficacy of the two endocrine therapies studied. The investigators reported that the FALCON trial met its primary endpoint: the PFS was statistically significantly longer for the fulvestrant treated group of patients compared to anastrozole. *Id.* at 6 ("The primary endpoint of this phase 3 study was met, with patients receiving fulvestrant having a significant longer progression-free survival than patients receiving anastrozole, supporting the hypothesis that fulvestrant is a more efficacious treatment than anastrozole in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not received previous treatment with endocrine therapy."). This was found to represent "a

meaningful and relevant finding for which clinical data are limited." *Id.* The hazard ratio (i.e., the comparison of the rate of events between two treatment groups) was 0.797 which indicates a 20% improvement in PFS of fulvestrant over anastrozole. This level of improvement of fulvestrant compared to anastrozole is similar to the level of improvement seen with the third-generation aromatase inhibitors such as anastrozole, letrozole, and exemestane when they were compared to tamoxifen and replaced tamoxifen as the standard of care. The primary analysis was supported by the secondary efficacy endpoints. Treatment effects were largely consistent across the pre-specified patient subgroups.

247. The results of FALCON are consistent with the data from the FIRST study. FALCON finds that fulvestrant is more efficacious than anastrozole in postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer who have not received prior endocrine therapy. Ex. 2154 (Robertson 2016) at 1-2 ("Fulvestrant has superior efficacy and is a preferred treatment option for patients with hormone receptor-positive locally advanced or metastatic breast cancer who have not received previous endocrine therapy compared with a third-generation aromatase inhibitor, a standard of care for first-line treatment of these patients. . . . Results from our study therefore add to the extensive data for the efficacy and safety of fulvestrant in patients with advanced breast cancer and consolidate evidence for superior efficacy for fulvestrant

compared with anastrozole shown in FIRST. . . . These findings consolidate the known clinical effectiveness of fulvestrant and support the use of fulvestrant monotherapy in endocrine-naïve patients with hormone receptor-positive advanced breast cancer."). And, the results indicate that "fulvestrant provides a lower toxicity option for first-line therapy that could be favoured for patients with low or intermediate risk disease with good prognosis (e.g., non-visceral disease), patients with high risk disease who have comorbidities restricting the use of combination targeted therapy, patients who cannot afford a CDK4 or CDK6 inhibitor, or in countries where CDK4 or CDK6 inhibitors have not been approved by regulatory authorities." *Id.* at 8. At the 2017 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, presentation of the overall survival results of the PALOMA 1 trial reported no significant difference in survival by the addition of the CDK4/6 inhibitor, palbociclib, to endocrine therapy. Thus, to date, none of the growth factor inhibitors or CDK4/6 inhibitors have shown a survival advantage in patients with ER-positive advanced breast cancer. This is in contrast to Faslodex® (fulvestrant) intramuscular injection which in CONFIRM and FIRST has shown significant improvements in overall survival (OS) as well as disease control (PFS/TTP) in the first and second-line settings, respectively. Survival data from FALCON is immature with only 31% of patients having died at the time of the first analysis. This shows an as yet non-significant benefit for the fulvestrant

treated group. A second analysis when overall survival is mature is part of the statistical analysis plan for the FALCON trial. It is envisaged that the significant improvement in PFS advantage will be accompanied by a significant improvement in overall survival similar to the overall survival improvement reported in the FIRST phase II trial and also the survival advantage reported in the CONFIRM trial—where advantages in PFS translated into overall survival advantages. Ex. 2155 (Cristofanilli) at 1 ("Nevertheless, the results of the current [FALCON] study support the outcome data of the CONFIRM study and indicate that fulvestrant should be considered as a potentially superior drug when a single agent treatment is preferred.").

248. FALCON was recently highlighted in The ASCO Post—which is sent out to 27,000 Oncologists and other cancer specialists including all ASCO members in the United States. Ex. 2156 (Stenger) at 2 ("Fulvestrant has superior efficacy and is a preferred treatment option for patients with hormone receptor–positive locally advanced or metastatic breast cancer who have not received previous endocrine therapy compared with a third-generation aromatase inhibitor, a standard of care for first-line treatment of these patients."). The results of the FALCON study continue to be released. At the 2017 annual meeting of ASCO the health related quality of life (HRQoL) was shown to be maintained and comparable with fulvestrant versus anastrozole. In a retrospective analysis there was less

reduction in HRQoL over time with fulvestrant compared with anastrozole. Therefore, the added efficacy benefits of Faslodex® (fulvestrant) intramuscular injection, 500 mg, do not come with increased side-effects. Indeed, the HRQoL is maintained on Faslodex® (fulvestrant) intramuscular injection and may even be improved compared to anastrozole. Further, results of the FALCON study will be released in due course but these results demonstrate that AstraZeneca's clinical development of Faslodex® (fulvestrant) intramuscular injection continues to this day. The fact that the FALCON study was done is testament to the statement in Howell 1997 that "phase II studies are notoriously unreliable in predicting superiority over old agents." Ex. 2040 (Howell 1997) at 3-4. Indeed, even after the more robust FIRST study with 200 randomized patients—showing an improvement in time to progression and survival over a third-generation aromatase inhibitor—compared to Howell 1996's non-randomized open-label study in 19 "highly selected" patients, AstraZeneca still conducted the FALCON study.

249. By receiving FDA approval in 2002, Faslodex® (fulvestrant) injection became the first marketed pure antiestrogen, and none have been approved since.

250. I understand that Dr. Harris disagrees with my opinion that there are secondary considerations warranting a finding of nonobviousness and instead opines that any secondary considerations are due to the compound fulvestrant itself. Ex. 1015 at ¶¶ 232-248. As discussed above, the choice of active ingredient is but

one part of the invention method. Further, an active ingredient alone cannot treat disease—it must be delivered in an effective manner to the human body. Here, in the almost 30 years since the invention of the active ingredient, no other delivery mechanism has been invented that has been proven to effectively deliver fulvestrant efficaciously, safely and conveniently for long-term use.

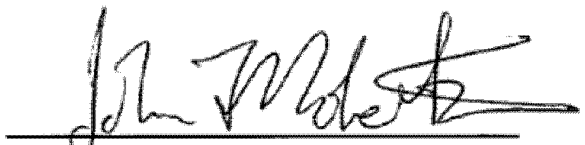
XIV) CONCLUSION

251. Fulvestrant was a very difficult drug to formulate and administer according to the claimed method of treatment. It took eleven clinical trials and countless preclinical studies to discover the unique method of treatment claimed in the '680 Patent.

252. For the foregoing reasons, it is my opinion that claims 1-3 and 6 of the '680 Patent are not obvious.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: June 9, 2017



John F.R. Robertson, M.D.

EXHIBIT A

C U R R I C U L U M V I T A E

Professor John F.R. Robertson

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INDEX

PERSONAL DETAILS

NAME	John Forsyth Russell Robertson
DATE OF BIRTH	20th February 1956
QUALIFICATIONS	M.B. Ch.B. (Glasgow), B.Sc. (Glasgow) F.R.C.S. (Glasgow) M.D. (Glasgow) Specialist Accreditation in General Surgery Cambridge Diploma in Religious Studies
FELLOWSHIP	Moynihan Travelling Fellowship

APPOINTMENTS

August 11 -	Professor of Surgery based at the Royal Derby Hospital, Derby
Aug 98 – July 11	Professor of Surgery based at the City Hospital, Nottingham
Aug 96 - July 98	Reader in Surgery (Honorary Consultant Surgeon) based at the City Hospital, Nottingham
June 92 - July 96	Senior Lecturer in Surgery (Honorary Consultant Surgeon) based at the City Hospital, Nottingham

CLINICAL EXPERIENCE

i) Breast Surgery

Over the last 32 years I have acquired extensive clinical experience in breast disease. I am Professor of Breast Surgery at the University of Nottingham, based at the Royal Derby Hospital, Derby. The Breast Unit has a multi-disciplinary team which looks after patients from high risk/prevention through screening, symptomatic primary breast cancer, locally advanced and metastatic disease to terminal care. I have clinical experience in all these areas.

Prior to moving to Derby in 2011 the academic unit was based at the City Hospital, Nottingham which also has a large Breast Unit seeing approximately 6,000 new breast referrals, and treated between 500 - 600 new breast cancer patients, each year. This number of patients allowed us to run clinics for specific conditions - e.g. benign breast pain, benign breast lumps, family history, primary operable breast cancer, locally advanced breast cancer, elderly primary breast cancer and systemically advanced breast cancer. These specialist clinics formed the basis for much of the clinical research programme and is the model we are further developing at Royal Derby Hospital.

With regard to surgery for operable breast cancer I perform conservation surgery or mastectomy as appropriate. I was responsible for establishing a joint reconstructive service between breast and plastic surgeons in Nottingham in 1992, which was one of the first in the UK, offering a full range of breast reconstruction techniques in a multi-disciplinary approach. Our research interest in developing a blood test for early detection has meant we have a particular focus on early stage disease. Nevertheless one of my major clinical (and research) interests has been (and remains) advanced breast cancer – both locally advanced and metastatic disease, which I jointly run with my clinical oncology colleagues. As a surgical oncologist with both a major clinical and laboratory interest in endocrine and growth factor therapies I find myself in a central position – i.e. able to provide a link between surgical and non-surgical (clinical and medical) oncologists which ensures seamless continuity of care for patients and a rich base from which clinical and laboratory research can proceed. The Department's interest in systemic therapies has placed it

as one the vanguard of surgical units performing pre-surgical ('window of opportunity') studies which allows us to combine our skillsets in surgery and systemic therapies into a translational research programme investigating biological changes in breast cancers which matches our therapeutic clinical trials in advanced disease. I am currently one of the three Chief Investigators (CIs) on the POETIC trial which is the largest trial of peri-operative endocrine therapy in the world. I am also the CI of the STAKT trial, which is the first pre-surgical study under the AstraZeneca-NCRN concordat: this is a dose ranging study of an AKT inhibitor, AZD5363. I have been CI, or local Principal Investigator (PI), in a number of multicenter trials for new drugs produced by a variety of pharmaceutical companies including Astrazeneca, Novartis, Amgen, Schering, and Bayer.

ii) General Surgery

I trained and worked as a General Surgeon for almost 30 years. During my first 10 years as a Consultant Surgeon I was routinely looking after, and operating on, patients with gastro-intestinal (GI) problems, especially gastric and colorectal cancers, as well as breast cancer. With the introduction of site-specialisation following the Calman-Hine Report the treatment of GI tumours was taken over by site-specific teams. Following this my general surgical work decreased and after 18 years I came off the emergency general surgical rota. However my training and initial involvement in the treatment of GI cancers gave me experience of a wide spectrum of solid tumour types.

TEACHING

1. Departmental

i) Clinical

The University of Nottingham has a systems based undergraduate curriculum. I was involved in implementing the undergraduate curriculum at the City Hospital when it was re-designed some years ago. I was particularly involved in teaching the subjects of breast cancer and gastrointestinal malignancies. For three years I also had responsibility for the MCQs for the Final Year MCQ paper. I then took on responsibility

for a Special Study module based around 'Female Cancers' which I subsequently passed on to one of the Associate Professors in my Department.

I also have experience of organising Teaching Courses on Counselling and Communication Skills both for undergraduate medical students and postgraduate junior surgical staff. The students' assessment of these teaching courses was carried out by the external facilitator. These courses were subsequently incorporated by the post-graduate tutor at the City Hospital into a plan for similar courses for medical staff. I sat on the initial Steering Committee for this programme.

ii) Supervision of Research

I have supervised a number of under- and post-graduate medical trainees and non-clinical scientists over the years. For example over the last five years I have had seven physicians presenting themselves for post-graduate MD degrees, seven scientists presenting for PhDs one M. Phil and five MSc students.
They have been involved in translational research work in the areas of endocrine and growth factor therapies and serum tumour markers in breast cancer.

2. Other teaching commitment:

The Nottingham Breast Cancer Screening Unit is one of the four national screening teaching centres. I was one of the faculty of speakers for the Nottingham Breast Cancer Screening Training Programmes which include a multi-disciplinary course twice per year on breast screening as well as regular one day update seminars and workshops.

The British Association of Surgical Oncology (BASO) and the Royal College of Surgeons of England jointly host an advanced course on "The Management of Breast Disease". This was a week-long course for senior surgical trainees and consultants with a special interest in breast disease. I was one of the original teaching faculty on this course being responsible for the section in the course on advanced breast cancer. I have

been a teacher on the Breast Disease section of the local FRCS course and have also previously examined for the FRCS (Glasgow) examination.

I have organised two, and three, day Oncology Training Programmes focused primarily on breast cancer. These courses have run regularly two or three times a year, for 20 years (since 1993). I have delivered training on endocrine therapies to over 175 breast cancer oncologists who have travelled from over 40 countries to attend training courses since 2008 at the University of Nottingham. I have also been an invited speaker on endocrine therapy and growth factor therapies at over 50 international breast cancer meetings covering six continents since 2008. For five years (1994-99) I organised regular specialist Workshops on Serum Tumour Markers in Breast Cancer under the auspices of the European Group for Serum Tumour Markers in Breast Cancer. I have previously organized a symposium on the Design and Analysis of Clinical Trials, run jointly under the University Departments of Surgery and Epidemiology and Public Health.

MD Thesis

"New criteria for assessment of response in systemic breast cancer"

My post-graduate thesis examined the role of tumour markers in breast cancer and was awarded the degree of M.D by the University of Glasgow. This study identified a biochemical serum measurement of tumour mass and of response to endocrine therapy in systemic breast cancer which is objective, reproducible, gives an early result and can therefore be used in monitoring therapy and should replace the UICC criteria for comparing response rates.

The biochemical index established in my thesis has been confirmed both in our own centre and in a European multicentre study. This was the catalyst for the programme of research on autoantibodies in cancer which has resulted to the first blood test for early detection of lung cancer based on detection of autoantibodies to cancer antigens in a blood sample – the EarlyCDT-Lung test.

RESEARCH EXPERIENCE

Breast Cancer - Breast cancer has been my major research interest over 28 years. Throughout this period I have focused my research in two main areas:- endocrine and growth factor therapies and serum tumour markers.

Endocrine Therapy - my research in this field has focused on the following areas:

i) Clinical studies of endocrine therapy

Summary - I have experience in running clinical studies investigating all the major classes of endocrine therapy and more recently investigating growth factor therapies. I have been CI of national and international multi-centre trials of both endocrine and growth factor therapies. I have been a leading international investigator on fulvestrant (Faslodex): the only new endocrine therapy for breast cancer registered worldwide in last 10 yrs. I have participated in 13 clinical studies involving fulvestrant and was CI in nine of these (7/9 were multi-centre RCTs – 3 UK and 4 international), more than any other clinical academic worldwide.

Details - I have overseen a number of clinical studies on the role of endocrine therapy in patients with different stages of disease.

In primary breast cancer these have included the following randomized clinical trials (RCTs):-

a) Tamoxifen versus mastectomy in elderly patients with primary operable breast cancer (unselected for ER),

b) Tamoxifen versus Tamoxifen and mastectomy in patients with highly positive ER tumours,

c) Tamoxifen versus radical radiotherapy in patients with locally advanced breast cancer

d) Tamoxifen versus multiple modality treatment (neoadjuvant chemotherapy, mastectomy, radiotherapy and endocrine therapy) again in patients with locally advanced primary tumours.

e) POETIC - Trial of Perioperative Endocrine Therapy - Individualising Care – to assess if 4 weeks of an aromatase inhibitor can affect long term outcome. (one of 3 CIs: UK multi-centre RCT)

f) STAKT study – RCT looking at the biological effect of an AKT inhibitor on primary breast cancer.

In advanced breast cancer I have been the local PI on many international Phase 2 and/or 3 studies of all classes of endocrine agent. In a number of these RCTs my contribution to these studies overall has lead to me being first, second or senior author on the study publication.

I have also been CI on a number of multi-centre phase 2 and 3 studies of endocrine and growth factor therapies. Studies I have been CI on include:-

a) Onapristone study – Phase 2 study of a new progesterone receptor antagonist in hormone naïve post-menopausal women with advance breast cancer (CI: Single centre study)
b) Study 59 – dose and pharmacokinetic study of fulvestrant in post-menopausal patients with advanced breast cancer (CI: UK multi-centre RCT)
c) Study 003 – Phase 2 study of gefitinib (EFGR tyrosine kinase inhibitor) in patients with either (i) tamoxifen resistant ER positive tumours or (ii) ER negative tumours. (CI: UK single cente study)
d) FIRST study – Phase 2 RCT comparing fulvestrant 500mg versus anastrozole in hormone naïve patients with advanced breast cancer (CI: international multi-centre RCT)
e) FALCON study Phase 3 RCT comparing fulvestrant 500mg versus anastrozole in hormone naïve patients with advanced breast cancer (CI: international multi-centre RCT)
f) GAMG 362 study – RCT looking at and anti-IGFR monoclonal antibody therapy in endocrine resistant advanced breast cancer (CI: international multi-centre RCT)

I have been involved in clinical studies from prevention (e.g. IBIS 1 and 2) through to metastatic disease and have investigated all major types of endocrine agents (e.g. GnRH agonists (goserelin), SERMs (tamoxifen), aromatase inhibitors, pure ER antagonists, PR antagonists). I have also been CI of a number of investigator initiated phase II studies of endocrine therapies and new growth factor therapies (e.g. gefitinib, IGFR monoclonal antibody therapy). A number of these studies have been focused on serum and tumour biopsies as a means of understanding the effects of these drugs on endocrine resistance. I have also been local PI as part of a number of other multi-centre clinical trials of new agents such as mTOR and Pi3Kinase inhibitors.

ii) Factors predicting response of breast cancer to endocrine therapy

Summary - This has been one of the long-term areas of collaborative research between the Department of Surgery and Tenovus Institute, Cardiff. This programme has examined clinical and biological factors as predictors of de-novo response/resistance and also acquired resistance to endocrine therapy.

Details - These studies have included investigation of both clinical factors (e.g. patient age, site of disease) and tumour biology (e.g. ER, PgR, pS2, EGFR, TGFalpha, HER-2, IGFR1, AKT, MAPK, Ki 67) and the interactions between these factors and response to the Selective Estrogen Receptor Modulator (SERM), tamoxifen and the Selective Estrogen Receptor Down-regulator (SERD), fulvestrant. ER still appears the best single factor in that ER negativity is a powerful predictor of de-novo resistance. However thirty percent of ER positive tumours do not respond to initial endocrine therapy and we initially identified that these tend to show a combined phenotype of weak/moderate ER expression along with high expression of the proliferation antigen Ki67. Since then we have published extensively on other biological factors in the untreated primary tumour which predict for de-novo resistance. We have, however, been unable to identify biological markers in the primary tumour which predict for acquired resistance in each individual patient. This therefore led us into studies of sequential biopsies to look at changes in breast tumour biology which may be associated with acquired endocrine resistance. We are also one of the few groups who have investigated biological factors and response to second-line endocrine therapy.

iii) The effect of endocrine and growth factor therapies on the biology of invasive breast cancers

Summary - Sequential biopsies of breast tumours pre-treatment and during endocrine therapies have allowed us to study the effect of different endocrine and growth factor therapies on the biology of human breast cancers.

Details – It was in 1987 that I initiated one of the first studies in our unit looking at the effect of endocrine therapy (Tamoxifen) on breast tumours – an area which is now called 'translational research'. Following publication of the results of the study this area of our research was expanded and became a major part of

the joint Nottingham/Tenovus Breast Cancer Programme. The research has assessed the effects on sequential biopsies of human primary breast tumours of a number of agents, including tamoxifen, gamma linoleic acid, aromatase inhibitors, fulvestrant, gefitinib and the pure anti-progesterone, onapristone. These sequential biopsies have been analysed for markers of tumour differentiation, programmed cell death, proliferation, growth factors and their receptors (particularly tyrosine kinase mediated receptors), markers of endocrine resistance (e.g. AKT, ras) and also a number of oestrogen inducible genes and their respective proteins.

A separate series of sequential biopsy studies have been short term treatment (<3 weeks) in the pre-surgical setting. I have been CI in the following pre and peri-operative RCT studies:

a) Pre-surgical treatment comparing the biological effects of fulvestrant (25, 125 and 250mg) versus tamoxifen 20mg versus placebo in post-menopausal patients (CI: UK multi-centre RCT)
b) Pre-surgical treatment comparing the biological effects of fulvestrant 250mg versus placebo in pre-menopausal patients (CI: international multi-centre RCT)
c) Pre-surgical treatment comparing the biological effects of fulvestrant 500mg versus anastrozole versus fulvestrant 500mg + anastrozole. (CI: UK multi-centre RCT)
d) POETIC - Trial of Perioperative Endocrine Therapy - Individualising Care – to assess if four weeks of an aromat6ase inhibitor can affect long term outcome. (one of three CIs: UK multi-centre RCT)
e) STAKT trial – dose ranging study of a new AKT inhibitor (AZD5363) (CI: UK multi-centre RCT)

iv) Oestrogen receptor and endocrine therapy

Summary - Oestrogen receptor (ER) has been linked to both primary and acquired endocrine resistance. While ER undoubtedly plays a part in acquired resistance it appears to be not the sole or possibly even not the most important cause of acquired resistance.

Details - ER is currently the most generally used predictor of response to endocrine therapy. In the early 1990s it was proposed that that loss of ER was a major mechanism of acquired endocrine resistance. I proposed a contrary view that ER is a stable phenotype in breast cancer which was published in the British

Journal of Cancer in 1996 (REF 91). This is based on (i) review of the literature, (ii) unpublished data from our own laboratories showing ER in breast tumours at the time of acquired resistance and (iii) a clinical study which we had just published in which tumours post-tamoxifen responded to the specific anti-oestrogen ICI 182,780 implying ER was still functional. Today most experts believe that while a minority of tumours (probably <10%) do seem to lose ER expression the majority of acquired resistance is caused through other mechanisms such as 'cross-talk'. We have ongoing studies investigating alternative mechanisms for acquired resistance-e.g. type 1 or insulin-like growth factor pathways, AKT pathway. Pre-surgical studies have provided opportunities to look at short term effects of these drugs on different cellular pathways.

v) Progesterone receptor antagonists in breast cancer

Summary - This is a new class of compound which we have shown is an effective endocrine agent. The biological effects are different from current anti-oestrogen agents.

Details - I was the PI of a phase II study of Onapristone (Type 1 PgR antagonist) in patients with locally advanced breast cancer. This study showed Onapristone was an effective endocrine therapy. During treatment we also obtained sequential biopsies of these human tumours. The development of Onapristone was discontinued due to transient liver function test (LFT) abnormalities I identified. Subsequently (ie ten years later), a second generation progesterone receptor antagonist was available. A Phase 2 study of lonaprisan (type 3 PgR antoagonist) has recently published lack of efficacy of this endocrine agent. Future research looks to be focused on alternative anti-progesterone antagonsits (e.g. non-steroidal agents) or better selection for Onapristone such that the therapeutic benefits outweigh the potential risks of transient LFT abnormalities.

vi) Specific calmodulin antagonists with no anti-oestrogenic action

Summary - We developed a programme to investigate whether such compounds (i) inhibit tumours resistant de-novo to anti-oestrogen (tamoxifen) therapy and/or (ii) are additive or synergistic with established endocrine agents in hormone sensitive tumours.

Details - I carried out a pilot study in our laboratories in collaboration with Nottingham Trent University on the effect of specific calmodulin antagonists in breast cancer cell lines. There appears to have been no systematic attempt to develop non-oestrogenic calmodulin inhibitors as anti-proliferative agents. Endocrine agents such as tamoxifen and idoxifene possess both anti-oestrogenic properties and inhibit calmodulin. A series of calmodulin inhibitors related to W-7 with no anti-oestrogenic activity was developed which in pilot experiments were shown to be potent anti-proliferative agents. Unfortunately funding to further develop this programme was not secured and it was therefore discontinued. However calmodulin antagonists have recently become a focus for new drug development.

Serum tumour markers

i) Laboratory research on established markers

Summary - I established a biochemical index combining three serum tumour markers for use in measuring response in patients with metastatic breast cancer.

Details - My interest in serum tumour markers started with my MD thesis which investigated the role of serum markers in the assessment of therapeutic response to endocrine therapy in patients with advanced breast cancer. In patients with metastases the pre-treatment level of serum markers was of no value in predicting subsequent therapeutic response. However, changes in concentration of serum markers did provide an early measure of subsequent therapeutic response to endocrine therapy. Subsequent studies have shown that changes in these serum markers also measure therapeutic response to chemotherapy.

We then set up a multi-centre European study involving 11 centres in six EU countries for which I was the PI. This confirmed, in a European multicentre setting, the use of the biochemical index in measuring therapeutic response, which in fact in many patients identified response and progression before imaging tests (e.g. CT, ultrasound). The pilot study was in preparation for a randomised clinical trial comparing serum tumour markers versus standard response assessment criteria (UICC) but we were unable to secure funding for the randomized controlled trial.

We also set up a clinical study assessing the use of blood tumour markers in the disease-free interval follow-up of patients treated for primary breast cancer. This study was set up to assess the lead-time provided by tumour markers in diagnosis of recurrence and also to estimate the cost-effectiveness of this form of follow-up. The study was set up so that it would, in due course, lead to a multi-centre study to test the concept of early therapeutic intervention based on sequential blood marker measurements.

ii) New markers in advanced disease

Summary - We have investigated a number of new blood tumour markers for metastatic disease.

Detail - We instigated a laboratory project looking for new serum markers of tumour proliferation (e.g. thymidine kinase, tissue polypeptide specific antigen), apoptosis and oestrogen regulated markers (e.g. c-erbB-2) which might provide additional information to current markers which reflect tumour bulk. None appeared to add anything to the established markers. An interesting result of this work was the unexpected finding that serum HER2 expression is prognostic of patient outcome (i.e. survival) at all stages of breast cancer. This may be related to the well established fact that tissue expression of HER2 is also of prognostic significance.

iii) Development of "near patient" assays

We completed a collaborative study to assess whether the current commercially available assays could be compressed thereby making it possible to produce serum marker results for patients during their outpatient visit. Unfortunately this was not possible with the assays tested.

iv) Other research in breast cancer

I have substantial experience in investigating prognostic factors in locally and systemically advanced breast cancer as well as the area of primary disease for which the Nottingham Breast Unit is widely known for the 'Nottingham Prognostic Index' (NPI).

I initiated studies to define optimal treatment for elderly patients with breast cancer - work which has been taken up and developed by an Associate Professor in my department.

Surgical oncology

Summary - In other cancers (e.g. gastrointestinal) I concentrated my research on endocrine therapy and tumour markers, thereby linking it to my main research interests in breast cancer.

Details - I have had other oncology research interests - principally the gastro-intestinal tract. I have had both laboratory and clinical projects on hormone receptors and on the role of hormones and growth factors in gastrointestinal cancer. A post-graduate scientist completed a research programme under my direction assessing the value of sex steroid hormones in GI tumours. I have also previously been involved in research on the role of GI peptide hormones in gastrointestinal tumours. I have also carried out studies assessing the role of serum tumour markers (e.g. CA19-9, thymidine kinase) in gastrointestinal malignancies.

Screening

Summary - I was exposed to 3 screening programmes (for breast, colorectal and gastric cancers) during my surgical training. Subsequently I have been involved in breast screening for 26 years. More recently I have been involved in the developing programmes for lung cancer screening, the latter in relation to our blood test for early detection (see below).

Nottingham is a National Breast Screening Training Centre. We had an ongoing research programme focused on the radiology, pathology and treatment of screen detected cancers compared with symptomatic breast cancers. These studies were carried out in collaboration between the different disciplines.

CURRENT RESEARCH

The focus of my current research is on endocrine and growth factor therapies in breast cancer and serum tumour markers.

Endocrine Therapy in Breast Cancer

i. Clinical and Translational research

Summary - We plan to extend our research programme looking at a) tumour biology as a predictor of outcome on subsequent endocrine therapy, b) the effect of different endocrine and growth factor therapies on tumour biology.

Details - We have constructed a large database of over 500 patients treated with endocrine therapy on whom we have samples (tumour tissue and/or serum) and clinical data. This forms the basis for our studies to investigate the interactions between markers of oestrogen mediated pathways (ER, PgR, pS2) and growth factors (such as EGFR, HER2, HER3 TGFalpha, TGFbeta, IGFR1, MAPK, AKT, etc). Previous studies including our own have had too few patients to investigate subpopulations particularly ones such as ER positive, primary endocrine resistant tumours where, despite the presence of ER, other non-oestrogenic factors appear to control cell proliferation.

I also have a collection of sequential tumour biopsy and serum samples from patients on different types of endocrine and growth factor therapies. These involve breast tumours which were biopsied pre-treatment, while it was in response and which have then subsequently developed acquired resistance. It takes a long time and painstaking clinical research to accrue sufficient numbers of these particular specimens. However such biopsies have the potential to provide important insights into the mechanisms of acquired endocrine resistance and how this may be circumvented. These studies form a significant part of the continuing joint Nottingham/Derby/Tenovus Research Programme.

In the last five years I have been PI on early Phase 2 studies of four new drugs and PI of two international and two UK multicentre studies. I am currently one of the two CIs on a new Phase 3 RCT in first line metastatic disease comparing fulvestrant 500mg versus anastrozole. I am also CI of a multi-centre RCT assessing different doses of an AKT inhibitor in a pre-surgical study.

ii. Laboratory studies

Summary – I currently have an ongoing laboratory research programme with the Tenovus Institute in Cardiff investigating factors involved in acquired endocrine resistance.

Details - A significant part of my research in this area continues to be carried out in collaboration with the Tenovus Institute, Cardiff. In these studies we are interested in the expression of oestrogen regulated genes, and intracellular signaling pathways in-vitro cell culture and in-vivo models. The in-vitro and in-vivo effects inform our research on human tumour biopsy samples, especially where tissue is valuable such as in the sequential core biopsy studies. We have previously reported on the importance of type 1 growth factor pathway markers (e.g. EGFR, HER2, HER3, MAPK, etc) and insulin-like growth factor pathway markers (e.g. IGFR1, IR, etc). One of our current research interests is looking at the PI3Kinase and AKT pathway in relation to hormone resistance.

SERUM MARKERS

Serum Markers in Breast Cancer

i) Clinical

We established a multicentre study on the use of blood markers in monitoring disease recurrence after primary surgery. This study has collected blood samples for between 5-10 years while the clinical follow-up data was collected as part of the ATAC trial. The collection of samples is now completed and we plan to measure both antigen-based tumour associated markers and more novel markers such as auto antibodies to assess whether of not any rise in the markers measured will correlate with those patients who subsequently show overt metastatic disease. It is envisaged that the results from this study will lead to a subsequent randomised study of early therapeutic intervention based on rising markers versus standard follow-up which we have called the SATS study (Secondary Adjuvant Therapy Study).

ii) Laboratory studies

In 1996 I established a small laboratory programme to identify new serum tumour markers for screening and early detection of primary breast cancer. The project was focused on the use of molecular technologies to try and amplify signals/markers of early carcinogenesis. Initially we investigated both ex-vivo amplification (using PCR techniques) and in-vivo amplification signal (by measuring autoantibodies to cancer associated antigens). In the first instance the auto-antibodies detected in the peripheral blood of patients with primary disease were to markers such as MUC1 mucin, p53, c-erbB2 and c-myc. The assays for these markers, along with a number of new markers were developed in our laboratories. We also developed a focus on lung cancer through an EU grant.

The autoantibody technology we developed was placed in a University of Nottingham spinout company, Oncimmune (see below) for commercialization while the academic department continued its research in lung cancer, breast cancer and more recently hepatocellular and colon cancer. As a result of this work the University has created the Centre of Excellence for Autoimmunity in Cancer (CEAC) of which I am the Director (http://www.nottingham.ac.uk/ceac).

CEAC

There is an urgent need for new, more effective and more patient-acceptable screening tests for most types of cancer. We believe our research team is one of a very few, if not the only one, in the world currently able to deliver blood based screening tests based on autoantibody technology for all types of solid cancers. This programme is very ambitious in its goal, but justifiable, given The University of Nottingham's experience in delivering the world first autoantibody blood test for lung cancer, EarlyCDT-Lung. Establishing a programme to assess the value of a wide range of Tumour-Associated Antigens (TAAs) and how each relates to a different type of tumours will be crucial in the development of tests for each type of cancer. We now have Medical Research Council (MRC) funding to support research projects looking at autoantibodies to tumour antigens as early detection tests for colon, pancreatic and hepatocellular cancers. We have also started a project to develop an early breast cancer detection test.

In addition to developing new tests we established a number of international collaborations to investigate, for example, i) how early pre-diagnosis of cancer the autoantibody signal can be detected, ii) are there autoantibodies to cancer stem cells, iii) the value of the autoantibody signal in relation to differentiating benign and malignant lung nodules, iv) understanding the biology of early carcinogenesis. These collaborations include centres in North America (e.g. British Columbia Cancer Centre in Vancouver, Vanderbilt University, Mayo Clinic, National Jewish Hospital in Colorado, University of Pittsburg, Georgetown University in Washington, Mount Sinai Hospital in New York) and Europe (e.g. Munich, Trondheim, Malmo, Milan, Navarra). We also gained approval to access two lung cancer screening study sample banks (PLCO and NLST – both NIH funded RCTs).

SPINOUT COMPANIES

I have started three spinout companies from my research work:-

i) Oncimmune

Oncimmune is a spinout company from the University of Nottingham which has developed the autoantibody technology and IP which came out of my academic laboratories. The company has raised over £30M and developed the first commercially available autoantibody test for the early detection of lung cancer (EarlyCDT-Lung). With the support of the University of Nottingham I have been responsible for the scientific and technical developmental work of Oncimmune.

In addition to EarlyCDT-Lung being commercially available the company has committed to two prospective tests – one in the USA and the other in UK - which will specifically assess the health economic benefit of EarlyCDT-Lung.

EarlyCDT is a platform technology which is applicable to all solid tumours. The company is now focused on developing tests for other solid cancers (eg hepatocellular cancer) (www.oncimmune.com).

ii) FaHRAS

FaHRAS developed software to help physicians assess breast cancer risk (using different breast cancer risk models) and links with the UK NICE guidelines. The software has been extensively tested is now used in secondary and tertiary NHS units in the UK and Ireland, Australia and the Caribbean. A version for primary care has been developed and launched. FaHRAS is also now developing lung and colon cancer risk models.

iii) Specimen collection company

I was one of four individuals who established a specimen collection company which could collect samples from patients with most types of tumours and also appropriate controls. I resigned from the company soon after starting it because of potential conflicts of interest with a second of the spinout companies. This company continues to develop 10 years after I helped start it.

BREAST CANCER ON-LINE

I was the founding Editor-in-Chief of the web journal, Breast Cancer On-Line (BCO). This website (www.bco.org) was the first dedicated solely for professionals working in the field of breast cancer. The membership reached over 25,000.

GUIDELINES

i) BASO GUIDELINES FOR MANAGEMENT OF BONE METASTASES IN BREAST CANCER

I was a member of a working party which has produced the first edition of the BASO Guidelines for Management of Bone Metastases in Breast Cancer. These guidelines follow the highly respected work by BASO in producing guidelines both for surgeons in breast cancer screening and for symptomatic breast disease.

ii) GUIDELINES FOR SCREEN-DETECTED AND SYMPTOMATIC BREAST CANCER

I was an invited, expert reviewer for the latest National Breast Guidelines which were issued in 2009.

TRAVELLING FELLOWSHIPS

Moynihan Travelling Fellowship from Association of Surgeons of Great Britain and Ireland, 1993

Wellington Foundation. 1993

Dr Robert Malcolm Trust, l993

Royal College of Physicians and Surgeons of Glasgow, 1993

I had the opportunity in 1993 as the Moynihan Travelling Fellow to visit six of the large comprehensive cancer centres in the USA (Boston, Washington, Duke University at Durham, San Francisco, San Antonio and New York). At each centre I focused my visit on the breast cancer programme. This further widened my clinical experience as well as my personal contacts with clinical, and basic, scientists in the USA. These initial contacts have developed over the past twenty years and have resulted in a variety of valuable collaborations.

MEMBERSHIP OF LEARNED SOCIETIES

Society of Academic and Research Surgery

British Association of Surgical Oncology

Association of Breast Surgery

British Association of Cancer Research

British Breast Group

Association of Surgeons of Great Britain and Ireland

American Society of Clinical Oncology

MEMBERSHIP OF COMMITTEES (Past and Current)

University

Member of Faculty Board

Member of Admissions Committee (Faculty of Medicine and Health Sciences)

University representative on Post-graduate Education Centre Council

Masters Steering Committee

Medicine and Surgery Working Party for the undergraduate curriculum

Health Authority

Mid Trent Higher Surgical Training Committee

Nottingham City Hospital

Trustee of the Medical Research Centre

Member of Breast Services Directorate

Medical Records Committee
Counselling and Communication Skills Steering Group

Hospital Medical Committee

Nottingham Cancer Centre

Education and Training Committee (Chairman)

Scientific

British Association of Surgical Oncology (BASO)
(National Committee)

BASO Education and Training Committee (member)

UKCCCR Tumour Marker Sub-Committee (member)

European Study Group for Blood Tumour Markers in Breast Cancer
(Chairman of Administrative Board)

Nottingham International Breast Cancer Meeting

(Scientific and Organising Committee)

Breast Cancer On-line
Editor-in-Chief

BASO Working Party for Guidelines on Management of Bone Metastases in Breast Cancer (member)

European Healthcare Innovation Leadership Network - Breast Cancer Working Group 2009 (member)

STEERING COMMITTEES, DATA and SAFETY MONITORING COMMITTEES

Steering Committees

FH01
FH02
Neo-excel
EPHOS
POETIC
FALCON
STAKT

DSMC

SOFEA
TNT
PRIMETIME

INTERESTS AND OTHER ACTIVITIES

B.SC. IN PARASITOLOGY

During 1976-77 I took time out of my medical course to complete an intercalated B.Sc. in Parasitology at the University of Glasgow. This was carried out under the Zoology Department and included lectures, seminars and laboratory work in Protozoology, Parasitology and Medical Entomology. During this period I also successfully completed a degree course in Biophysics.

CAMBRIDGE DIPLOMA IN RELIGIOUS STUDIES

During 1981-82, following my year as a house officer in general surgery and medicine, I took one year out of my post-graduate medical education. During this year I was in full-time study funded by myself. This

was a two-year course which I completed in one year. At the end of that year I successfully presented myself for the Cambridge Diploma in Religious Studies. One of six papers was a medical ethics thesis.

CLUBS AND SOCIETIES

i) Arderne Surgical Society (Secretary) - Nottingham Surgical Society

ii) Nottingham University Club

PUBLICATIONS - Papers in refereed journals

1985

1) Local anaesthesia of the great toe
Robertson JFR, Muckart DJJ. J Royal Coll. Surg Edinburgh 1985; 30: 237-8

1986

2) Intravenous nutrition and hepatic dysfunction
Robertson JFR, Garden OJ, Shenkin A. J Parent Enter Nutr. 1986; 10: 17 -6

3) Simultaneous intussusception and volvulus due to a congenital band
Roberson JFR, Howatson A. Scot Med J. 1986; 31: 245-6

4) Local excision of ampullary carcinoma
Robertson JFR, Imrie CW. Acta Chir Scand. 1986; 152: 537-9

1987

5) Facial paralysis due to acute parotitis
Robertson JFR, Azmy AF. Kinderchirurgie. 1987; 42: 312

6) Circumcaval ureter: treatment of an asymptomatic child
Robertson JFR, Azmy AF. Akt Urol. 1987; 18: 1555 – 1565

7) Surgery in necrotising enterocolitis
Robertson JFR, Azmy AF, Young DG. Br J Surg. 1987; 74: 387-9

8) Intradiaphragmatic abscess
Ballantyne KC, Robertson JFR. Br JHM. 1987; 38: 369

9) Acute pancreatitis associated with carcinoma of the ampulla of Vater
Robertson JFR, Imrie CW. Br J Surg. 1987; 74: 395-7

10) Management of periampullary carcinoma
Robertson JFR, Imrie CW, Hole DJ, Carter DC, Blumgart H. Br J Surg. 1987; 74: 816-9

1988

11) The effect of LHRH agonist, Zoladex, on ovarian histology
Williamson K, Robertson JFR, Ellis IO, Nicholson RI, Elston CW, Blamey RW. Br J Surg. 1988; 75: 595-6

12) Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer
Robertson JFR, Todd JH, Ellis IO, Elston CW, Blamey RW. BMJ. 1988; 297: 511–4

13) Immunocytochemical localisation of oestrogen receptors in human breast tissue
Walker KJ, Bouzubar N, Robertson JFR, Ellis IO, Elston CW, Blamey RW, Wilson DW, Griffiths K, Nicholson RI. Cancer Res. 1988; 48: 6517-22

14) Cholelithiasis in children - a follow-up study
Robertson JFR, Carachi R, Sweet EM, Raine PAM. J Paed Surg. 1988; 23: 246-9

15) Assent to ascent of the testis
Robertson JFR, Azmy AF, Cochrane W. Br J Urol. 1988; 61: 146-7

16) Bladder calculus: a complication of the Gel Vernet technique of ureteric re-implantation
Robertson JFR, Azmy AF. Br J Urol. 1988; 61: 95

17) Choledochal cysts in children and adults - a 30 year review of Glasgow Teaching Hospitals
Robertson JFR, Raine PAM. Br J Surg. 1988; 75: 799-801

18) Appropriate technology spring retractor
Richardson JB, Robertson JFR. Tropical Doctor. 1988,;18: 143 – 144

19) Patients with ampullary carcinoma are prone to other malignant tumours
Robertson JFR, Boyle P, Imrie CW. Br J Cancer. 1988; 58: 216-8

1989

20) Scrotal carcinoma following prolonged use of crude coal tar ointment
McGarry G, Robertson JFR. Br J Urol. 1989; 63: 211

21) Factors predicting the response of patients with advanced breast cancer to endocrine (Megace) therapy
Robertson JFR, Williams MR, Todd JH, Nicholson RI, Morgan DAL, Blamey RW. Eur J Cancer Clin Oncol. 1989; 25: 469-75

22) Endocrine effects of combination antioestrogen and LH-RH agonist therapy in premenopausal advanced breast cancer patients
Walker KJ, Turkes A, Robertson JFR, Blamey RW, Griffiths K, Nicholson RI. Eur J Cancer Clin Oncol. 1989; 25: 651-4

23) Combined endocrine effects of LHRH agonist (Zoladex) and Tamoxifen (Nolvadex) in pre-menopausal women with breast cancer
Robertson JFR, Walker K, Nicholson RI, Blamey RW. Br J Surg. 1989; 76: 1262-5

24) Mitoxantrone - a useful palliative therapy in advanced breast cancer
Robertson JFR, Williams MR, Todd JH, Blamey RW. Am J Clin Oncol. 1989; 12: 393-6

25) Granulomatous lobular mastitis
Galea M, Robertson JFR, Ellis IO, Elston CW, Blamey RW. ANZ J Surg. 1989; 59: 547-50

26) Ki 67 immunostaining in primary breast cancer: pathological and clinical associations
Bouzubar N, Walker K, Nicholson RI, Ellis IO, Elston CW, Robertson JFR, Blamey RW. Br J Cancer. 1989; 59: 943-7

27) Carcinoembryonic antigen immunocytochemistry of primary breast cancer
Robertson JFR, Ellis IO, Bell J, Todd JH, Robins A, Elston CW, Blamey RW. Cancer. 1989; 64: 1638-45

28) An observation of DNA ploidy, histological grade, and immunoreactivity for tumour-related antigens in primary and metastatic breast carcinoma
Hitchcock A, Ellis IO, Robertson JFR, Gilmour A, Elston CW, Blamey RW. J Pathol. 1989; 159: 129-34

1990

29) Goserelin (Zoladex) in premenopausal advanced breast cancer : duration of response and survival
Dixon AR, Robertson JFR, Jackson L, Nicholson RI, Walker KJ, Blamey RW.
Br J Cancer. 1990; 62: 868-70

30) Automated quantitation of immunocytochemically localised estrogen receptor in human breast cancer
McLelland RA, Finlay P, Walker KJ, Nicholson D, Robertson JFR, Blamey RW, Nicholson R.I.
Cancer Res. 1990; 50: 3545-50

31) Zoladex plus Nolvadex versus Zoladex alone in pre- and peri-menopausal metastatic breast cancer
Nicholson RI, Walker KJ, McClelland R, Dixon AR, Robertson JFR, Blamey RW. J.Steroid Biochem Molec Biol. 1990; 37: 989-95

32) Detection of polymorphic epithelial mucins in the serum of systemic breast cancer patients using a monoclonal antibody NCRC-11
Price MR, Clarke AJ, Robertson JFR, O'Sullivan C, Baldwin RW, Blamey RW. Cancer Immunol Immunother. 1990; 31: 269 – 72

33) Serum thymidine kinase in breast cancer
Robertson JFR, O'Neill K, Thomas MW, McKenna PG, Blamey RW. Br J Cancer. 1990; 62: 663-7

34) Assessment of four monoclonal antibodies as serum markers in breast cancer
Robertson JFR, Pearson D, Price MR, Selby C, Badley RA, Pearson J, Blamey RW, Howell A. Eur J Cancer. 1990; 26: 1127-32

35) Weekly low dosage Epirubicin in advanced breast cancer
Dixon AR, Robertson JFR, Athanassiou E, Jackson L, Blamey RW. Eur J Cancer 1990; 26: 847-8

1991

36) Combined goserelin and tamoxifen in premenopausal advanced breast cancer: duration of response and survival
Dixon AR, Jackson L, Robertson JFR, Nicholson RI, Blamey RW. Eur J Cancer. 1991; 27: 806-7

37) Hormone sensitivity in breast cancer: influence of heterogeneity of oestrogen receptor expression and cell proliferation
Nicholson RI, Bouzubar N, Walker KJ, McClelland R, Dixon AR, Robertson JFR, Ellis IO, Blamey RW. Eur J Cancer. 1991; 27: 908-13

38) Cellular effects of Tamoxifen in primary breast cancer
Robertson JFR, Ellis IO, Nicholson RI, Robins A, Bell J, Blamey RW. Br Cancer Res Treat. 1991; 20: 117-23

39) Prospective assessment of the role of five serum markers in breast cancer
Robertson JFR, Pearson D, Price MR, Selby C, Pearson J, Blamey RW, Howell A. Cancer Immunol Immunother. 1991; 33: 403-10

40) Objective measurement of therapeutic response in breast cancer using serum markers
Robertson JFR, Pearson D, Price MR, Selby C, Blamey RW, Howell A. Br J Cancer. 1991; 64: 757-63

41) C-erb B2 oncoprotein expression in primary and advanced breast cancer
Lovekin C, Ellis IO, Locker AP, Robertson JFR, Elston CW, Blamey RW. Br J Cancer. 1991; 63: 439-43

42) An evaluation of differences in prognosis and recurrence patterns between invasive lobular and ductal carcinoma
du Toit RS, Locker AP, Robertson JFR, Ellis IO, Elston CW, Nicholson RI, Blamey RW. Eur J Surg Oncol. 1991; 17: 251-7

43) Occult regional lymph node metastases from breast carcinoma: immunohistological detection with antibodies CAM 5.2 and NCRC-11
Galea M, Athanassiou E, Bell J, Dilks B, Robertson JFR, Elston CW, Blamey RW, Ellis IO. J Pathol. 1991; 165: 221-7

44) Failure of CA 19-9 to detect asymptomatic colorectal carcinoma
Thomas MW, Robertson JFR, Price MR, Hardcastle JD. Br J Cancer. 1991; 63: 975-6

45) The prognostic value of the monoclonal antibody (D5) detected protein, p29, in primary colorectal carcinoma
Robertson JFR, Morris DL, Ellis IO, Armitage NC, Hardcastle JD. Br J Cancer. 1991; 64: 379-80

1992

46) Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5 year follow-up
Robertson JFR, Ellis IO, Elston CW, Blamey RW. Eur J Cancer. 1992; 28: 908-10

47) Comparison of two oestrogen receptor assays in the prediction of the clinical course of patients with advanced breast cancer
Robertson JFR, Bates K, Pearson D, Blamey, RW, Nicholson RI. Br J Cancer. 1992; 65: 727-30

48) Tumour oestrogen receptor content allows selection of elderly patients with breast cancer for conservative tamoxifen treatment
Low SC, Dixon AR, Bell J, Ellis IO, Elston CW, Robertson JFR, Blamey RW. Br J Surg. 1992; 79: 1314-6

49) Systemic treatment of early breast cancer by hormonal, cytotoxic and immune therapy
Early Breast Cancer Trialists' Collaborative Group. (Trialist) Lancet. 1992; 339: 1-15

50) Systemic treatment of early breast cancer by hormonal, cytotoxic and immune therapy
Early Breast Cancer Trialists' Collaborative Group (Trialist) Lancet. 1992; i: 71-85

51) Silver-stained nucleolar organiser region counts are of no prognostic value in primary breast cancer
Sacks N, Robertson JFR, Ellis IO, Nicholson RI, Crocker J, Blamey RW. Eur J Surg Oncol. 1992; 18: 98-102

52) Confirmation of a prognostic index for metastatic breast cancer
Robertson JFR, Nicholson RI, Dixon AR, Ellis IO, Elston CW, Blamey RW. Br Cancer Res Treat. l992; 22: 221-7

53) Therapeutic effect of the Gastrin Receptor Antagonist, CR2093, on gastrointestinal tumour cell growth
Watson SA, Crosbee DM, Morris DL, Robertson JFR, Makovec F, Rovati LC, Hardcastle JD. Br J Cancer. 1992; 65: 879-83

54) Inhibition of gastrin stimulated growth of gastrointestinal tumour cells by Octreotide and the Gastrin/Cholecystokinin receptor antagonists, Proglumide and Lorglumide
Watson SA, Morris DL, Durrant LG, Robertson JFR, Hardcastle JD. Eur J Cancer. 1992; 28A: 1462-7

1993

55) DNA ploidy of the primary tumour as a predictor of endocrine sensitivity in breast cancer
Robertson JFR, Galea MH, Gilmour A, Robins A, Nicholson RI, Blamey RW. Internat J Oncol. l993; 2: 111-3

56) Relationship between EGF-R, c-erb-B2 protein expression and Ki67 immunostaining in breast cancer and hormone sensitivity
Nicholson RI, McCelland RM, Finlay P, Eaton CL, Gullick W, Dixon AR, Robertson JFR,
Ellis IO, Blamey RW. Eur J Cancer. 1993; 29A: 1018-23

57) Immunocytochemically localised epidermal growth factor receptor and oestrogen receptor in breast cancer: relationship to endocrine sensitivity
McLelland RA, Finlay P, Dixon AR, Robertson JFR, Ellis IO, Blamey RW, Nicholson RI. Oncology (Life Sciences Adv). 1993; 12: 143-55

58) Expression of tumour-associated antigens in breast cancer primary tissue compared with serum levels
Cannon PM, Ellis IO, Blamey RW, Bell J, Elston CW, Robertson JFR. Eur J Surg Oncol. l993; 19: 523-7

59) Interactions between Oestradiol and Danazol on the growth of Gastrointestinal tumour cells
Watson SA, Crosbee DM, Dilks KL, Robertson JFR, Hardcastle JD. Anticancer Res. 1993; 13: 97-102

60) Effect of histamine on the growth of human gastrointestinal tumours: reversal with Cimetidine
Watson SA, Wilkinson LJ, Robertson JFR, Hardcastle JD.
Gut. 1993; 34: 1091-6

61) Timing of antibiotic administration in knee replacement under tourniquet
Richardson JB, Roberts A, John PJ, Robertson JFR, Sweeney G.
BJBS. 1993; 75B: 32-5

1994

62) Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer
DeFriend DJ, Howell A, Nicholson RI, Anderson E, Dowsett M, Mansel RE, Blamey RW, Bundred NJ, Robertson JFR, Saunders C, Baum M, Walton P, Sutcliffe F, Wakeling AE. Cancer Res. 1994; 54: 408-14

63) Transforming growth factor and endocrine sensitivity in breast cancer
Nicholson RI, McClelland RA, Gee JMW, Manning DL, Cannon P, Robertson JFR, Ellis IO, Blamey RW. Cancer Res. 1994; 54: 1684-9

64) Epidermal growth factor receptor expression in breast cancer: Association with response to endocrine therapy
Nicholson RI, McClelland RA, Gee JMW, Manning D, Cannon P, Robertson JFR, Ellis IO, Blamey RW. Br Cancer Res Treat. 1994; 29: 117-25

65) Oestrogen regulated genes in breast cancer: Association of pLIV1 with lymph node involvement
Manning DL, Robertson JFR, Ellis IO, Elston CW, McClelland RA, Gee JMW, Jones RJ, Green CD, Cannon P, Blamey RW, Nicholson RI. Eur J Cancer. l994; 30A, 675-8

66) Immunocytochemical localisation of BCL-2 protein in human breast cancers and its relationship to a series of prognostic markers and response to endocrine therapy
Gee JMW, Robertson JFR, Hoyle HB, Kyme SR, McClelland RA, Ellis IO, Willshire P, Blamey RW, Nicholson RI. Int J Cancer. 1994; 59: 619-28

67) Biological factors of prognostic significance in stage III breast cancer
Robertson JFR, Ellis IO, Pearson D, Elston CW, Nicholson RI, Blamey RW. Br Cancer Res Treat. 1994; 29: 259-64

68) Pathological-radiological correlations in benign lesions excised during a breast screening programme
Spencer N, Evans AJ, Galea M, Sibbering DM, Yeoman LJ, Pinder S, Ellis IO, Elston CW, Blamey RW, Robertson JFR, Wilson ARM. Clin Radiol. 1994; 49: 853-6

69) Pleural effusion in breast cancer: A review of the Nottingham experience
Banerjee AK, Willetts I, Robertson JFR, Blamey RW. Eur J Surg Oncol. 1994; 20: 33-6

1995

70) Differential expression of oestrogen regulated genes in breast cancer
Manning D.L., McClelland R.A., Knowlden J. M., Bryant S., Gee J. M. W., Green C. D., Robertson JFR, Blamey RW, Sutherland RI, Ormandy J, Nicholson RI. Acta Oncol. 1995; 34: 641-6

71) Response to a specific antioestrogen (ICI 182,780) in tamoxifen-resistant breast cancer
Howell A, DeFriend D, Robertson JFR, Blamey RW, Walton P. Lancet. 1995; 345: 29-30.

72) A new immunohistochemical antibody for the assessment of oestrogen receptor status on routine formalin fixed tissue samples
Goulding H, Pinder S, Cannon P, Pearson D, Nicholson RI, Snead D, Bell J, Elston CW, Robertson JFR, Blamey RW, Ellis IO. Hum Pathol. 1995; 26: 291-4

73) Prognostic value of immunocytochemistry of the primary tumour in patients with metastatic breast cancer
Robertson JFR, Cannon P, Ellis IO, Bell J, Nicholson RI, Elston CW, Blamey RW. The Breast. 1995; 4: 277-81.

74) Expression of ras-p21, p53 and c-erbB-2 in advanced breast cancer and response to first line hormonal therapy
Archer S, Eliopoulos A, Spandidos D, Barnes D, Ellis IO, Blamey RW, Nicholson RI, Robertson JFR. Br J Cancer. 1995; 72: 1259-66

75) Immunocytochemical localization of FOS protein in human breast cancers and its relationship to a series of prognostic markers and response to endocrine therapy
Gee JMW, Ellis IO, Robertson JFR, Willsher P, McClelland RA, Hewitt KN, Blamey RW Nicholson RI. Int J Cancer. 1995; 64: 269-73

76) Potential for cost economies in guiding therapy in patients with metastatic breast cancer
Robertson JFR, Whynes DK, Dixon A, Blamey RW. Br J Cancer. 1995; 72: 174-7

77) Pretreatment serum levels of tumour markers in metastatic breast cancer: a prospective assessment of their role in predicting response to therapy and survival
Albuquerque K, Price MR, Badley RA, Jonrup I, Pearson D, Blamey RW, Robertson JFR. Eur J Surg Oncol. 1995; 21: 504-9

78) Serum tissue polypeptide specific antigen (TPS) in breast cancer patients: comparison with CA 15.3 and CEA
Willsher P, Beaver J, Blamey RW, Robertson JFR. Anticancer Res. 1995; 15: 1609-11

79) Analysis of the temporal compressibility of breast tumour marker assays: Development of a "near patient" assay
Murray A, Robertson JFR, Price MR. Int J Biol Markers. 1995; 10: 200-5

80) Metallothionein expression in human breast cancer
Goulding H, Jasani B, Pereira H, Reid A, Galea M, Bell JA, Elston CW, Robertson JFR, Blamey RW, Nicholson RA. Br J Cancer. 1995; 72: 968-72

81) The assessment of multiple variables on breast carcinoma fine needle aspiration cytology specimens: method, preliminary results and prognostic associations
Pinder S, Wencyk PM, Naylor H, Bell JA, Elston CW, Robertson JFR, Blamey RW, Ellis IO. Cytopathology. 1995; 6: 316-24

82) Assessment of angiogenesis in breast carcinoma: an important factor in prognosis?
Goulding H, Nik Abdul Rashid NF, Robertson JFR, Bell JA, Elston CW, Blamey RW, Ellis IO. Human Pathol. 1995; 26: 1176-1200

83) Pathological prognostic factors in primary breast cancer. IV should you be a typer or a grader? A comparative study of two histological prognostic features in operable breast cancer
Pereira H, Pinder SE, Galea MH, Sibbering DM, Elston CW, Blamey RW, Robertson JFR, Ellis IO. Histopathology. 1995; 27: 21-6

84) Assessment of the new proliferation marker MIB1 in breast carcinoma using imager analysis: associations with other prognostic factors and survival
Pinder SE, Wencyk P, Sibbering DM, Bell JA, Elston CW, Nicholson RI, Robertson JFR, Blamey RW, Ellis IO. Br J Cancer. 995; 7: 146-9

85) Safe selection criteria for breast conservation without radical excision in primary operable invasive breast cancer
Sibbering DM, Galea MH, Morgan DAL, Elston CW, Ellis IO, Robertson JFR, Blamey RW. Eur J Cancer. 1995; 3: 2191-5

86) Mammographic sensitivity in women under 50 presenting symptomatically with breast cancer
Sibbering DM, Burrell HC, Robertson JFR, Blamey RW, Yeoman LJ, Wilson ARM, Evans AJ. The Breast. 1995; 4: 127-9

87) Effects of radiotherapy and surgery in early breast cancer
Early Breast Cancer Trialists' Collaborative Group (Trialist). NEJM. 1995; 333: 1444-55

88) Anti-gastrin antibodies raised by gastrimmune inhibit the growth of the human colorectal tumour, AP5
Watson SA, Michaeli D, Grimes S, Morris TM, Crosbee D, Wilkinson M, Robinson G, Robertson JFR, Steel RJC, Hardcastle JD. Int J Cancer. 1995; 61: 233-40

89) The effects of gastro-intestinal hormones and synthetic analogues on the growth of pancreatic cancer
Robertson JFR, Watson SA, Hardcastle JD. Int J Cancer. 1995; 63: 69-75

90) Serum thymidine kinase in colorectal neoplasia
Thomas MW, Robertson JFR, McKenna PG, O'Neill K, Robinson M, Hardcastle JD. Eur J Surg Oncol. 1995; 21: 632-4

1996

91) Oestrogen receptor - A stable phenotype in breast cancer
Robertson JFR. Br J Cancer. 1996; 73: 5-12.

92) Locally advanced breast cancer: Long term results of a randomised trial comparing primary treatment with tamoxifen or radiotherapy in post-menopausal women
Willsher P, Robertson JFR, Armitage NC, Morgan DAL, Nicholson RI, Blamey RW. Eur J Surg Oncol. 1996; 22: 34-7

93) Oestrogen and progesterone receptors as prognostic variables in hormonally treated breast cancer
Robertson JFR, Cannon P, Nicholson RI, Blamey RW. Intern J Biol Markers. 1996; 1: 29-33

94) Pharmacokinetics, pharmacological and antitumour effects of the specific antioestrogen ICI 182,780 in women with advanced breast cancer
Howell A, DeFriend DJ, Robertson JFR, Blamey RW, Anderson L, Anderson E, Sutcliffe FA, Walton P. Br J Cancer. 1996; 74: 300-8

95) Effects of short-term anti-estrogen treatment of primary breast cancer on estrogen receptor mRNA and protein expression on estrogen regulated genes
McClelland RA, Manning DL, Gee JMW, Anderson E, Howell A, Dowsett M, Robertson JFR, Blamey RW, Wakeling AE, Nicholson RI. Br Cancer Res Treat. 1996; 4: 31-41

96) Short term effects of the pure antioestrogen ICI 182,780 treatment on oestrogen receptor, epidermal growth factor receptor and transforming growth factor-alpha protein expression in human breast cancer
McClelland RA, Gee JMW, Francis AB, Robertson JFR, Blamey RW, Wakeling AE, Nicholson RI. Eur J Cancer. 1996; 32A: 413-6

97) Prospective confirmation of a biochemical index for measuring therapeutic efficacy in metastatic breast cancer in a multicentre study
Robertson JFR. The Breast. 1996; 5: 372-3

98) The significance of P53 auto antibodies in the serum of patients with breast cancer
Willsher PC, Pinder SE, Robertson L, Nicholson RI, Ellis IO, Bell JA, Blamey RW, Green JA, Robertson JFR. Anticancer Res. 1996;16: 927-30

99) Prognostic significance of serum c-erbB2 protein in breast cancer patients
Willsher P, Beaver J, Pinder S, Bell JA, Ellis IO, Blamey RW, Robertson JFR. Br Cancer Res Treat. 1996; 40: 251-5

100) Cyclin D1 and estrogen receptor messenger RNA levels are positively correlated in primary breast cancer
Hui R, Cornish AL, McClelland RA, Robertson JFR, Blamey RW, Musgrove EA, Nicholson RI, Sutherland RL. Clin Cancer Res. 1996; 2: 923-8

101) Biological factors and response to radiotherapy in locally advanced breast cancer
Willsher PC, Kapucvoglu N, Ellis IO, Blamey RW, Robertson JFR. Oncology Report. 1996; 3: 545-7

102) C-erbB3 in human breast carcinoma - expression and relation to prognosis and established prognostic indicators
Travis A, Pinder SE, Robertson JFR, Bell JA, Wencyk P, Gullick WK, Nicholson RI, Poller DN, Blamey RW, Elston CW, Ellis IO. Br J Cancer. 1996; 74: 229-33

103) Screening interval cancers: mammographic features and prognostic factors
Burrell HC, Sibbering DM, Wilson ARM, Pinder SE, Evans AJ, Yeoman LJ, Elston CW, Ellis IO, Blamey RW, Robertson JFR. Radiology. 1996; 199: 811-7

104) Do the mamographic features of locally recurrent breast cancer mimic those of the original tumour?
Burrell HC, Sibbering DM, Evans AJ, on behalf of the Nottingham Breast Team. The Breast. 1996; 5: 233-6

105) Diagnosis of breast cancer with core-biopsy and fine needle aspiration cytology
Poole GH, Willsher PC, Pinder SE, Robertson JFR, Elston CW, Blamey RW. ANZJ Surg. 1996; 66: 592-4

106) Oestrogen and progesterone receptors in gastrointestinal cancer cell lines
Jacobs E, Watson SA, Hardcastle JD, Robertson JFR. Eur J Cancer. 1996; 32: 2348-53

107) The inhibitory effect of the anti-progestogen, megestrol acetate, on the growth of gastrointestinal tumour cells
Watson SA, Wilkinson L, Hardcastle JD, Robertson JFR. GI Cancer. 1996; 2: 55-65

1997

108) Locally advanced breast cancer: early results of a randomised trial of multimodal therapy versus initial hormone therapy
Willsher P, Robertson JFR, Chan S, Jackson L, Blamey RW.
Eur J Cancer. 1997; 33: 45-9

109) Duration of remission to ICI 182,780 compared to megestrol acetate in tamxoifen resistant breast cancer
Robertson JFR, Howell A, DeFriend D, Blamey RW, Walton P. The Breast. 1997; 6: 186-9

110) Predictors of response to second-line endocrine therapy for breast cancer
Cheung KL, Willsher P, Pinder SE, Ellis IO, Elston CW, Nicholson RI, Blamey RW, Robertson JFR.
Br Cancer Res Treat. 1997; 45: 219-24

111) The clinical relevance of static disease (no change) category for 6 months on endocrine therapy in patients with breast cancer
Robertson JFR, Willsher PC, Cheung KL, Blamey RW. Eur J Cancer. 1997; 33: 1774-9

112) Induction of apoptosis by Tamoxifen and ICI 182,780 in primary breast cancer
Ellis PA, Saccani-Jotti G, Clarke R, Johnston SRD, Anderson E, Howell A, A'hern R, Salter J, Detre J, Nicholson R, Robertson JFR, Smith IE, Dowsett M. Int J Cancer. 1997; 72: 608-13

113) Investigation of primary tamoxifen therapy for elderly patients with operable breast cancer
Willsher PC, Robertson JFR, Jackson LJ, Al-Hilaly M, Blamey RW. The Breast. 1997; 6: 150-4

114) Co-expression and cross-regulation of the prolactin receptor and sex steroid hormone receptors in breast cancer
Ormandy CJ, Hall RE, Manning DL, Robertson JFR, Blamey RW, Kelly PA, Nicholson RI, Sutherland RL. J Clin Endocrinol Metab. 1997; 82: 3692-9

115) Use of reverse transcription polymerase chain reaction methodology to detect estrogen regulated genes primarily in small breast cancer specimens
Knowlden JM, Gee JMW, Bryant S, McClelland RA, Manning D, Mansell R, Ellis IO, Blamey RW, Robertson JFR, Nicholson RI. Clin Cancer Research. 1997; 3: 2165-72

116) erbB signalling in clinical breast cancer: relationship to endocrine sensitivity
Nicholson RI, Gee JMW, Jones H, Harper ME, Wakeling AE, Willsher PC, Robertson JFR.
Endocr relat Cancer. 1997; 4: 1-9

117) A randomised comparison of oestrogen suppression with anastrozole and formestane in postmenopausal patients with advanced breast cancer
Kleeberg UR, Dowsett M, Carrion RP, Dodwell DJ, Vorobiof DA, Aparicio LA, Robertson JFR.
Oncology. 1997; 54 (s2): 19-22

118) Evaluation of the immulite BR-MA and CEA assays and comparison with immunoradiometric assays for CA15-3 and CEA in breast cancer
Murray A, Willsher P, Price MR, Blamey RW, Sibley P, Robertson JFR. Anticancer Res. 1997; 17: 1945-50

119) Use of reverse transcription-polymerase chain reaction methodology to detect estrogen- regulated gene expression in small breast cancer specimens
Knowlden JM, Gee JM, Bryant S, McClelland RA, Manning DL, Mansel R, Ellis IO, Blamey RW, Robertson JFR, Nicholson RI. Clin Cancer Res. 1997; 3: 2165-72

120) A comparison of outcome of male breast cancer with female breast cancer
Willsher PC, Leach I, Ellis IO, Bourke JB, Blamey RW, Robertson JFR. Am J Surg. 1997; 173: 185-8

121) Automated grading of breast carcinoma
Pinder SE, Wencyk P, Sibbering DM, Elston CW, Bell J, Nicholson RI, Robertson JFR, Blamey RW, Ellis IO. Br J Cancer. 1997.

122) Early-onset breast cancer - histological and prognostic considerations
Kollias J, Elston CW, Ellis IO, Robertson JFR, Blamey RW. Br J Cancer. 1997; 75: 1318-23

123) Male breast cancer: pathological and immunohistochemical features
Willsher P, Leach IH, Ellis IO, Bell JA Elston CW, Bourke JB, Blamey RW, Robertson JFR.
Anticancer Res. 1997; 17: 2335-8

124) Subcutaneous mastectomy for primary breast cancer and ductal carcinoma in situ
Cheung KL, Blamey RW, Robertson JFR, Elston CW, Ellis IO. Eur J Surg Oncol. 1997; 23: 343-7

125) Intratumoural heterogeneity of proliferation in invasive breast carcinoma evaluated with MIB1 antibody
Connor AJM, Pinder SE, Elston CW, Bell J, Wencyk P, Robertson JFR, Blamey RW, Nicholson RI, Ellis, IO. The Breast. 1997; 6: 171-6

126) A comparison outcome of male breast cancer with female breast cancer
Willsher PC, Leach IH, Ellis IO, Bourke JB, Blamey RW, Robertson JFR. Am J Surg. 1997; 173: 185-8

127) Diagnosis and prognosis of primary breast cancer
Robertson JFR, Evans AJ. Q J Nucl Med. 1997; 41: 200-10

128) Mammographic and pathological features of breast cancer detected at first incident round screening
Wheatley DC, Yeoman LJ, Burrell H, Pinder SE, Evans AJ, Wilson ARM, Ellis IO, Elston CW, Robertson JFR, Blamey RW. The Breast .1997; 6: 259-265

129) Omental transposition flap for locally recurrent breast cancer
Cheung KL, Willsher P, Robertson JFR, Blamey RW. ANZ J Surg. 1997; 67: 185-6

130) Subcutaneous mastectomy for primary breast cancer and ductal carcinoma in-situ
Cheung KL, Blamey RW, Robertson JFR, Elston CW, Ellis IO. Eur J Surg Oncol. 1997; 23: 343-7

131) A one year audit of 255 operable breast cancers
McCarthy D, Mitchell AK, Robertson JFR, Blamey RW. Eur J Surg Oncol. 1997; 23: 399-402

132) Audit of conservative management policy of the axilla in elderly patients with operable breast cancer
Al-Hilaly M, Willsher PC, Robertson JFR, Blamey RW. Eur J Surg Oncol. 1997; 23: 339-40

133) The effect of onapristone, a progesterone antagonist, on the growth of human gastrointestinal cancerxenografts
Jacobs E, Watson SA, Ellis IO, Hardcastle JD, Robertson JFR. Eur J Cancer. 1997; 33: 1130-5

1998

134) Tamoxifen for early breast cancer: an overview of the randomised trials
Early Breast Cancer Trialists' Collaborative Group. The Lancet. 1998; 35: 1451-67

135) c-erbB3 and c-erbB4 expression is a feature of the endocrine responsive phenotype in clinical breast cancer
Knowlden JM, Gee JMW, Seery LT, Farow L, Gullick WL, Ellis IO, Blamey RW, Robertson JFR, Nicholson RI. Oncogene. 1998; 17: 1949-57

136) Oestrogen-regulated genes in breast cancer: Association of pLIV1 with response to endocrine therapy
McClelland RA, Manning DL, Gee JMW, Willshire P, Robertson JFR, Ellis IO, Blamey RW, Nicholson RI. Br J Cancer. 1998; 77: 1653-6.

137) The primary use of endocrine therapies
Howell A, Anderson E, Blamey RW, Clarke RB, Dixon JM, Dowsett M, Johnston SR, Miller WR, Nicholson RI, Robertson JFR. Rec Res Cancer Res. 1998; 152: 227-44

138) Endocrine response and resistance in breast cancer: a role for the transcription factor FOS
Gee JMW, Willshire PC, Kenny FS, Robertson JFR, Pinder SE, Ellis IO, Nicholson RI.
Int J Cancer. 1999; 84: 54-61

139) C-erbB2 expression predicts response to preoperative chemotherapy for locally advanced breast cancer
Willsher PC, Pinder SE, Gee JM, Ellis IO, Chan SY, Nicholson RI, Blamey RW, Robertson JFR.
Anticancer Res. 1998; 18: 3695-8

140) EMS1 gene expression in primary breast cancer: relationship to cyclin D1 and oestrogen receptor expression and patient survival
Hui R, Ball JR, Macmillan RD, Kenny FS, Prall OWJ, Campbell DH, Cornish AL, McClelland RA, Daly RJ, Forbes JF, Blamey RW, Musgrove EA, Robertson JFR, Nicholson RI, Sutherland RL.
Oncogene. 1998; 17: 1053-9

141) C-erbB2 expression predicts response to preoperative chemotherapy in locally advanced breast cancer
Willsher PC, Pinder S, Gee JMW, Ellis IO, Chan SY, Nicholson RI, Blamey RW, Robertson JFR.
Anticancer Res. 1998; 18: 3695-8

142) Long-term follow-up of elderly patients randomised to primary tamoxifen or wedge mastectomy as initial therapy for operable breast cancer
Kenny FS, Robertson JFR, Ellis IO, Elston CW, Blamey RW. The Breast. 1998; 7: 335-9

143) Prognostic factors at the time of diagnosis of metastatic breast cancer
Robertson JFR, Blamey RW. Br J Cancer. 1998; 78: 1397

144) Polychemotherapy for early breast cancer: an overview of the randomised trials
Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998; 352: 930-42

145) The growth rate of human gastrointestinal cancer cell lines as xenografts relates to the sex of the tumour bearing mice
Jacobs E, Watson SA, Hardcastle JD, Robertson JFR.
GI Cancer. 1998; 2: 321-7

1999

146) p21 (WAF1) expression and endocrine response in breast cancer
McClelland RA, Gee JMW, O'Sullivan L, Barnes DM, Robertson JFR, Ellis IO, Nicholson RI. J Pathol. 1999; 188: 126-32.

147) Onapristone, a progesterone receptor antagonist, as first-line therapy in primary breast cancer
Robertson JFR, Willsher PC, Winterbottom L, Blamey RW. Eur J Cancer. 1999; 35: 214-8

148) Anti-gonadotrophin releasing hormone antibodies inhibit the growth of MCF7 human breast cancer xenografts
Jacobs E, Watson SA, Michaeli D, Ellis IO, Robertson JFR. Br J Cancer. 1999; 80: 352-9

149) Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor positive breast cancer
Kenny FS, Hui R, Musgrove EA, Gee JMW, Blamey RW, Nicholson RI, Sutherland RL, Robertson JFR. Clin Cancer Res. 1999; 5: 2069-76

150) A randomised open parallel group trial to compare the endocrine effects of oral anatrozole (Arimidex) with intramuscular formestane in postmenopausal women with advanced breast cancer
Vorobiof DA, Kleeberg UR, Perez-Carrion R, Dodwell DJ, Robertson JFR, Calvo L, Dowsett M, Clack G. Ann Oncol. 1999; 10: 1-7

151) Immunohistomchemical analysis reveals a tumour suppressor-like role for the transcription factor AP-2 in breast cancer
Gee JMW, Robertson JFR, Ellis IO, Nicholson RI, Hurst HC. J Pathol. 1999; 189: 514-20

152) Involvement of steroid hormone and growth factor cross-talk in endocrine response in breast cancer
Nicholson RI, McClelland RA, Robertson JFR, Gee JMW. Endocr Relat Cancer. 1999; 6: 1-16

153) Static disease on anastrozole provides similar benefit as objective response in patients with advanced breast cancer
Robertson JFR, Howell A, Buzder A, von Euler M, Lee D. Br Cancer Res Treat. 1999; 58: 157-62

154) The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers
European Group for Serum Tumour Markers in Breast Cancer. Eur J Cancer. 1999; 35: 47-53

155) An immunohistochemical examination of the expression of E-cadherin, alpha- and beta/gamma-catenins, and alpha2- and beta1-integrins in invasive breast cancer
Gonzalez MA, Pinder SE, Wencyk PM, Bell JA, Elston CW, Nicholson RI, Robertson JFR, Blamey RW, Ellis IO. J Pathol. 1999; 187: 523-9

156) c-erbB-2 expression in primary breast cancer
Tagliabue E, Menard S, Robertson JFR, Harris L. Int J Biol Markers. 1999; 14: 16-26

157) c-erbB2 in serum of patients with breast cancer
Harris L, Luftner D, Jaeger W, Robertson JFR. Int J Biol Markers. 1999; 14: 8-15

158) The prognosis of small primary breast cancers
Kollias J, Murphy CA, Elston CW, Ellis IO, Robertson JFR, Blamey RW. Eur J Cancer. 1999; 35: 908-12

159) BRCA1 expression levels predict distant metastasis of sporadic breast cancers
Seery LT, Knowlden JM, Gee JMW, Robertson JFR, Kenny FS, Ellis IO, Nicholson RI. Int J Cancer. 1999; 84: 258-62

160) An immunohistochemical examination of the expression of E-Cadherin, α and β/γ Catenins, $\alpha 2$ and $\beta 1$ integrins in invasive breast cancer
Gonzales MA, Pinder SE, Wencyk PM, Bell JA, Elston CW, Nicholson RI, Robertson JFR, Blamey RW, Ellis IO. J Pathol. 1999; 187: 523-9

2000

161) New calmodulin antagonists inhibit in-vitro growth of human breast cancer cell lines independent of their estrogen receptor status
Jacobs E, Bulpitt PCA, Coutts IGC, Robertson JFR. Anticancer Drugs. 2000; 11: 63-8

162) A divergent role for the oestrogen receptor alpha and beta sub-types in clinical breast cancer
Knowlden JM, Gee JMW, Robertson JFR, Ellis IO, Nicholson RI. Int J Cancer. 2000; 89:209-12

163) Gamma linolenic acid with tamoxifen as primary therapy in breast cancer
Kenny FS, Pinder S, Ellis IO, Gee JMW, Nicholson RI, Bryce RP, Robertson JFR. Int J Cancer. 2000; 85: 643-8

164) INK4a gene expression and methylation in primary breast cancer: overexpression of p16 INK4a messenger RNA is a marker of poor prognosis
Hui R, Macmillan RD, Kenny FS, Musgrove EA, Blamey RW, Nicholson RI, Robertson JFR, Sutherland RL. Clin Can Res. 2000; 6: 2777-87

165) Preoperative endocrine therapy for breast cancer
Cheung KL, Howell A, Robertson JFR. Endocr Relat Cancer. 2000; 7: 131-41

166) Anastrozole versus tamoxifen as first line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or Arimidex randomised group efficacy and tolerability study
Bonneterre J, Thurlimann B, Robertson JFR, Krzakowski M, Mauriac L, Koralewski P, Vergote I, Webster A, Steinberg M, von Euler M. J Clin Oncol. 2000; 18: 3748-57

167) Can biological markers improve the management of breast cancer patients?
Biomarkers Ad Hoc Group of the UKCCCR Brit J Cancer. 2000; 82: 1625-6

168) The role of blood tumor marker measurement (using a biochemical index score and c-erbb2) in directing chemotherapy in metastatic breast cancer
Cheung KL, Pinder SE, Paish C, Sadozye AH, Chan SY, Evans AJ, Blamey RW, Robertson JFR.
Int J Biol Markers. 2000; 15: 203

169) Objective measurement of remission and progression in metastatic breast cancer by the use of serum tumour markers. Cheung KL, Robertson JFR. Estrarro da Minerva Chirurgica. 2000; 58; 3: 297-303

170) Tumour marker measurements in the diagnosis and monitoring of breast cancer
Cheung KL, Graves CR, Robertson JFR. Cancer Treat Rev. 2000; 26: 91-102

171) Biological and clinical associations of c-jun activation in human breast cancer
Gee JM, Barroso AF, Ellis IO, Robertson JFR, Nicholson RI. Int J Cancer. 2000; 89: 177-86

172) Up-regulation of the protein tyrosine phosphatase SHP-1 in human breast cancer and correlation with GRB2 expression
Yip SS, Crew AJ, Gee JM, Hui R, Blamey RW, Robertson JFR, Nicholson RI, Sutherland RL, Daly RJ. Int J Cancer. 2000; 88: 363-8

173) Magnetic resonance imaging versus radionuclide scintigraphy for screening in bone metastases
Evans AJ, Robertson JFR. Clin Radiol 2000, 55: 653

174) The missing mammographic abnormality
Wilson AR, Evans AJ, Robertson JFR. Br J Surg. 2000; 87: 374-5

175) The effect of Evening Primrose Oil on clinically diagnosed fibroadenomas
Kollias J, Macmillan RD, Sibbering M, Burrell H, Robertson JFR. The Breast. 2000; 9: 35-6

2001

176) Preoperative hormone therapy trials for breast cancer
Cheung KL, Robertson JFR. The Breast. 2001; 10: 1-5

177) Selection of primary breast cancer patients for adjuvant endocrine therapy – is oestrogen receptor alone adequate?
Cheung KL, Nicholson RI, Blamey RW, Robertson JFR. Br Cancer Res Treat. 2001; 65: 155-62

178) Change in expression of ER, bcl-2 and MIB1 on primary tamoxifen and relation to response in ER positive breast cancer
Kenny FS, Willsher PC, Gee JMW, Nicholson RI, Pinder SE, Ellis IO, Robertson JFR. Br Cancer Res Treat. 2001; 65: 135-44

179) Phosphorylation of ERK1/2 mitogen-activated protein kinase is associated with poor response to anti-hormonal therapy and decreased patient survival in clinical breast cancer
Gee JMW, Robertson JFR, Ellis IO, Nicholson RI. Int J Cancer. 2001; 95: 247-54

180) Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Bonneterre J, Buzdar A, Nabholtz JM, Robertson JFR, Thurlimann B, von Euler M, Sahmoud T, Webster A, Steinberg M, Arimidex Writing Committee, Investigators Committee Members
Cancer. 2001; 92: 2247-58

181) Faslodex (ICI 182, 780), a novel estrogen receptor downregulator--future possibilities in breast cancer. Robertson JFR. J Steroid Biochem Mol Biol. 2001; 79: 209-12

182) Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer
Robertson JFR, Nicholson RI, Bundred NJ, Anderson E, Rayter Z, Dowsett M, Fox JN, Gee JM, Webster A, Wakeling AE, Morris C, Dixon M. Cancer Res. 2001; 61: 6739-46

183) Locally advanced primary breast cancer: medium-term results of a randomised trial of multimodal therapy versus initial hormone therapy
Tan SM, Cheung KL, Willsher PC, Blamey RW, Chan SY, Robertson JFR. Eur J Cancer. 2001; 37: 2331-8

184) The use of blood tumour markers in the monitoring of metastatic breast cancer unassessable for response to systemic therapy
Cheung KL, Evans AJ, Robertson JFR. Breast Cancer Res Treat. 2001; 67: 273-8

185) CA27.29: a valuable marker for breast cancer management. A confirmatory multicentric study on 603 cases
Gion M, Mione R, Leon AE, Luftner D, Molina R, Possinger K, Robertson JFR. Eur J Cancer. 2001; 37: 355-63

186) Effect of dietary GLA +/- tamoxifen on the growth, ER expression and fatty acid profile of ER positive human breast cancer xenografts
Kenny FS, Gee JMW, Nicholson RI, Ellis IO, Morris TM, Watson SA, Bryce RP, Robertson JFR. Int J Cancer. 2001; 92: 342-7

187) E-cadherin as a prognostic indicator in primary breast cancer
Parker C, Rampaul RS, Pinder SE, Bell JA, Wencyk PM, Blamey RW, Nicholson RI, Robertson JFR. Br J Cancer. 2001; 85: 1958-63

188) Imaging of metastatic breast cancer: distribution and radiological assessment of involved sites at presentation
Whitlock JPL, Evans AJ, Jackson L, Chan SY, Robertson JFR. Clin Oncol (R Coll Radiol). 2001; 13:181-6

189) Extent of ductal carcinoma in situ within and surrounding invasive primary breast carcinoma
Crombie N, Rampaul RS, Pinder SE, Elston CW, Robertson JFR, Ellis IO. Br J Surg. 2001; 88: 1324-9

2002

190) Fulvestrant, an estrogen receptor downregulator, reduces cell turnover index more effectively than tamoxifen.
Bundred NJ, Anderson E, Nicholson RI, Dowsett M, Dixon M, Robertson JFR. Anticancer Res. 2002; 22: 2317-9

191) An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane
Buzdar AU, Robertson JFR, Eiermann W, Nabholtz JM. Cancer. 2002; 95: 2006-16

192) Fulvestrant
Cheung KL, Robertson JFR. Expert Opin Investig Drugs. 2002; 11: 303-8

193) Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment
Howell A, Robertson JFR, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, Vergote I, Erikstein B, Webster A, Morris C. J Clin Oncol. 2002; 20: 3396-403

194) Current role of endocrine therapy in the management of breast cancer
Robertson JFR. Breast Cancer. 2002; 9: 276-81

195) Estrogen receptor downregulators: new antihormonal therapy for advanced breast cancer
Robertson JFR. Clin Ther. 2002; 24: A17-A30

196) HER-2 in breast cancer--methods of detection, clinical significance and future prospects for treatment
Rampaul RS, Pinder SE, Gullick WJ, Robertson JFR, Ellis IO. Crit Rev Oncol Hematol. 2002; 43: 231-44

197) Neuroendocrine differentiation and prognosis in breast adenocarcinoma
Miremadi A, Pinder SE, Lee AH, Bell JA, Paish EC, Wencyk P, Elston CW, Nicholson RI, Blamey RW, Robertson JFR, Ellis IO. Histopathology. 2002; 40: 215-22

198) The Internet: the future source of information for professionals in the field of breast cancer
Robertson JFR. Breast. 2002; 11: 398-401

2003

199) A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases
Howell A, Robertson JFR, Vergote I. Breast Cancer Res Treat. 2003; 82: 215-22

200) Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results
Nabholtz JM, Bonneterre J, Buzdar A, Robertson JFR, Thurlimann B. Eur J Cancer. 2003; 39: 1684-9

201) Equivalent single-dose pharmacokinetics of two different dosing methods of prolonged-release fulvestrant ('Faslodex') in postmenopausal women with advanced breast cancer
Robertson JFR, Harrison MP. Cancer Chemother Pharmacol. 2003; 52: 346-8

202) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials
Robertson JFR, Osborne CK, Howell A, Jones SE, Mauriac L, Ellis M, Kleeberg UR, Come SE, Vergote I, Gertler S, Buzdar A, Webster A, Morris C. Cancer. 2003; 98: 229-38

203) Pharmacokinetics of a single dose of fulvestrant prolonged-release intramuscular injection in postmenopausal women awaiting surgery for primary breast cancer
Robertson JFR, Odling-Smee W, Holcombe C, Kohlhardt SR, Harrison MP. Clin Ther. 2003; 25: 1440-52

204) The use of gonadotrophin-releasing hormone (GnRH) agonists in early and advanced breast cancer in pre- and perimenopausal women
Robertson JFR, Blamey RW. Eur J Cancer. 2003; 39: 861-9

205) Efficacy of tamoxifen following anastrozole('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women
Thurlimann B, Robertson JFR, Nabholtz, JM, Buzdar A, Bonneterre J, Arimidex Study Group. Eur J Cancer. 2003; 39: 2310-7

206) Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy
Vergote I, Robertson JFR, Kleeberg U, Burton G, Osborne CK, Mauriac L, Trial 0020 Investigators, Trial 0021 Investigators. Breast Cancer Res Treat. 2003; 79: 207-11

207) Expression of p27kip1 in breast cancer and its prognostic significance
Barnes A, Pinder SE, Bell JA, Paish EC, Wencyk PM, Robertson JFR, Elston CW, Ellis IO. J Pathol. 2003; 201: 451-9

208) Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features
James JJ, Evans AJ, Pinder SE, Gutteridge E, Cheung KL, Chan S, Robertson JFR. Br J Cancer. 2003; 89:660-5

209) Prognostic factors for patients with hepatic metastases from breast cancer
Wyld L, Gutteridge E, Pinder SE, James JJ, Chan SY, Cheung KL, Robertson JFR, Evans AJ. Br J Cancer. 2003; 89: 284-90

210) Spindle cell carcinoma of the breast: a case series of a rare histological subtype
Khan HN, Wyld L, Dunne B, Lee AH, Pinder SE, Evans AJ, Robertson JFR. Eur J Surg Ocol. 2003; 29: 600-3

2004

211) Preoperative hormone therapy trials for breast cancer
Cheung KL, Robertson JFR. Breast. 2004; 10: 1-5

212) Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer
Forward DP, Cheung KL, Jackson L, Robertson JFR. Br J Cancer. 2004; 90: 590-4

213) Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial
Howell A, Robertson JFR, Abram P, Lichinitser MR, Elledge R, Bajetta E, Watanabe T, Morris C, Webster A, Dimery I, Osborne CK. J Clin Oncol. 2004; 22:1605-13

214) Selective oestrogen receptor modulators/new antioestrogens: a clinical perspective
Robertson JFR. Cancer Treat Rev. 2004; 30:695-706

215) Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer
Robertson JFR, Erikstein B, Osborne KC, Pippen J, Come SE, Parker LM, Gertler S, Harrison MP, Clarke DA. Clin Pharmacokinet. 2004; 43:529-38

216) Fulvestrant: pharmacokinetics and pharmacology
Robertson JFR, Harrison M. Br J Cancer. 2004; 90:S7-S10

217) Expression and co-expression of the members of the epidermal growth factor receptor (EGFR) family in invasive breast carcinoma
Abd El-Rehim DM, Pinder SE, Paish CE, Bell JA, Rampaul RS, Blamey RW, Robertson JFR, Nicholson RI, Ellis IO. Br J Cancer. 2004; 91:1532-42

218) Expression of luminal and basal cytokeratins in human breast carcinoma
Abd El-Rehim DM, Pinder SE, Paish CE, Bell J, Blamey RW, Robertson JFR, Nicholson RI, Ellis IO. J Pathol. 2004; 203:661-71

219) Identification of carcinoma cells in peripheral blood samples of patients with advanced breast carcinoma using RT-PCR amplification of CK7 and MUC1
Felton T, Harris GC, Pinder SE, Snead DR, Carter GI, Bell JA, Haines A, Kollias J, Robertson JFR, Elston CW, Ellis IO. Breast. 2004; 13:35-41.

220) Analysis of the level of mRNA expression of the membrane regulators of complement, CD59, CD55 and CD46, in breast cancer
Rushmere NK, Knowlden JM, Gee JM, Harper ME, Robertson JFR, Morgan BP, Nicholson RI. Int J Cancer. 2004; 108:930-6

221) The role of PTEN and its signalling pathways, including AKT, in breast cancer; an assessment of relationships with other prognostic factors and with outcome
Panigrahi AR, Pinder SE, Chan SY, Paish EC, Robertson JFR, Ellis IO. J Pathol. 2004; 204:93-100

222) Expression of E2F-4 in invasive breast carcinomas is associated with poor prognosis
Rakha EA, Pinder SE, Paish EC, Robertson JFR, Ellis IO. J Pathol. 2004; 203:754-61

223) Epidermal growth factor receptor status in operable invasive breast cancer: is it of any prognostic value?
Rampaul RS, Pinder SE, Wencyk PM, Nicholson RI, Blamey RW, Robertson JFR, Ellis IO. Clin Cancer Res. 2004; 10:2578

224) Brain metastases from breast cancer: identification of a high-risk group
Evans AJ, James JJ, Cornford EJ, Chan SY, Burrell HC, Pinder SE, Gutteridge E, Robertson JFR, Hornbuckle J, Cheung KL. Clin Oncol (R Coll Radiol). 2004; 16: 345-9

225) Metastatic carcinoma of the breast with tubular features: differences compared with metastatic ductal carcinoma of no specific type
Hamilton LJ, Evans AJ, Pinder SE, James JJ, Gutteridge E, Cornford EJ, Burrell HC, Chan SY, Robertson JFR, Cheung KL. Clin Oncol (R Coll Radiol). 2004; 16:119-24

226) Patterns of metastatic breast carcinoma: influence of tumour histological grade
Porter GJ, Evans AJ, Pinder SE, James JJ, Cornford EC, Burrell HC, Chan SY, Cheung KL, Robertson JFR. Clin Radiol. 2004; 59:1094-8

2005

227) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma
Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, Come SE, Osborne CK, Robertson JFR. Cancer. 2005; 104: 236-39

228) Endocrine treatment options for advanced breast cancer - the role of fulvestrant
Robertson JFR, Come SE, Jones SE, Beex L, Kaufmann M, Makris A, Nortier JWR, Possinger K, Rutqvist L-E. Eur J Cancer. 2005; 41: 346-56

229) Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant
Robertson JFR, Howell A, Gorbunova VA, Watanabe T, Pienkowski T, Lichinitser MR. Breast Cancer Res Treat. 2005; 2:169-74

230) High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses
Abd El-Rehim DM, Ball G, Pinder SE, Rakha EA, Paish C, Robertson JFR, Macmillan D, Blamey RW, Ellis IO. Int J Cancer. 2005; 116:340-50

231) Malignancy induced auto-immunity to MUC1: initial antibody characterisation
Graves, C. R. L., Robertson, J. F. R., Murray, A., Price, M. R., Chapman, C. J. J Peptide Res. 2005;66 (6):357-63.

232) Clinical value of epidermal growth factor receptor expression in primary breast cancer.
Rampaul RS, Pinder SE, Nicholson RI, Robertson JFR, Ellis IO. Advan Anat Pathol. 2005; 12(5) 271-273.

233) Expression of mucins (MUC1, MUC2, MUC3, MUC4, MUC5AC and MUC6) and their prognostic significance in human breast cancer
Rakha EA, Boyce RW, Abd El-Rehim DM, Kurien T, Green AR, Paish EC, Robertson JFR, Ellis IO. Mod Pathol. 2005; 18 (10):1295-1304

234) Selective use of post-mastectomy flap irradiation in high-risk breast cancer patients.
Asgeirsson KS, Holroyd B, Morgan DA, Robertson JFR, Blamey RW, Pinder SE, Macmillan RD. Breast. 2005; 14(4): 298-303.

235) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.
Early Breast Cancer Trialists' Collaborative Group. Lancet. 2005; 365(9472):1687-1717.

2006

236) Endocrine response after prior treatment with fulvestrant in postmenopausal women with advanced breast cancer: experience from a single centre. Cheung KL, Owers R, Robertson JFR. Endocr Relat Cancer. 2006;13 (1):251-5.

237) Nuclear targeting of a midregion PTHrP fragment is necessary for stimulating growth in breast cancer cells.
Kumari R, Robertson JFR, Watson SA. Int J Cancer. 2006;119 (1):49-59

238) Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation.
Rakha EA, Putti TC, Abd El-Rehim DM, Paish C, Green AR, Powe DG, Lee AH, Robertson JFR, Ellis IO. J Pathol. 2006; 208(4):495-506.

239) Basal phenotype identifies a poor prognostic subgroup of breast cancer of clinical importance.
Rakha EA, El-Rehim DA, Paish C, Green AR, Lee AH, Robertson JF, Blamey RW, Macmillan D, Ellis IO. Eur J Cancer. 2006 Dec;42 (18):3149-56.

240) Use of autoantibodies in breast cancer screening and diagnosis.
Storr SJ, Chakrabarti J, Barnes A, Murray A, Chapman CJ, Robertson JF.Expert Rev Anticancer Ther. 2006;6 (8):1215-23.

241) Fulvestrant: pharmacologic profile versus existing endocrine agents for the treatment of breast cancer.
Buzdar AU, Robertson JF. Ann Pharmacother. 2006;40(9):1572-83.

242) Efficacy and tolerability of high dose "ethinylestradiol" in post-menopausal advanced breast cancer patients heavily pre-treated with endocrine agents.
Agrawal A, Robertson JF, Cheung K. World J Surg Oncol. 2006;4:44.

243) "Resurrection of clinical efficacy" after resistance to endocrine therapy in metastatic breast cancer.
Agrawal A, Robertson JF, Cheung K. World J Surg Oncol. 2006;4:40.

2007

244) Effects of fulvestrant 250mg in premenopausal women with oestrogen receptor-positive primary breast cancer
Robertson JFR, Semiglazov V, Nemsadze G, Dzagnidze G, Janjalia M, Nicholson RI, Gee JM, Armstrong J, Study 41 investigators. Eur J Cancer2007;43(1):64-70. Epub 2006 Oct 24.

245) Prognostic markers in triple-negative breast cancer.
Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Cancer. 2007;109 (1):25-32.

246) Using array-comparative genomic hybridization to define molecular portraits of primary breast cancers.
Chin SF, Wang Y, Thorne NP, Teschendorff AE, Pinder SE, Vias M, Naderi A, Roberts I, Barbosa-Morais NL, Garcia MJ, Iyer NG, Kranjac T, Robertson JF, Aparicio S, Tavare S, Ellis I, Brenton JD, Caldas C.
Oncogene. 2007;26 (13):1959-70.

247) A gene-expression signature to predict survival in breast cancer across independent data sets.
Naderi A, Teschendorff AE, Barbosa-Morais NL, Pinder SE, Green AR, Powe DG, Robertson JF, Aparicio S, Ellis IO, Brenton JD, Caldas C.
Oncogene. 2007; 26 (10):1507-16.

248) Fulvestrant in advanced male breast cancer.
Agrawal A, Cheung KL, Robertson JF. Breast Cancer Res Treat. 2007; 101 (1):123.

249) The reliability of assessment of oestrogen receptor expression on needle core biopsy specimens of invasive carcinomas of the breast.
Hodi Z, Chakrabarti J, Lee AH, Ronan JE, Elston CW, Cheung KL, Robertson JF, Ellis IO.
J Clin Pathol. 2007; 60 (3):299-302.

250) Neoadjuvant chemotherapy in locally advanced primary breast cancers – The Nottingham experience.
Mathew J, Asgeirsson KS, Agrawal A, Mukherjee A, Ellis IO, Cheung KL, Chan SY, Robertson JF. Eur J Surg Oncol. 2007 Oct; 33 (8):972-6.

251) Successful management of elderly breast cancer patients treated without radiotherapy.
Valassiadou K, Morgan DA, Robertson JFR, Pinder SE, Cheung KL. World J Surg Oncol. 2007 Jun 3; 5(1):62. [Epub ahead of print]

252) Two-step method to isolate target recombinant protein from co-purified bacterial contaminant SlyD after immobilised metal affinity chromatography.
Parsy CB, Chapman CJ, Barnes AC, Robertson JFR, Murray A. J Chromatogr B Analyt Technol Biomed Life Sci. 2007 Jun 15; 853 (1-2):314-319.

253) Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999.
Blamey RW, Ellis IO, Pinder SE, Lee AH, Macmillan RD, Morgan DA, Robertson JF, Mitchell MJ, Ball GR, Haybittle JL, Elston CW. Eur J Cancer. 2007; 43 (10):1548-55.

254) Autoantibodies in breast cancer: their use as an aid to early diagnosis.
Chapman C, Murray A, Chakrabarti J, Thorpe A, Woolston C, Sahin U, Barnes A, Robertson JFR. Ann. Oncol. 2007 May; 18 (5):868-73.

255) Male breast cancer: a review of clinical management.
Agrawal A, Ayantunde AA, Rampaul R, Robertson JF. Breast Cancer Res. Treat. 2007 May; 103 (1):11-21.

256) The emerging role of the LIV-1 subfamily of zinc transporters in breast cancer.
Taylor KM, Morgan HE, Smart K, Zahari NM, Pumford S, Ellis IO, Robertson JFR, Nicholson RI. Mol Med. Mol Med. 2007 Jul-Aug;13 (7-8):396-406.

257) Fulvestrant (faslodex) how to make a good drug better.
Robertson JFR. Oncologist. 2007 Jul;12 (7):774-84.

258) Heregulin beta1 drives gefitinib-resistant growth and invasion in tamoxifen-resistant MCF-7 breast cancer cells.
Hutcheson IR, Knowlden JM, Hiscox SE, Barrow D, Gee JM, Robertson JFR, Ellis IO, Nicholson RI. Breast Cancer Res. 2007;9 (4):R50

259) Biologic and clinical characteristics of breast cancer with single hormone receptor positive phenotype
Rakha EA, El-Sayed ME, Green AR, Paish EC, Powe DG, Gee J, Nicholson RI, Lee AH, Robertson JFR, Ellis IO. J Clin Oncol. 2007;25 (30):4772-8

260) Serum EGFR and HER-2 expression in primary and metastatic breast cancer patients.
Asgeirsson KS, Agrawal A, Allen C, Hitch A, Chapman C, Ellis IO, Cheung KL, Robertson JFR. Breast Cancer Res. 2007;9 (6):R75

261) Protein kinase C isoform expression as a predictor of disease outcome on endocrine therapy in breast cancer.
Assender JW, Gee JM, Lewis I, Ellis IO, Robertson JFR, Nicholson RI. J Clin Pathol. 2007 Nov;60 (11):1216-21.

262) Autoantibodies in Lung Cancer - possibilities for early detection and subsequent cure.
Chapman CJ, Murray A, McElveen JE, Sahin U, Luxemburger U, Türeci O, Wiewrodt R, Barnes AC, Robertson JFR. Thorax. 2007;63(3):228-33.

263) Incidence of intramammary nodes in completion mastectomy specimens after axillary node sampling: Implications for breast conserving surgery
Rampaul RS, Dale OT, Mitchell M, Blamey RW, Macmillan RD, Robertson JFR, Ellis IO. Breast. 2007 Dec 27 [Epub ahead of print]

2008

264) Double -blind, randomized placebo controlled trial of Fulvestrant compared with Exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFFECT.

Chia S, Gradishar W, Mauriac L, Bines J, Amant F, Federico M, Fein L, Romieu G, Buzdar A, Robertson JFR, Brufsky A, Possinger K, Rennie P, Sapunar F, Lowe E, Piccart M. J Clin Oncol. 2008; 26(10): 1664-70.

265) The O-linked glycosylation of secretory/shed MUC1 from advanced breast cancer patient serum.
Storr SJ, Royle L, Chapman CJ, Hamid UM, Robertson JFR, Murray A, Dwek RA, Rudd PM. Glycobiology. 2008 Mar 10 [Epub ahead of print]

266) Can computerised tomography replace bone scintigraphy in detecting bone metastases from breast cancer? A prospective study.
Bristow AR, Agrawal A, Evans AJ, Burrell HC, Cornford EJ, James JJ, Hamilton L, Robertson JFR, Chan SY, Lawton PA, Cheung KL. Breast. 2008 Feb;17 (1):98-103

267) Invasive lobular carcinoma of the breast: Response to hormonal therapy and outcomes.
Rakha EA, El-Sayed ME, Powe DG, Green AR, Habashy H, Grainge MJ, Robertson JFR, Blamey R, Gee J, Nicholson RI, Lee AH, Ellis IO. Eur J Cancer. 2008 Jan;44 (1):73-83

268) Neoadjuvant chemotherapy for locally advanced breast cancer: A review of the literature and future directions.
Mathew J, Asgeirsson KS, Cheung KL, Chan S, Dahda A, Robertson JFR. Eur J Surg Oncol. 2008 May 22. [Epub ahead of print]

269) Nuclear and cytoplasmic expression of ERbeta1, ERbeta2, and ERbeta5 identifies distinct prognostic outcome for breast cancer patients.
Shaaban AM, Green AR, Karthik S, Alizadeh Y, Hughes TA, Harkins L, Ellis IO, Robertson JFR, Paish EC, Saunders PT, Groome NP, Speirs V. Clin Cancer Res. 2008;14(16):5228-35.

270) A strategy to reveal potential glycan markers from serum glycoproteins associated with breast cancer progression.
Abd Hamid UM, Royle L, Saldova R, Radcliffe CM, Harvey DJ, Storr SJ, Pardo M, Antrobus R, Chapman CJ, Zitzmann N, Robertson JFR, Dwek RA, Rudd PM. Glycobiology. 2008;18 (12):1105-18

2009

271) Overexpression of TFAP2C in invasive breast cancer correlates with a poorer response to anti-hormone therapy and reduced patient survival.
Gee JMW, Eloranta JJ, Ibbitt JC, Robertson JFR, Ellis IO, Williams T, Nicholson RI, Hurst HC J Pathol. 2009; 217: 32-41.

272) Bone turnover markers in postmenopausal breast cancer treated with fulvestrant - a pilot study.
Agrawal A, Hannon RA, Cheung KL, Eastell R, Robertson JFR. Breast. 2009 Jun;18 (3):204-7.

273) Neoadjuvant endocrine treatment in primary breast cancer – review of literature
Mathew J, Asgeirsson KS, Jackson LR, Cheung KL, Robertson JFR. Breast. 2009: Dec;18 (6):339-44

274) Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced cancer: the results from the FIRST study
Robertson JFR, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, Lindemann J, Ellis MJ. J Clin Oncol. 2009: 27(27):4530-5.

275) Are current drug development programmes realising the full potential of new agents? Tyrosine kinase inhibitors.
Gutteridge E, Robertson JFR. Breast Cancer Res. 2009; 11 Suppl 3:S24

2010

276) Technical validation of an autoantibody test for lung cancer.
Murray A, Chapman CJ, Healey G, Peek LJ, Parsons G, Baldwin D, Barnes A, Sewell HF, Fritsche HA, Robertson JFR. Ann Oncol. 2010; 21(8):1687-93.

277) Autoimmunity to SOX2, clinical phenotype and survival in patients with small-cell lung cancer.
Maddison P, Thorpe A, Silcocks P, Robertson JFR, Chapman CJ. Lung Cancer. 2010; 70(3):335-9.

278) Bony metastases from breast cancer - a study of foetal antigen 2 as a blood tumour marker.
Cheung KL, iles RK, Robertson JFR. World Journal of Surgical Oncology 2010, 8:38

279) A Randomised Trial of Mastectomy Only versus Tamoxifen for Treating Elderly Patients with Operable Primary Breast cancer - Final Results at 20-year Follow-up
Chakrabarti J, Kenny FS, Syed BM, Robertson JFR, Blamey RW, Cheung KL. Critical Reviews in Oncology / Hematology. 2010 May 5 [EPub ahead of print]

280) Activity of fulvestrant in HER2-overexpressing advanced breast cancer.
Robertson JFR, Steger GG, Neven P, Barni S, Gieseking F, Nolè F, Pritchard KI, O'Malley FP, Simon SD, Kaufman B, Petruzelka L. Ann Oncol. 2010; 21(6):1246-53.

281) The effects of gefitinib in tamoxifen-resistant and hormone-insensitive breast cancer: a phase II study.
Gutteridge E, Agrawal A, Nicholson R, Leung Cheung K, Robertson JFR, Gee J. Int J Cancer. 2010; 126 (8):1806-16.

282) Suppression of ovarian function in combination with an aromatase inhibitor as treatment for advanced breast cancer in pre-menopausal women.
Cheung KL, Agrawal A, Folkerd E, Dowsett M, Robertson JF, Winterbottom L. Eur J Cancer. 2010;46(16):2936-42.

283) Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study Duffy S and FH01 steering committee. Lancet. 2010; published online November 18.

2011

284) Clinical Validation of an Autoantibody Test for Lung Cancer.
Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, Maddison P, Healey G, Fairley GH, Barnes AC, Robertson JF. Ann Oncol. 2011 Feb;22 (2):383-9.

285) Immunobiomarkers in small cell lung cancer: potential early cancer signals.
Chapman CJ, Thorpe AJ, Murray A, Parsy-Kowalska CB, Allen J, Stafford KM, Chauhan AS, Kite TA, Maddison P, Robertson JF. Clin Cancer Res. 2011 Mar 15;17 (6):1474-80.

286) erbB3 recruitment of insulin receptor substrate 1 modulates insulin-like growth factor receptor signalling in oestrogen receptor-positive breast cancer cell lines.
Knowlden JM, Gee JM, Barrow D, Robertson JF, Ellis IO, Nicholson RI, Hutcheson IR. Breast Cancer Res. 2011 Sep 22;13 (5):R93. [Epub ahead of print]

287) Identifying Gaps in the Locoregional Management of Early Breast Cancer: Highlights from the Kyoto Consensus Conference
Masakazu Toi, Eric P Winter, Takashi Inamoto, John R Benson,
John F Forbes, Michihide Mitsumori, John F R Robertson, Hironobu Sasano, Gunter von Minckwitz, Akira Yamauchi, V Suzanne Klimberg Ann Surg Oncol (2011) 18:2885-2892

288) EarlyC-Lung: an Immuno-biomarker Test as an Aid to Early Detection of Lung Cancer.
Lam S, Boyle P, Healey G, Maddison P, Peek L, Murray A, Chapman CJ, Allen J, Wood WC, Sewell HF, Robertson JFR. Cancer Prev Res 2011; 4 (7) 1126-1134.

289) Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study
Duffy, S. W., et al including Robertson J) Lancet Oncology, 2011; 11 (12). pp. 1127-1134.

290) Dowsett M, Smith I, Robertson J, Robison L, Pinhel I, Johnson L, et al: Endocrine therapy, new biologicals, and new study designs for presurgical studies in breast cancer. Journal of the National Cancer Institute Monographs 2011, 2011(43):120-123

2012

291) A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up
S. J. Johnston; F. S. Kenny; B. M. Syed; J.F.R. Robertson; S. E. Pinder; L. Winterbottom; I. O. Ellis; R. W. Blamey; K. L. Cheung. Annals of Oncology 2012; 23(9), 2296-2300

292) Clinical relevance of "withdrawal therapy" as a form of hormonal manipulation for breast cancer
Agrawal A, Robertson JFR, Cheung KL. World J Surg Oncol. 2011 Sep 9;9 (1):101 [PMID: 21906312]

293) Fulvestrant 500 mg in the Treatment of Advanced Breast Cancer
Robertson JFR. European Journal of Clinical & Medical Oncology (in press)

294) EarlyCDT®-Lung test: improved clinical utility through additional autoantibody assays.
Chapman CJ, Healey GF, Murray A, Boyle P, Robertson , Peek LJ, Allen J, Hamilton-Fairley G, Parsy-Kowalska CB, MacDonald IK, Jewell W, Maddison P and Robertson JF. Tumor Biology 2012;33(5):1319-26. PMID 22492236

295) Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Emerson L, Dean A, Ellis MJ. Breast Cancer Res Treat. 2012 Nov;136(2):503-11. doi:10.1007/s10549-012-2192-4. Epub 2012 Oct 13.

296) The sequential use of endocrine treatment for advanced breast cancer: where are we? C. Barrios, J. F. Forbes, W. Jonat, P. Conte, W. Gradishar, A. Buzdar, K. Gelmon, M. Gnant, J. Bonneterre, M. Toi, C. Hudis & JFR Robertson Annals of Oncology 2012 doi:10.1093/annonc/mdr593

297) Preoperative systemic therapy in locoregional management of early breast cancer: highlights from the Kyoto Breast Cancer Concensus Conference.

Masakazu Toi, John R Benson, Eric P Winer, John F Forbes, Gunter von Minckwitz, Mehra Golshan, John FR Robertson, Hironobu Sasano, Bernard F Cole, Louis WC Chow, Mark D Pegram, Wonshik Han, Chium-Sheng Huang, Tadashi Ideda, Shotaro Kanao, Eun-Sook Lee, Shinzaburo Noguchi, Shinji Ohno, Ann H Partridge, Roman Rouzier, Mitsuhiro Tozaki, Tomaharu Sugie, Akira Yamauchi, Takashi Inamoto. Breast Cancer Res Treat (2012) 136:919-926

298) Application of a High Throughput Method of Biomarker Discovery to Improvement of the EarlyCDT®-Lung Test.
Macdonald IK, Murray A, Healey G, Parsy-Kowalska C, Allen J, Chapman CJ, Sewell H, Robertson JFR. PLoS One. 2012;7(12):e51002.

299) Development and Validation of a High Throughput System for Discovery of Antigens for Autoantibody Detection.
Macdonald IK, Murray A, Allen J, Parsy-Kowalska C, Healey G, Chapman CJ, Sewell H, Robertson JFR. PLoS ONE 2012 7(7): e40759. doi:10.1371/journal.pone.0040759

2013

300) Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial
Robertson JFR, Ferrero J-M, Bourgeois H, Kennecke H, de Boer RH, Jacot W, McGreivy J, Suzuki S, Zhu M, McCaffery I, Loh E, Gansert JL, Kaufman PA. Lancet Oncology 2013; 14: 228-235

301) A randomized trial to assess the biological activity of short-term (pre-surgical) fulvestrant 500 mg plus anastrozole versus fulvestrant 500 mg alone or anastrozole alone on primary breast cancer.
Robertson JF, Dixon JM, Sibbering DM, Jahan A, Ellis IO, Channon E, Hyman-Taylor P, Nicholson RI, Gee JM. Breast Cancer Res. 2013 Mar 5;15 (2):R18.

302) Randomized Phase II study of lonaprisan as second-line therapy for progesterone receptor-positive breast cancer.
W. Jonat, T. Bachelot, T. Ruhstaller, I. Kuss, U. Reimann & JFR Robertson. Annals of Oncology Ann Oncol 2013; doi: 10.1093/annonc/mdt216

303) Signal Stratification of Autoantibody Levels in Serum Samples and Its Application to the Early Detection of Lung Cancer Journal of Thoracic Disease.
Healey GF, Lam S, Boyle P, Hamilton-Fairley G, Peek LJ, and Robertson JFR. J Thorac Dis 2013 Oct:5 (5: 618-25

2014

304) Audit of the autoantibody test, EarlyCDT®-Lung, in 1600 patients with clinical outcome data: an evaluation of its performance in routine clinical practice

Jett JR, Peek LJ, Fredericks L, Jewell W, Pingleton W.W, and Robertson JFR. Lung Cancer 2014: 83; 51-55

305) A good drug made better: the fulvestrant dose-response story.
Robertson JF, Lindemann J, Garnett S, Anderson E, Nicholson RI, Kuter I, Gee JM.
Clin Breast Cancer. 2014 Dec; 14(6):381-9. doi: 10.1016/j.clbc.2014.06.005. Epub 2014 Jun 24. Review.

306) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.

307) Serum autoantibody measurement for the detection of hepatocellular carcinoma.
Middleton CH, Irving W, Robertson JF, Murray A, Parsy-Kowalska CB, Macdonald IK, McElveen J, Allen J, Healey GF, Thomson BJ, Ryder SJ, Holdenrieder S, Chapman CJ.
PLoS One. 2014 Aug 5;9(8):e103867. doi: 10.1371/journal.pone.0103867. eCollection 2014.

308) Pilot randomised study of early intervention based on tumour markers in the follow-up of patients with primary breast cancer.
Mathew J, Prinsloo P, Agrawal A, Gutteridge E, Marenah C, Robertson JF, Cheung KL.
Breast. 2014 Oct;23(5):567-72. doi: 10.1016/j.breast.2014.04.003. Epub 2014 May 27.

309) EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Breast. 2014 Oct;23(5):567-72. doi: 10.1016/j.breast.2014.04.003. Epub 2014 May 27.

2015

310) Personalization of loco-regional care for primary breast cancer patients (part 1).
Toi M, Winer EP, Benson JR, Inamoto T, Forbes JF, von Minckwitz G, Robertson JF, Grobmyer SR, Jatoi I, Sasano H, Kunkler I, Ho AY, Yamauchi C, Chow LW, Huang CS, Han W, Noguchi S, Pegram MD, Yamauchi H, Lee ES, Larionov AA, Bevilacqua JL, Yoshimura M, Sugie T, Yamauchi A, Krop IE, Noh DY, Klimberg VS; 2014 Kyoto Breast Cancer Consensus Conference.
Future Oncol. 2015;11(9):1297-300. doi: 10.2217/fon.15.65.

311) Personalization of loco-regional care for primary breast cancer patients (part 2).
Toi M, Winer EP, Benson JR, Inamoto T, Forbes JF, von Minckwitz G, Robertson JF, Grobmyer SR, Jatoi I, Sasano H, Kunkler I, Ho AY, Yamauchi C, Chow LW, Huang CS, Han W, Noguchi S, Pegram MD, Yamauchi H, Lee ES, Larionov AA, Bevilacqua JL, Yoshimura M,

Sugie T, Yamauchi A, Krop IE, Noh DY, Klimberg VS; 2014 Kyoto Breast Cancer Consensus Conference.
Future Oncol. 2015;11(9):1301-5. doi: 10.2217/fon.15.66.

312) Biological effects of fulvestrant on estrogen receptor positive human breast cancer: short, medium and long-term effects based on sequential biopsies.
Agrawal A, Robertson JF, Cheung KL, Gutteridge E, Ellis IO, Nicholson RI, Gee JM.
Int J Cancer. 2015 Jul 14. doi: 10.1002/ijc.29682. [Epub ahead of print]

313) Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis from the Phase II FIRST Study.
Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N, Rukazenkov Y, Robertson JF. J Clin Oncol. 2015 Sep 14. pii: JCO.2015.61.5831. [Epub ahead of print]

2016

314) Brief Report: Autoantibody Signature Enhances the Positive Predictive Power of Computed Tomography and Nodule-based Risk Models for Detection of Lung Cancer.
Massion PP, Healey GF, Peek LJ, Fredericks L, Sewell HF, Murray A, Robertson JF.
J Thorac Oncol. 2016 Sep 8. pii: S1556-0864(16)30928-5. doi: 10.1016/j.jtho.2016.08.143. [Epub ahead of print] [IF: 5.5]

315) Human Blood Autoantibodies in the Detection of Colorectal Cancer
Negm OH, Hamed MR, Schoen RE, Whelan RL, Steele RJ, Scholefield J, Dilnot EM, Shantha Kumara HM, Robertson JF, Sewell HF. PLoS One. 2016 Jul 6;11(7):e0156971. doi: 10.1371/journal.pone.0156971. eCollection 2016.

316) Heterogeneity in global gene expression profiles between biopsy specimens taken peri-surgically from primary ER-positive breast carcinomas.
López-Knowles E, Gao Q, Cheang MC, Morden J, Parker J, Martin LA, Pinhel I, McNeill F,Hills M, Detre S, Afentakis M, Zabaglo L, Dodson A, Skene A, Holcombe C, Robertson J, Smith I, Bliss JM, Dowsett M; POETIC trialists.
Breast Cancer Res. 2016 Apr 1;18(1):39. doi: 10.1186/s13058-016-0696-2.
PMID: 27036195 Free PMC Article

317) Biological effects of fulvestrant on estrogen receptor positive human breast cancer: short, medium and long-term effects based on sequential biopsies.
Agrawal A, Robertson JF, Cheung KL, Gutteridge E, Ellis IO, Nicholson RI, Gee JM.
Int J Cancer. 2016;138 (1):146-59. doi: 10.1002/ijc.29682. Epub 2015 Jul 30. [IF: 5.5]

318) Impact of mutational profiles on response of primary oestrogen receptor-positive breast cancers to oestrogen deprivation
Pascal Gellert, Corrinne Segal, Qiong Gao, Elena López-Knowles, Lesley-Ann Martin, Andrew Dodson, Tiandao Li, Christopher Miller, Charles Lu, Elaine Mardis, Alexa Gillman, James Morden, Manuela Graf, Kally Sidhu, Abigail Evans, Michael Shere, Christopher Holcombe, Stuart McIntosh, Nigel Bundred, Anthony Skene, William Macwell, John Robertson, Judith M Bliss, Ian Smith, and Mitch Dowsett
Nature Communications (in press) [IF: 11.3]

319) Breast conservation in ductal carcinoma in situ (DCIS); what defines optimal margins?
Toss MS, Pinder SE, Green AR, Thomas J, Morgan DAL, Robertson JFR, Ellis IO, Rakha EA
Histopathology (in press) [IF: 3.4]

320) Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON):an international, randomised, double-blind, phase 3 trial
John F R Robertson*, Igor M Bondarenko, Ekaterina Trishkina, Mikhail Dvorkin, Lawrence Panasci, Alexey Manikhas, Yaroslav Shparyk, Servando Cardona-Huerta, Kwok-Leung Cheung, Manuel Jesus Philco-Salas, Manuel Ruiz-Borrego, Zhimin Shao, Shinzaburo Noguchi, Jacqui Rowbottom, Mary Stuart, Lynda M Grinsted, Mehdi Fazal, Matthew J Ellis
Lancet: 2016; dx.doi.org/10.1016/S0140-6736(16)32389-3

2017

321) Breast conservation in ductal carcinoma in situ (DCIS); what defines optimal margins?
Michael S Toss, Sarah E Pinder, Andrew R Green, Jeremy Thomas, David A.L. Morgan, John FR Robertson, Ian O Ellis, Emad A Rakha. Histopathology; 2017; 70: 681-692

Invited Publications and Book Chapters

1) Oestrogen deprivation in breast cancer using LH-RH agonists and antioestrogens
Nicholson, R.I., Walker, K.J., Walker, R.F., Read, C.F., Finley, E., Robertson, J.F.R., Blamey, R.W., Griffiths, K.
Proceedings of 3rd International Congress of Hormones in Cancer, Raven Press, 1988

2) Distribution and prognostic significance of oestrogen receptor negative cells in oestrogen receptor positive breast tumours
Walker, K.J., Bouzabar, N., Elston, C.W., Ellis, I.O., Robertson J.F.R., Blamey, R.W., Griffiths, K.
Proceedings of 3rd International Congress of Hormones in Cancer, Raven Press, 1988

3) GnRH analogues in breast cancer
Robertson, J.F.R.

GnRH-analogien, ICI-PharmaOy, 1988 pp 29-36

4) McKenna, P.G., O'Neill, K.L., Abram, W.P., Robertson, J.F.R., Blamey R.W.
In : Thymidine Kinase - A marker for neoplastic and viral diseases (Oehr, P. ; Ed)
Thieme Verlag : Stuttgart 1988

5) Review of the endocrine actions of LH-RH analogues in premenopausal women with breast cancer
Nicholson, R.I, Walker, K.J, Walker, R.F, Read, G.F, Turkes, A, Robertson, J.F.R, Blamey, R.W.
Horm. Res. 1989; 32 (suppl 1) : 198-201

6) Zoladex in advanced breast cancer
Robertson, J.F.R., Nicholson, R.I., Walker, K.J. and Blamey, R.W.
Horm. Res. 1989; 32 (suppl 1) : 206-208

7) The management of breast cancer
Blamey, R.W., Robertson, J.F.R. Prescriber's Journal 1990; 30 : 101-108

8) Pure antioestrogens in breast cancer: Experimental and . In: Hormones and antihormones in endocrine dependent pathology: Basic and Clinical aspect.
Nicholson, R.I., Gee, J.M. W., Eaton, C.W., Manning, D.L., Mansel, R.E., Sharma, N., Douglas-Jones, A., Price-Thomas, M., Howell, A., DeFriend, D.J., Bundred, N.J., Anderson, E., Robertson, J.F.R., Blamey, R.W., Dowsett, M., Baum, M., Walton, P., Wakeling, A.E. Elsevier Science, Exerpta Medicine (1994), International Congress Series 1064 pp347-360, Amsterdam.

9) The role of serum markers in breast cancer.
Robertson, J.F.R.
The Breast 1995; 4: 62-63.

10) Oncology - Surgery. Medicine International 1995; 23:10: 433-435.

11) Prospective confirmation of a biochemical index for measuring therapeutic efficacy in metastatic breast cancer in a multicentre study.
Robertson J. F.R.
The Breast 1996; 5: 372-373.

12) Clinical studies with the specific "pure" anti-oestrogen ICI 182,780.
Howell, A., DeFriend, D.J., Robertson, J.F.R., Blamey, R.W., Anderson, L., Anderson, E., Sutcliffe, F.A., Walton, P.
The Breast 1996; 5: 192-195.

13) The role of serum tumour markers for monitoring therapy in metastatic breast cancer
Robertson, J.F.R.
J. Europ. Ligand Assay Society 1996; 1: 257-262.

14) erbB signalling and endocrine sensitivity of human breast cancer. In: EGF receptor in tumour growth and progression.
Nicholson, R.I, Gee, J.M.W, Jones, H, Harper, M.E, Wakeling, A.E, Willsher, P.C, Robertson, J.F.R.
Harkin et al. ed. Boston Springer Verlag Publ. 1997; pp 105-128.

15) Diagnosis and prognosis of primary breast cancer.
Robertson, J. F R., Evans, A.J.
Quart. J Nuclear Medicine 1997: 41: 200-210.

16) Prognostic and response markers in the management of breast cancer.
Robertson, J.F.R.
Cancer Treatment Reviews 1997; 23 (1): S41-S48.

17) p53 protein expression in human breast cancer: relationship to tumour differentiation and endocrine response.
Nicholson, R.I., Gee, J.M.W., Seery, L.T., McClelland, R.A., Harper, M.E., Holt, B., Barnes, D., Robertson, J.F.R., Pinder, S., Ellis, I.O.
In ESO Scientific Updates. Vol 1. Prognostic and predictive value of p53. Ed. Klijn J.G.M.
Elsevier Science 1997.

18) Blood tumour markers in breast cancer.
Robertson, J.F.R.
Tumour Marker Update 1998; 10: 31-37.

19) Influence of growth factor signalling pathways on endocrine response in breast cancer: new therapeutic initiatives.
Pharmacology handbook. Eds. Furr B.J.A. and Jordan, V.C. 1998.

20) MUC-1 mucin assays for monitoring therapy in metastatic breast cancer.
Graves, R., Hilgers, J., Fritsche, H., Hayes, D., Robertson, J.F.R.
The Breast 1997; 7: 181-186.

21) Involvement of steroid hormone and growth factor cross-talk in endocrine response in breast cancer.
Nicholson, R.I., McClelland, R.A., Robertson, J.F.R., Gee, J.M.W.
Endocrine-related Cancer (accepted for publication).

22) Benign disorders of the female breast.
Macmillan, R.D., Robertson, J.F.R.
Current Obstetrics & Gynaecology 1998; 8 (4): 209-217.

23) Endocrine response and failure in breast cancer: a role for the interplay of steroid and growth factor signalling pathways and therapeutic implications.
Nicholson, R.I., Robertson, J.F.R., Seery L.T., Gee, J.M.W.
Furr, B.J.A. & Jordan, V.C. (Eds.)

24) The importance of stable disease in patients treated with endocrine therapy.
Cheung, K.L., Robertson, J.F.R.
Breast Cancer Abstracts 1999; May: 2 – 4

25) The primary use of endocrine therapies.
Howell, A., Robertson, J.F.R. In: Primary Medical Therapy for Breast Cancer: Clinical & Biological Aspects. Ed. Dowsett, M. & Howell, A. Elsevier 1999; 4: p 23-37.

26) Preoperative endocrine therapy for breast cancer.
Cheung, K.L., Howell, A., Robertson, J.F.R.
Endocrine Related Cancer 2000; 7: 131-141

27) Nipple discharge
Macmillan, R.D., Robertson, J.F.R.
Surgery 2001; 19:5: 109-110.

28) Surgical management of early breast cancer
Ying M, Cheung KL, Robertson JFR
In: Baum M (ed), Lectures in Early Breast Cancer – Part 2 Management of Early Breast Cancer, Current Medicine Group, London, UK 2006; 1-7

29) Fulvestrant in metastatic disease
Agrawal A, Robertson JFR, Cheung KL
In: AU Buzdar (ed), Endocrine Therapies in Breast Cancer. Oxford Oncology Library, Oxford University Press, UK 2006; Chapter 5, 51-64

30) Pathology and the biology of breast cancer.
Rampaul RS, Rakha EA, Robertson JFR, Ellis IO.
In: A Companion to Specialist Surgical Practice: Breast Surgery . Dixon JM, ed. Saunders Elsevier, 2009, chapter 2, pp 19-42.

31) Overview and Concepts of Endochrine Therapy
Hayes DF, Robertson JFR
In: Endochrine Therapy of Breast Cancer. Robertson JFR, Nicholson RI, Hayes DF (eds). Martin Dunitz Ltd: 2002, pp 3-10.

32) Fulvestrant (ICI 182,780, Faslodex): A 'pure' antiestrogen.
Howell A, Robertson JFR
In: Endochrine Therapy of Breast Cancer. Robertson JFR, Nicholson RI, Hayes DF (eds). Martin Dunitz Ltd: 2002, pp 63-74.

33) The Clinical Efficacy of Progesterone Antagonists in Breast Cancer.
Jonat W, Giurescu M, Robertson JFR
In: Endochrine Therapy of Breast Cancer. Robertson JFR, Nicholson RI, Hayes DF (eds). Martin Dunitz Ltd: 2002, pp 117-126

34) Clinical Response and Resistance to SERMs
Gee JM, Madden TA, Robertson JFR, Nicholson RI
In: Endochrine Therapy of Breast Cancer. Robertson JFR, Nicholson RI, Hayes DF (eds). Martin Dunitz Ltd: 2002, pp 155-190.

35) Biological changes in primary breast cancer during antiestrogen therapies
Willsher P, Kenny F, Gee JM, Nicholson RI, Robertson JFR
In: Endochrine Therapy of Breast Cancer. Robertson JFR, Nicholson RI, Hayes DF (eds). Martin Dunitz Ltd: 2002, pp209-232

36) Surgical management of early breast cancer
Ying M, Cheung KL, Robertson JFR
In: Baum M (ed), Lectures in Early Breast Cancer – Part 2 Management of Early Breast Cancer, Current Medicine Group, London, UK 2006; 1-7

37) Fulvestrant in metastatic disease
Agrawal A, Robertson JFR, Cheung KL
In: AU Buzdar (ed), Endocrine Therapies in Breast Cancer. Oxford Oncology Library, Oxford University Press, UK 2006; Chapter 5, 51-64

38) Pathology and the biology of breast cancer.
Rampaul RS, Rakha EA, Robertson JFR, Ellis IO.
In: A Companion to Specialist Surgical Practice: Breast Surgery . Dixon JM, ed. Saunders Elsevier, 2009, chapter 2, pp 19-42.

39) Prognostic Indices in Breast Cancer
Rampaul R, Ellis I.O., Robertson JFR In World Breast Cancer Report 2012 pp323-332. Ed Boyle P. Autier P, Adebamowo C, Anderson BO, Badwe RA, Ashton LP, Yamaguchi N;

40) Challenges in Biomarker Development and Validation
Murray A, Fritsche HA, Wood WC, Hamilton-Fairley G & Robertson JFR
World Breast Cancer Report 2012 pp389-401. Ed Boyle P. Autier P, Adebamowo C, Anderson BO, Badwe RA, Ashton LP, Yamaguchi N

41) The Breast.
Kelly K. Hunt, John F.R. Robertson, and Kirby I. Bland. in Schwartz's Principles of Surgery, 10th edition. Edited by F.C. Brunicardi, et al. McGraw-Hil, 2014. pp 565-604

42) Surgical Management of Breast Cancer after Preoperative Systemic Therapy.
Mathew J, Courtney Carol-Ann, Hunt Kelly, Robertson JF In, Personalised Treatment of Breast Cancer. Eds Toi M, Winer E, Benson J, Klimberg S 2016, pp 263-293

43) Treatment of the axilla in patients with primary breast cancer and low burden axillary disease: Limitations of the evidence from randomized controlled trials.
JFR Robertson, PJJ Herrod, J Mathew, LS Kilburn, CE Coles, I Bradbury. In: Critical Reviews in Oncology/Hematology 2017; 110: 74-80

EXHIBIT B: MATERIALS CONSIDERED LIST

Exhibit	Description
2004	Angelo Di Leo et al., *Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor-Positive Advanced Breast Cancer*, 28 J. CLIN. ONCOL. 4594 (2010) ("Di Leo 2010")
2005	Angelo Di Leo et al., *Final Overall Survival: Fulvestrant 500 mg vs 250 mg in the Randomized CONFIRM Trial*, 106 J. NAT'L CANCER INST. 1 (2014) ("Di Leo 2014")
2006	S. Ohno et al., *Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study*, 21 ANNALS ONCOL. 2342 (2010) ("FINDER 1")
2007	Kathleen I. Pritchard et al., *Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2)*, 123 BREAST CANCER RES. & TREAT. 453 (2010) ("FINDER 2")
2008	Robert T. Greenlee et al., *Cancer Statistics, 2000*, 50 CA CANCER J. CLIN. 7 (2000) ("Greenlee")
2009	J.F.R. Robertson, *Oestrogen receptor: a stable phenotype in breast cancer*, 73 BRIT. J. CANCER 5 (1996) ("Robertson 1996")
2010	Monica Fornier et al., *Update on the Management of Advanced Breast Cancer,* 13 ONCOLOGY 647 (1999) ("Fornier")
2011	V. Craig Jordan, *Alternate Antiestrogens and Approaches to the Prevention of Breast Cancer*, 22 J. CELL. BIOCHEM. 51 (Supp. 1995) ("Jordan Supp. 1995")
2012	Gabriel N. Hortobagyi et al., *Anastrozole (Arimidex®), a New Aromatase Inhibitor for Advanced Breast Cancer: Mechanism of Action and Role in Management*, 16 CANCER INVESTIGATION 385 (1998) ("Hortobagyi Cancer Investigation 1998")
2013	S.R.D. Johnston et al., *The novel anti-oestrogen idoxifene inhibits the growth of human MCF-7 breast cancer xenografts and reduces the frequency of acquired anti-oestrogen resistance*, 75 BRIT. J. CANCER 804 (1997) ("Johnston 1997")
2014	Kathleen Pritchard, *Effects on Breast Cancer: Clinical Aspects*, *in* ESTROGENS AND ANTIESTROGENS: BASIC AND CLINICAL ASPECTS, Ch. 13 (Robert Lindsay et al. eds., 1997) ("Pritchard 1997")

Exhibit	Description
2015	Aman U. Buzdar et al., *Tamoxifen and Toremifene in Breast Cancer: Comparison of Safety and Efficacy,* 16 J. CLIN. ONCOL. 348 (1998) ("Buzdar Clin. Oncol. 1998")
2016	A. Howell et al., *Response after withdrawal of tamoxifen and progestogens in advanced breast cancer*, 3 ANNALS ONCOL. 611 (1992) ("Howell 1992")
2017	V. Craig Jordan, *TAMOXIFEN: Toxicities and Drug Resistance During the Treatment and Prevention of Breast Cancer*, 35 ANN. REV. PHARMACOL. TOXICOL. 195 (1995) ("Jordan 1995")
2018	Monica Morrow et al., *Molecular Mechanisms of Resistance to Tamoxifen Therapy in Breast Cancer*, 128 ARCH. SURG. 1187 (1993) ("Morrow")
2019	Valerie J. Wiebe et al., *Tamoxifen resistance in breast cancer*, 14 CRIT. REVS. ONCOL. HEMATOL. 173 (1993) ("Wiebe")
2020	V. Craig Jordan, *The Strategic Use of Antiestrogens to Control the Development and Growth of Breast Cancer*, 70 CANCER 977 (Supp. 1992) ("Jordan Supp. 1992")
2021	V. Craig Jordan, *The Role of Tamoxifen in the Treatment and Prevention of Breast Cancer*, CURR. PROBL. CANCER 134 (1992) ("Jordan 1992")
2022	Susan E. Minton, *New Hormonal Therapies for Breast Cancer*, 6 CANCER CONTROL J. 1 (1999) ("Minton")
2023	T.A. Grese et al., *Selective Estrogen Receptor Modulators (SERMs)*, 4 CURRENT PHARM. DESIGN 71 (1998) ("Grese 1998")
2024	Gabriel N. Hortobagyi, *Treatment of Breast Cancer*, 339 NEW ENG. J. MED. 974 (1998) ("Hortobagyi New Eng. J. Med. 1998")
2025	Shigeru Masamura et al., *Aromatase inhibitor development for treatment of breast cancer*, 33 BREAST CANCER RES. & TREAT. 19 (1994) ("Masamura 1994")
2026	Gary J. Kelloff et al., *Aromatase Inhibitors as Potential Cancer Chemopreventives*, 7 CANCER EPIDEMIOL., BIOMARKERS & PREVENTION 65 (1998) ("Kelloff 1998")
2027	M. Dukes et al., *Effects of a non-steroidal pure antioestrogen, ZM 189,154, on oestrogen target organs of the rat including bones*, 141 J. ENDOCRINOL. 335 (1994) ("Dukes 1994")

Exhibit	Description
2028	A. Howell et al., *Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment*, 20 J. CLIN. ONCOL. 3396 (2002) ("Howell 2002")
2029	C.K. Osborne et al., *Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial*, 20 J. CLIN. ONCOL. 3386 (2002) ("Osborne 2002")
2030	John F. Robertson et al., *Comparison of the Short-Term Biological Effects of 7-α-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17β-diol (Faslodex) versus Tamoxifen in Postmenopausal Women with Primary Breast Cancer*, 61 CANCER RES. 6739 (2001) ("Robertson 2001")
2031	John F.R. Robertson et al., *Pharmacokinetics of a Single Dose of Fulvestrant Prolonged-Release Intramuscular Injection in Postmenopausal Women Awaiting Surgery for Primary Breast Cancer*, CLIN. THER. 1440 (2003) ("Robertson Clin. Ther. 2003")
2032	Fernand Labrie et al., *Activity and Safety of the Antiestrogen EM-800, the Orally Active Precursor of Acolbifene, in Tamoxifen-Resistant Breast Cancer*, 22 J. CLIN. ONCOL. 864 (2004) ("Labrie 2004")
2033	P. Van de Velde et al., *RU 58668: Further* In Vitro *And* In Vivo *Pharmacological Data Related to its Antitumoral Activity*, 59 J. STEROID BIOCHEM. MOLEC. BIOL. 449 (1996) ("Van de Velde")
2034	Fernand Labrie et al., *EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium*, 69 J. STEROID BIOCHEM. & MOLEC. BIOL. 51 (1999) ("Labrie 1999")
2035	Gabriel N. Hortobagyi, *Progress in Endocrine Therapy for Breast Carcinoma*, 83 CANCER 1 (1998) ("Hortobagyi 1998")
2036	J.F.R. Robertson et al., *Onapristone, a Progesterone Receptor Antagonist, as First-line Therapy in Primary Breast Cancer*, 35 EUR. J. CANCER 214 (1999) ("Robertson 1999")
2037	Gabriel Hortobagyi, *What New Drugs, Biologics, and Treatment Approaches Show Promise in Breast Cancer?*, 4 CANCER CONTROL J. 1 (Supp. 1997) ("Hortobagyi 1997")

Exhibit	Description
2038	M. Dowsett et al., *Response to specific anti-oestrogen (ICI182780) in tamoxifen-resistant breast cancer*, 345 LANCET 525 (1995) ("Dowsett 1995")
2039	Daniel F. Hayes et al., *Randomized Comparison of Tamoxifen and Two Separate Doses of Toremifene in Postmenopausal Patients With Metastatic Breast Cancer*, 13 J. CLIN. ONCOL. 2556 (1995) ("Hayes 1995")
2040	Anthony Howell et al., *Recent advances in endocrine therapy of breast cancer*, 315 BRIT. MED. J. 863 (1997) ("Howell 1997")
2041	Helge Haarstad et al., *Droloxifene—A New Anti-estrogen*, 31 ACTA ONCOL. 425 (1992) ("Haarstad 1992")
2042	AACR Journals Online
2043	Declaration of Sandra McLeskey, Ph.D. (Oct. 1, 2014) ("McLeskey Declaration")
2044	Innovative Research of America, Time Release Pellets for Biomedical Research, 2014 Product Catalog ("Innovative Research")
2045	PHYSICIAN'S DESK REFERENCE, 53rd ed., 3425-28 (1999) ("PDR 1999 Nolvadex®")
2046	PHYSICIAN'S DESK REFERENCE, 53rd ed., 2025-28 (1999) ("PDR 1999 Femara®")
2047	Winrich Rauschning et al., *Droloxifene, a new antiestrogen: Its role in metastatic breast cancer*, 31 BREAST CANCER RES. & TREAT. 83 (1994) ("Rauschning 1994")
2049	*AstraZeneca Pharmaceuticals LP v. Sagent Pharmaceuticals, Inc.*, C.A. No. 1:14-cv-03547 (RMB-KMW) (July 14, 2016 D.N.J.), Trial Transcript ("July 14 Trial Tr.")
2050	D.G. Bratherton et al., *A comparison of two doses of tamoxifen (Nolvadex*) in postmenopausal women with advanced breast cancer: 10 mg bd versus 20 mg bd*, 50 BRIT. J. CANCER 199 (1984) ("Bratherton")
2051	Adam Cohen et al., *What does the investigator need to know about the drug?*, *in* A GUIDE TO CLINICAL DRUG RESEARCH, Ch. 3 (1995) ("Cohen")
2052	Stephanie Sweetana et al., *Solubility Principles and Practices for Parenteral Drug Dosage Form Development*, 50 PDA J. PHARM. SCI. & TECH. 330 (1996) ("Sweetana")

Exhibit	Description
2053	L. Fallowfield et al., *Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer*, 17 ANNALS ONCOL. 205 (2006) ("Fallowfield 2006")
2055	John F.R. Robertson et al., *Activity of Fulvestrant 500 mg Versus Anastrozole 1 mg as First-Line Treatment for Advanced Breast Cancer: Results from the FIRST Study*, 27 J. CLIN. ONCOL. 4530 (2009) ("Robertson 2009")
2056	John F.R. Robertson et al., *Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study*, 136 BREAST CANCER RES. & TREAT. 503 (2012) ("Robertson 2012")
2057	John F.R. Robertson et al., *Fulvestrant 500 mg versus Anastrozole as a First-line Treatment for Advanced Breast Cancer: Overall Survival from the Phase II 'FIRST' Study*, 37th Annual San Antonio Breast Cancer Symposium, Publication No. S6-04 (2014) ("Robertson SABCS 2014")
2058	Matthew J. Ellis et al., *Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis from the Phase II FIRST Study*, J. CLIN. ONCOL. 1 (2015) ("Ellis 2015")
2059	I. Vergote et al., *Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy*, 79 BREAST CANCER RES. & TREAT. 207 (2003) ("Vergote 2003")
2060	John F.R. Robertson et al., *Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer*, 43 CLIN. PHARMACOKINET. 529 (2004) ("Robertson 2004")
2061	J. Bellmunt et al., *European Early Phase II Dose-Finding Study of Droloxifene in Advanced Breast Cancer*, 14 AM. J. CLIN. ONCOL. S36 (1991) ("Bellmunt 1991")
2062	Stephen Chia et al., *Double-Blind Randomized Placebo Controlled Trial of Fulvestrant Compared with Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women with Hormone Receptor-Positive, Advanced Breast Cancer: Results from EFECT*, 26 J. CLIN. ONCOL. 1664 (2008) ("Chia 2008")

Exhibit	Description
2063	Stephen R.D. Johnston et al., *Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicenter, phase 3 randomised trial*, 14 LANCET ONCOL. 989 (2013) ("Johnston 2013")
2064	J.F.R. Robertson et al., *Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant*, 92 BREAST CANCER RES. & TREAT. 169 (2005) ("Robertson 2005")
2065	S. Johnston, *Fulvestrant and the sequential endocrine cascade for advanced breast cancer*, 90 BRIT. J. CANCER S15 (Supp. 2004) ("Johnston 2004")
2066	Pharma Marketletter, *AstraZeneca's Faslodex Meets Unmet Need in Breast Cancer*, March 29, 2004, *available at* 2004 WLNR 21943944 ("Pharma Marketletter 2004")
2067	Cancer Weekly, *European Launch of Faslodex Reported, Breast Cancer*, April 13, 2004, *available at* 2004 WLNR 542429 ("Cancer Weekly April 2004")
2068	R. Jeffrey Baumann et al., *Clomiphene Analogs with Activity* In Vitro *and* In Vivo *Against Human Breast Cancer Cells*, 55 BIOCHEM. PHARMACOL. 841 (1998) ("Baumann 1998")
2069	Seppo Pyrhönen et al., *High dose toremifene in advanced breast cancer resistant to or relapsed during tamoxifen treatment*, 29 BREAST CANCER RES. & TREAT. 223 (1994) ("Pyrhönen 1994")
2070	Lars E. Stenbygaard et al., *Toremifene and tamoxifen in advanced breast cancer - a double-blind cross-over trial*, 25 BREAST CANCER RES. & TREAT. 57 (1993) ("Stenbygaard 1993")
2071	John F.R. Robertson et al., *A Good Drug Made Better: The Fulvestrant Dose-Response Story*, 14 CLIN. BREAST CANCER 381 (2014) ("Robertson 2014")
2072	C. Barrios et al., *The sequential use of endocrine treatment for advanced breast cancer: where are we?*, 23 ANNALS ONCOL. 1378 (2012) ("Barrios 2012")
2073	J.F.R. Robertson et al., *Endocrine treatment options for advanced breast cancer – the role of fulvestrant*, 41 EUR. J. CANCER 346 (2005) ("Robertson Eur. J. Cancer 2005")

Exhibit	Description
2074	"Clinical Practice Guidelines in Oncology: Breast Cancer," National Comprehensive Cancer Network, version 1 (2003) ("Clinical Practice Guidelines 2003")
2075	I. Vergote et al., *Fulvestrant, a new treatment option for advanced breast cancer: tolerability versus existing agents*, 17 ANNALS ONCOL. 200 (2006) ("Vergote 2006")
2076	A. Agrawal et al., *Bone turnover markers in postmenopausal breast cancer treated with fulvestrant – A pilot study*, 18 BREAST 204 (2009) ("Agrawal 2009")
2077	Irene Kuter et al., *Dose-dependent change in biomarkers during neoadjuvant endocrine therapy with fulvestrant: results from NEWEST, a randomized Phase II study*, 133 BREAST CANCER RES. & TREAT. 237 (2012) ("Kuter 2012")
2078	Aman U. Buzdar et al., *Fulvestrant: Pharmacologic Profile Versus Existing Endocrine Agents for the Treatment of Breast Cancer*, 40 ANN. PHARMACOTHER. 1572 (2006) ("Buzdar 2006")
2083	A. Buzdar et al., *Phase III randomized trial of droloxifene and tamoxifen as first-line endocrine treatment of ER/PgR-positive advanced breast cancer*, 73 BREAST CANCER RES. & TREAT. 161 (2002) ("Buzdar 2002")
2085	Aman U. Buzdar et al., *Phase I trial of droloxifene in patients with metastatic breast cancer*, 33 CANCER CHEMOTHER. PHARMACOL. 313 (1994) ("Buzdar 1994")
2088	J. Baselga et al., *Randomized, double-blind, multicenter trial comparing two doses of arzoxifene (LY353381) in hormone-sensitive advanced or metastatic breast cancer patients*, 14 ANNALS ONCOL. 1383 (2003) ("Baselga 2003")
2108	A. U. Buzdar et al., *Preliminary Results of a Randomized Double-Blind Phase II Study of the Selective Estrogen Receptor Modulator (SERM) Arozoxifene (AZ) in Patients (Pts) with Locally Advanced or Metastatic Breast Cancer (MBC)*, 20 PROCEEDINGS OF ASCO 45a (2001) ("Buzdar ASCO 2001")
2111	Aman Buzdar et al., *Phase II, Randomized, Double-Blind Study of Two Dose Levels of Arzoxifene in Patients With Locally Advanced or Metastatic Breast Cancer*, 21 J. CLIN. ONCOL. 1007 (2003) ("Buzdar 2003")

Exhibit	Description
2119	Aman Buzdar et al., *Anastrozole, a Potent and Selective Aromatase Inhibitor, Versus Megestrol Acetate in Postmenopausal Women With Advanced Breast Cancer: Results of Overview Analysis of Two Phase III Trials*, 14 J. CLIN. ONCOL. 2000 (1996) ("Buzdar 1996")
2125	Affidavit of Internet Archive (Oct. 2016) ("Affidavit of Internet Archive")
2136	Declaration of John F.R. Robertson, M.D. in Support of Patent Owner's Preliminary Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, IPR2016-01325, Ex. 2002 (P.T.A.B. Oct. 6, 2016) ("Robertson Mylan Decl.")
2137	Aman U. Buzdar et al., *A Phase III Trial Comparing Anastrozole (1 and 10 Milligrams), a Potent and Selective Aromatase Inhibitor, with Megestrol Acetate in Postmenopausal Women with Advanced Breast Carcinoma*, 79 CANCER 730 (1997) ("Buzdar 1997")
2138	W. Jonat et al., *A Randomised Trial Comparing Two Doses of the New Selective Aromatase Inhibitor Anastrozole (Arimidex) With Megestrol Acetate in Postmenopausal Patients With Advanced Breast Cancer*, 32A EUR. J. CANCER 404 (1996) ("Jonat 1996")
2139	P. Dombernowsky et al., *Letrozole, a New Oral Aromatase Inhibitor for Advanced Breast Cancer: Double-Blind Randomized Trial Showing a Dose Effect and Improved Efficacy and Tolerability Compared with Megestrol Acetate*, 16 J. CLIN. ONCOL. 453 (1998) ("Dombernowsky")
2140	A. Buzdar et al., *Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate*, 19 J. CLIN. ONCOL. 3357 (2001) ("Buzdar 2001")
2141	Mitchell Dowsett et al., *In Vivo Measurement of Aromatase Inhibition by Letrozole (CGS 20267) in Postmenopausal Patients with Breast Cancer*, 1 CLIN. CANCER RES. 1511 (1995) ("Dowsett Clin. Cancer Res. 1995")
2142	Paul E. Goss, *Pre-clinical and clinical review of vorozole, a new third generation aromatase inhibitor*, 49 BREAST CANCER RES. & TREAT. S59 (1998) ("Goss 1998")

Exhibit	Description
2143	K. Hoffken et al., *Fadrozole Hydrochloride (CGS 16 949 A), A Double-Blind Dose-Finding Study in Postmenopausal Patients with Advanced Breast Cancer*, 3 ANNALS ONCOL. 76 (1992) ("Hoffken")
2144	J. Bonneterre et al., *Aminoglutethimide in Advanced Breast Cancer: Clinical Results of a French Multicenter Randomized Trial Comparing 500 mg and 1 g/day*, 21 EUR. J. CANCER CLIN. ONCOL. 1153 (1985) ("Bonneterre 1985")
2145	Gabriel Hortobagyi et al., *Oral medroxyprogesterone acetate in the treatment of metastatic breast cancer*, 5 BREAST CANCER RES. & TREAT. 321 (1985) ("Hortobagyi 1985")
2146	C. Rose et al., *Treatment of Advanced Breast Cancer with Medroxyprogesterone Acetate*, 4 PROCEEDINGS OF ASCO 57 (1985) ("Rose 1985")
2147	Hiroki Koyama et al., *A Randomized Controlled Comparative Study of Oral Medroxyprogesterone Acetate 1,200 and 600 mg in Patients with Advanced or Recurrent Breast Cancer*, 56 ONCOL. 283 (1999) ("Koyama")
2148	Hyman B. Muss et al., *High- Versus Standard-Dose Megestrol Acetate in Women With Advanced Breast Cancer: A Phase III Trial of the Piedmont Oncology Association*, 8 J. CLIN. ONCOL. 1797 (1990) ("Muss")
2149	Jeffrey S. Abrams et al., *Current Status of High-Dose Progestins in Breast Cancer*, 17 SEMINARS ONCOL. 68 (1990) ("Abrams 1990")
2150	Jeffrey Abrams et al., *Dose-Response Trial of Megestrol Acetate in Advanced Breast Cancer: Cancer and Leukemia Group B Phase III Study 8741*, 17 J. CLIN. ONCOL. 64 (1999) ("Abrams 1999")
2151	W. Jonat et al., *Randomized phase II study of lonaprisan as second-line therapy for progesterone receptor-positive breast cancer*, 24 ANNALS ONCOL. 2543 (2013) ("Jonat 2013")
2152	Paul E. Goss et al., *Treatment of Advanced Postmenopausal Breast Cancer with an Aromatase Inhibitor, 4-Hydroxyandrostenedione: Phase II Report*, 46 CANCER RES. 4823 (1986) ("Goss 1986")

Exhibit	Description
2153	M. Dowsett et al., *Dose-Related Endocrine Effects and Pharmacokinetics of Oral and Intramuscular 4-Hydroxyandrostenedione in Postmenopausal Breast Cancer Patients*, 49 CANCER RES. 1306 (1989) ("Dowsett 1989")
2154	John F.R. Robertson et al., *Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial*, LANCET (Nov. 28, 2016) ("Robertson 2016")
2155	Massimo Cristofanilli, *Metastatic breast cancer: focus on endocrine sensitivity*, LANCET (Nov. 28, 2016) ("Cristofanilli")
2156	Matthew Stenger, *Phase III Trial Shows Improved Progression-Free Survival With Fulvestrant vs Anastrozole in Advanced Breast Cancer*, ASCO POST (Mar. 10, 2017) ("Stenger")