IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG,

Plaintiffs;

v.

WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED,

Defendant.

Civil Action No. 15-cv-474-RGA

TRIAL OPINION

Daniel M. Silver, MCCARTER & ENGLISH, LLP, Wilmington, DE; Nicholas N. Kallas, Charlotte Jacobsen, Christina L. Schwarz, Susanne Flanders, Jared Stringham, and Laura Fishwick, FITZPATRICK, CELLA, HARPER & SCINTO, New York, NY.

Attorneys for Plaintiffs

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Attorneys for Defendant.

December 14, 2017

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs brought this patent infringement action against Roxane Laboratories, Inc.[1] in 2015. (D.I. 1). Roxane (now West-Ward) filed Abbreviated New Drug Application ("ANDA") No. 207486, seeking to engage in the commercial manufacture, use, and sale of generic versions of Novartis's Afinitor product. (D.I. 68-1 at 7-8). The parties have stipulated that this ANDA infringes claims 1-3 of U.S. Patent No. 8,410,131 ("the '131 patent") and claim 1 of U.S. Patent No. 9,006,224 ("the '224 patent"). (D.I. 66 at ¶¶ 3-4).

At issue in this case are methods for using everolimus to treat advanced renal cell carcinoma ("RCC") and advanced pancreatic neuroendocrine tumors ("PNETs"). Everolimus, which has the formula 40-O-(2-hydroxyethyl)-rapamycin, is a derivative of rapamycin and is the active ingredient in Novartis's Afinitor product. Everolimus itself is claimed in U.S. Patent No. 5,665,772 ("the '772 patent"), which is not at issue in this case.

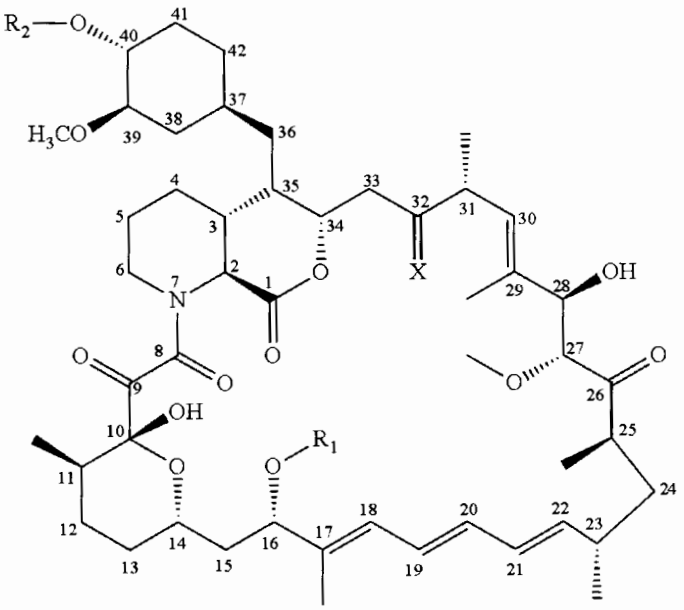
Rapamycin has long been known to have beneficial medicinal properties, such as immunosuppressive activity and anticancer activity. (Trial Transcript ("Tr.") 74:11-16).[2] Despite these beneficial properties, rapamycin is recognized as having limited utility in pharmaceutical applications as it has low bioavailability, high toxicity, and poor solubility. ('772 patent at 1:36-40; Tr. 74:16-21). Rapamycin derivatives such as everolimus, however, have been shown to have better stability and bioavailability, making them more desirable for pharmaceutical preparations. ('772 patent at 1:41-45). Temsirolimus, another rapamycin derivative, was a subject of active investigation to treat various cancers as of the priority date. (Tr. 58:12-19).

[1] On February 27, 2017, Defendant Roxane Laboratories, Inc. filed an unopposed motion to substitute West-Ward Pharmaceuticals International Limited to replace Roxane Laboratories, Inc., which the Court granted. (D.I. 55, 56). Defendant West-Ward is now the owner of the ANDA at issue in this litigation and has not contested jurisdiction of this Court. (D.I. 55 at ¶¶ 5-6).

[2] The trial transcript is available on the docket at D.I. 97-99. It is consecutively paginated.

The Court held a bench trial on September 13-15, 2017. Defendant argues that the asserted claims of the '131 and '224 patents are invalid as obvious. The '131 patent is directed to the use of rapamycin derivatives to treat solid tumors. ('131 patent at Abstract). Asserted claims 1-3 of the '131 patent require administering a therapeutically effective amount of everolimus to inhibit the growth of solid excretory system tumors, including advanced solid excretory system tumors and kidney tumors. (*Id.* at claims 1-3). Claims 1-3 of the '131 patent read as follows:

Claim 1

> 1. A method for inhibiting growth of solid excretory system tumors in a subject, said method consisting of administering to said subject a therapeutically effective amount of a compound of formula I
>
> I
>
> 
>
> wherein
> R_1 is CH_3,
> R_2 is —CH_2—CH_2—OH, and
> X is =O.

Claim 2

> 2. The method of claim 1 wherein the solid excretory system tumor is an advanced solid excretory system tumor.

Claim 3

> 3. The method of claim 1 wherein the solid excretory system tumor is a kidney tumor.

(*Id.* at claims 1-3).

The '224 patent is directed to treating endocrine tumors with an mTOR inhibitor as a monotherapy or in combination with another drug. ('224 patent at Abstract). Asserted claim 1 of the '224 patent reads as follows:

> 1. A method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need thereof a therapeutically effective amount of 40-O-(2-hydroxyethyl)-rapamycin as a monotherapy and wherein the tumors are advanced tumors after failure of cytotoxic chemotherapy.

(*Id.* at claim 1).

I. LEGAL STANDARDS

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1369 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight

bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1077-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight...." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101-02 (Fed. Cir. 2015). There must be enough evidence, however, for a finding that a given secondary consideration, if presented, exists by a preponderance of the evidence. *See Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). That burden stays always with the patent challenger. *Id.* at 1359-60.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Id.* at 1361. That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v.*

F. Hoffman-La Roche Ltd, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

II. VALIDITY OF THE '131 PATENT

A. Findings of Fact

1. The person of ordinary skill in the art ("POSA") has a medical degree and/or Ph.D. in biology, biochemistry, pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, and, if necessary, collaborates with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry.

2. The priority date for claims 1-3 of the '131 patent is February 19, 2001. (D.I. 68-1 at 3).

3. Hidalgo 2000, Hutchinson, the '772 patent, and U.S. Patent No. 6,004,973 ("the '973 patent") are prior art.

4. Hidalgo 2000 or Hutchinson and the '772 patent or the '973 patent, in view of what was known in the art, do not teach a POSA the administration of a therapeutically effective amount of everolimus to inhibit the growth of solid excretory system tumors.

5. Administration of a therapeutically effective amount of everolimus to treat advanced RCC would not have been obvious to a POSA.

B. Conclusions of Law

Defendant contends that administration of a therapeutically effective amount of everolimus to treat advanced RCC would have been obvious to a POSA. (D.I. 91 at 29). The essence of Defendant's obviousness argument is that knowledge in the art about the biology of advanced RCC, mTOR[3] inhibitors, and safe dosing ranges of everolimus, alongside phase I temsirolimus clinical trial results in advanced RCC, would have given a POSA a reasonable expectation of success of effectively treating advanced RCC with everolimus, as both everolimus and temsirolimus are mTOR inhibitors. (*Id.* at 14). Therefore, according to Defendant, the invention as a whole would have been obvious to a POSA.

[3] mTOR stands for the "mammalian target of rapamycin."

1. Scope and Content of the Prior Art

i. Background

Defendant asserts that "the prior art established a strong scientific rationale for using an mTOR inhibitor to treat advanced RCC." (*Id.* at 30). Plaintiffs counter that many different agents were under investigation for the treatment of advanced RCC, and that the relative success of immunotherapies would have motivated a POSA to investigate immunostimulants rather than immunosuppressants like everolimus. (D.I. 93 at 13; *see, e.g.*, JTX-30 at pp. 869-75; PTX-79 at pp. 43-45).

As of February 2001, clinical trials for advanced RCC treatments included immunotherapies (PTX-79 at p. 43-45), chemotherapy combinations (PTX-127 at p. 2425), and agents targeting growth factors (JTX-5 at p. 361). Temsirolimus was also in clinical trials to treat cancer at that time, but no mTOR inhibitor had been approved to treat any type of cancer (Tr. 463:6-15, 591:9-592:3), and no clinical data existed for everolimus as an antitumor agent (*id.* at 188:23-189:3, 464:22-24). Advanced RCC was difficult to treat (*id.* at 69:15-70:4), as demonstrated by clinical trial failures in immunotherapies and chemotherapy combinations (*id.* at 590:7-20). Despite these failures, scientists continued to develop and to test chemotherapy combination treatments for advanced RCC because they were active against a variety of cancers and many combinations were available. (D.I. 93 at 14; Tr. 461:2-462:8). Scientists continued to pursue immunotherapy treatments for advanced RCC because they had demonstrated the greatest success to date, with FDA approval for interleukin 2 ("IL-2"). (D.I. 93 at 13; Tr. 69:15-18, 431:7-11, 437:10-20). As of February 2001, there were no completed clinical trials of mTOR inhibitors for treatment of advanced RCC. (Tr. 595:13-24). The prior art also disclosed high failure rates of cancer drugs during clinical trials: more than 70% of cancer drugs failed during phase II, and a majority of cancer drugs failed during phase III. (*Id.* at 202:17-20, 518:18-23). I conclude that in

February 2001, (1) a failure of a particular agent for treatment of advanced RCC would not have dissuaded a POSA from pursuing as a whole the class of agents to which the failed agent belonged, and (2) as a class of drugs, mTOR inhibitors represented a relatively new line of research for treatment of advanced RCC.

Defendant asserts that the molecular biology of advanced RCC would have motivated a POSA to pursue treatment using mTOR inhibitors. (D.I. 91 at 24-28, 41; D.I. 92 at 15-16). According to Dr. Cho, the prior art established that in renal cell cancer, von Hippel-Lindau ("VHL") tumor suppressor gene function loss leads to the accumulation of hypoxia-inducible factor 1 ("HIF-1"), resulting in over-secretion of vascular endothelial growth factor ("VEGF"), which in turn leads to increased angiogenesis and cancer growth. (Tr. 127:7-128:2, 129:12-23).

The prior art's mixed results in studies investigating the molecular biology of advanced RCC had not explained the biology as clearly as Dr. Cho stated. As of February 2001, advanced RCC tumors were known to be highly vascularized (*id.* at 129:14-18), and several studies had demonstrated that a majority (55-60%) of clear cell RCC patients had VHL tumor suppressor gene mutations (*id.* at 132:4-133:13; JTX-11 at p. 793). It was also known that HIF-1 played a role in regulating VEGF gene expression, VHL gene inactivation was associated with VEGF gene expression, and VEGF gene expression correlated with blood vessel density in many tumor types. (JTX-29 at p. 76). The prior art also linked VHL-defective RCC cell lines to HIF-1 activation, hypothesizing that HIF-1 activation "may underlie the angiogenic phenotype of VHL-associated tumors," but also cautioning that HIF-1 activation may not be a "sufficient explanation for oncogenesis." (JTX-20 at pp. 271, 274). Immunohistochemical studies spanning multiple types of cancer cells had demonstrated HIF-1α overexpression in only one of the two samples of human advanced RCC cells studied. (Tr. 137:11-138:21; JTX-36 at pp. 5831-32, 5834).

The prior art also implicated multiple pathways in HIF-1 activation in human cancer (JTX-29 at p. 90 Fig. 4), and noted inconsistent results for HIF-1α expression across RCC biopsies and RCC cell lines (*id.* at p. 81). Reviewing studies of HIF-1 in human cancer, the Semenza paper was optimistic about the future "potential efficacy of combination therapy utilizing an angiogenesis inhibitor and a HIF-1 inhibitor" (*id.* at p. 89 (citations omitted)), but concluded that "the role of HIF-1α expression in [RCC] requires further analysis" (*id.* at p. 81; *accord* JTX-7 at p. 809 ("However, there is still much to learn on, firstly, the exact mechanisms by which mTOR controls the G1/S transition and, secondly, on any other cellular targets of rapamycin.")). Therefore, although the prior art provided a working hypothesis for the molecular biology of advanced RCC, it revealed multiple potential targets in the mTOR pathway, and scientists acknowledged that the precise role of HIF-1 in the molecular biology of advanced RCC was not completely understood.

Similarly, as of the priority date, some evidence existed to support the hypothesis that HIF-1α overexpression was related to the mTOR pathway, but the precise mechanism of action underlying that relationship was not clear. (*See, e.g.*, JTX-37 at p. 1543). The Zhong 2000 study examined human prostate cancer cell lines and concluded that "HIF-1α-dependent gene transcription and the expression of HIF-1-regulated gene product are modulated by the activity of the PI3K/AKT/FRAP pathway" in prostate cancer cells. (*Id.* at p. 1543; *see also id.* at p. 1545). From this, the authors further concluded that increased HIF-1α expression can be induced by both genetic mutations and physiological stimulation, and that HIF-1 expression "may play a major role in promoting angiogenesis and metabolic adaptation in [prostate cancer] and other common solid tumors." (*Id.* at p. 1545). The authors demonstrated correlations between treatment with either rapamycin or a phosphoinositide 3-kinase ("PI3K") inhibitor and reduced HIF-1α expression and VEGF secretion in the prostate cancer cell lines. (Tr. 140:8-20; JTX-37 at pp. 1543, 1544). Based

on these results and prior data, the authors hypothesized that "pharmacological inhibition of HIF-1 activity may represent a useful treatment strategy," and that "the effect of PI3K/AKT/FRAP pathway inhibitors on HIF-1α expression may provide a basis for therapeutic efficacy." (JTX-37 at p. 1545).

The Zhong 2000 authors cautioned, however, that additional studies would be required to determine the precise mechanism of action of the PI3K/protein kinase B ("AKT")/FKBP12 rapamycin-associated protein ("FRAP") pathway as it related to HIF-1α expression. (*Id.* at p. 1543; *accord* JTX-27 at p. 3512 ("Clearly, additional experiments are required to establish the relationship between deregulated PI3K-AKT activity and rapamycin sensitivity in human cancer cells."); JTX-29 at p. 91 ("[T]he accelerating pace of discovery [regarding the role of HIF-1 in cancer biology] hopefully will provide sufficient momentum for the transition from basic science to clinical application in the near future.")).

Finally, Defendant asserts that the prior art established a clear preference for an orally-administered cancer treatment. (D.I. 91 at 28 (citing JTX-10 at Abstract (identifying pharmacoeconomic principles, patient preference, and improved quality of life as driving the pursuit of oral formulations, and noting bioavailability and patient compliance concerns as limitations to oral chemotherapy formulations))). Plaintiffs disagree, arguing that "whether a drug [c]an be administered intravenously or by subcutaneous injection or by orally is not one of the important points for both physicians and patients in choosing a therapy." (Tr. 477:13-17). Whereas Plaintiffs' argument rests on their expert's experience, Defendant's argument finds support in the prior art. I agree with Defendant that the prior art established a general preference for orally-administered cancer treatments.

In light of the preference for oral cancer treatments, the molecular biology of advanced

RCC, and the prior art relating to mTOR inhibitors, Defendant argues a POSA would have been motivated to pursue everolimus to treat advanced RCC with a reasonable expectation of success. (D.I. 91 at 29). The prior art disclosed general antiproliferative properties of everolimus, and that oral administration of everolimus was safe and tolerable in treating renal and liver transplant patients. (JTX-19 at p. 160; JTX-22 at p. 694). According to Dr. Cho, since everolimus and rapamycin both target the mTOR pathway, a POSA would reasonably expect everolimus to have the same antiproliferative effect in advanced RCC patients that rapamycin had in prostate cancer cells. (D.I. 91 at 27; Tr. 139:20-140:1). This assertion is undermined, however, by Dr. Cho's admission that a POSA would not generalize results of a particular treatment across different cancer models. (Tr. 203:16-22). Additionally, although they are related compounds, rapamycin, temsirolimus, and everolimus differ in various pharmacological properties such as their binding affinities for FKBP-12 (*id.* at 523:18-524:4 (citing JTX-25 at p. 38)), elimination half-lives (Tr. 526:24-527:20 (citing JTX-22 at p. 703)), and the correlation between dose and drug duration in the bloodstream (Tr. 526:1-22 (citing JTX-22 at p. 702)). Therefore, the prior art at most would have identified an oral formulation of everolimus as one of many potential treatment options for advanced RCC.

Collectively, the background prior art disclosed a variety of approaches under development to treat advanced RCC, including the use of temsirolimus, an mTOR inhibitor, which was in the early stages of clinical development. It cautioned, however, that the role of HIF-1 and the mTOR pathway in the molecular biology of advanced RCC was not completely understood, and that cancer treatments generally demonstrated high failure rates at phase II and phase III clinical trials. The prior art also taught a preference for oral formulations for cancer treatments.

ii. Asserted Prior Art References

(a) Hidalgo 2000

The Hidalgo 2000 reference discusses the clinical development of rapamycin and temsirolimus as anti-cancer agents and the rapamycin-sensitive signal transduction pathways underlying rapamycin's antitumor mechanisms of action. (JTX-14 at pp. 6680, 6683; Tr. 82:4-7). Hidalgo 2000 includes summaries of the preliminary results of two phase I temsirolimus dose-finding studies (Hidalgo Abstract (JTX-15) and Raymond Abstract (JTX-24)) designed to determine the maximum tolerated dose of temsirolimus in patients with a variety of solid tumors. (JTX-14 at p. 6683; Tr. 83:18-84:13, 206:16-19, 209:10-13). Based on promising preliminary results that temsirolimus "consistently induced tumor regressions at relatively nontoxic doses in the phase I studies," Hidalgo 2000 notes, "Disease-directed efficacy studies of [temsirolimus] in a broad range of tumor types will be initiated following the completion of the phase I studies." (JTX-14 at p. 6683; Tr. 85:6-11). It is undisputed that Hidalgo 2000 does not provide any information regarding the use of everolimus to treat any form of cancer. (Tr. 202:24-203:3). It is further undisputed that Hidalgo 2000 does not suggest that rapamycin had demonstrated preclinical activity in RCC (*id.* at 203:10-15), and that both the Hidalgo Abstract study (*id.* at 209:4-17; JTX-15) and the Raymond Abstract study (Tr. 206:8-23; JTX-24) were not limited to patients with advanced RCC.

(b) Hutchinson

Hutchinson is a December 2000 publication that summarizes the clinical development of temsirolimus, and includes a review of updated results from the same phase I temsirolimus studies described in Hidalgo 2000. (JTX-16 at p. 198; Tr. 98:15-99:7). More specifically, Hutchinson notes one partial response, two minor responses, and three minor responses or prolonged stable

disease in patients with RCC across both phase I studies, and further states that a phase II temsirolimus trial in advanced RCC was underway in the United States. (JTX-16 at p. 198; Tr. 201:21-202:1). It is not disputed that Hutchinson was not formally peer reviewed and does not discuss everolimus. (JTX-16 at p. 198; Tr. 196:17-197:5).

(c) '772 Patent

U.S. Patent No. 5,665,772 issued on September 9, 1997. The '772 patent discloses certain novel derivatives of rapamycin (*id.* at 1:41-2:19), including everolimus; notes the general antitumor activity of rapamycin (*id.* at 1:34-36, 4:1-2); lists everolimus as a preferred compound for immunosuppressive use (*id.* at 2:55-56); and discloses various dosages of everolimus (*see, e.g.*, *id.* at 4:29-48). The '772 patent further claims inducing an immunosuppressant effect by administering everolimus in an effective amount. (*Id.* at 22:19-22). It is undisputed that the '772 patent does not contain any preclinical or clinical data demonstrating an antitumor effect of everolimus or any explicit disclosure that everolimus would be effective to treat advanced RCC. (Tr. 193:3-195:9).

(d) '973 Patent

U.S. Patent No. 6,004,973 issued on December 21, 1999. The '973 patent discloses oral formulations of rapamycin derivatives useful for treating, among other things, organ or tissue transplant rejection, autoimmune disease, asthma, multi-drug resistance, proliferative disorders such as tumors, fungal infections, inflammation, and infection. (*Id.* at 4:60-5:47). The '973 patent further discloses everolimus as a preferred compound and discloses various oral dose ranges for everolimus. (*Id.* at 2:5-11; 5:48-55). It is undisputed that the '973 patent does not contain preclinical or clinical data demonstrating any antitumor effect of everolimus, and does not suggest that everolimus would be effective to treat advanced RCC. (Tr. 196:4-14).

2. Comparing Prior Art and Claimed Subject Matter

Defendant's expert, Dr. Cho, opines that a POSA would have been motivated to administer therapeutically effective amounts of everolimus to inhibit the progression of advanced RCC with a reasonable expectation of success. (*Id.* at 60:8-15). According to Dr. Cho, the claimed invention would have been obvious over the teachings of Hidalgo 2000 or Hutchinson in combination with the '973 patent or the '772 patent, in view of the general knowledge in the art.

Specifically, Dr. Cho stated that the prior art references Hidalgo 2000 and Hutchinson showed that temsirolimus monotherapy had promising clinical activity in advanced RCC in phase I clinical trials. (*Id.* at 84:20-85:11, 97:12-98:4). According to Dr. Cho, a then-ongoing phase II clinical trial of temsirolimus in advanced RCC patients would have indicated to a POSA that the phase I results demonstrated unusually high activity in advanced RCC patients relative to patients with other cancers because the advanced RCC phase I results were sufficient to justify a phase II trial in advanced RCC. (*Id.* at 97:22-98:14 (discussing JTX-16)). Therefore, Defendant argues, either one of these prior art references, combined with the '772 or the '973 patents' disclosures of general antitumor properties of and oral dose ranges for pharmaceutical compositions of everolimus, would lead a POSA to believe everolimus could be administered in a therapeutically effective amount as a monotherapy to treat advanced RCC. (Tr. 108:12-20, 111:11-112:5, 157:17-159:5). Dr. Cho further opined that a POSA would be able to arrive at the claimed therapeutically effective dose of everolimus through routine experimentation. (*Id.* at 155:4-13). Thus, Defendant contends that combining these references in view of what was known in the art about advanced RCC would suggest to a POSA all limitations of claims 1-3 of the '131 patent. (D.I. 91 at 32-33).

The parties do not dispute that a POSA would have recognized the need for an effective treatment for advanced RCC, as it was difficult to treat and the available treatments had shortcomings. (*Id.* at 29; D.I. 93 at 11; Tr. 69:15-70:4, 439:7-21). The parties disagree, however,

over whether the prior art as a whole would have motivated a POSA to start with mTOR inhibitors, including everolimus, to treat advanced RCC. (Tr. 159:10-160:1, 428:23-429:3; D.I. 93 at 17). Plaintiffs assert that because Dr. Cho restricted his review and analysis to art regarding mTOR inhibitors, he failed to consider the full scope of the relevant prior art, and Defendant has failed to prove obviousness because it has failed to prove a motivation to select everolimus over other compounds. (D.I. 93 at 12 (citing Tr. 71:24-72:14)). Defendant counters that Plaintiffs' interpretation improperly requires Defendant to prove that everolimus was a preferred compound. (D.I. 92 at 10-11 (citing *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013) ("[A] finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed . . . is the preferred, or most desirable, combination.")).

I find that the relevant prior art would have included art relating to treatments beyond mTOR inhibitors. Against the backdrop of a strong desire to find an effective advanced RCC treatment and the general preference for orally-administered cancer treatments, promising temsirolimus phase I data, and shared properties of temsirolimus and everolimus, a POSA would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors, including advanced RCC. Dr. Cho acknowledged that, in addition to mTOR inhibitors, a POSA would have considered the many other options for the treatment of advanced RCC then under development, including immunotherapies and a wide variety of chemotherapy combinations. (Tr. 176:17-177:8, 447:6-448:3, 452:6-12, 461:17-462:4). Rather than reviewing references covering the entire scope of the prior art, Dr. Cho restricted his review to references concerning the mTOR pathway. (*Id.* at 71:24-72:14). To support the limited scope of Dr. Cho's prior art review, Defendant cites the failures associated with immunotherapies and

chemotherapies, the molecular biology of RCC, and active research regarding the mTOR pathway. (D.I. 92 at 12; Tr. 72:15-73:7). The prior art, however, taught that failures with a particular type of treatment category, such as immunotherapies, would not necessarily deter future development of treatments within that category. (Tr. 461:2-462:8, 590:7-20). This, along with the variety of treatments in development to treat advanced RCC, and the knowledge gaps in the molecular biology of advanced RCC, would have led a POSA searching for an advanced RCC treatment to consider prior art references beyond those involving the mTOR pathway. By limiting the scope of his prior art review to references regarding the mTOR pathway, Dr. Cho allowed hindsight bias to inform his analysis. Defendant has failed to prove by clear and convincing evidence that a POSA would have been motivated to select everolimus.

Even if a POSA would have been motivated to select everolimus to treat advanced RCC, I find that the asserted combinations would not have provided a POSA a reasonable expectation of success in using everolimus to treat advanced RCC. Defendant asserts that since there are no inconsistent clinical results in the use of mTOR inhibitors to treat advanced RCC, the hypothesis that mTOR inhibitors would be effective to treat advanced RCC is supported by a reasonable expectation of success. (D.I. 92 at 13-14). Dr. Cho admitted, however, that a POSA would not have a reasonable expectation of success that a drug would be effective to treat a particular type of cancer based only on the drug's phase I clinical trial results, or on the fact that the drug had entered phase II clinical trials. (Tr. 202:7-15). Additionally, the weight of the consistent clinical results here is diminished by small sample sizes and the fact that the available data came from phase I studies designed to test safety, not efficacy. (JTX-15; JTX-16; JTX-24). The studies discussed in the asserted combinations teach that seven advanced RCC patients across two temsirolimus phase I dose-finding studies demonstrated either some response or prolonged stable

disease. (JTX-15; JTX-16; JTX-24). Since the studies do not report the total number of advanced RCC patients enrolled, there is no indication of the number of RCC patients who did not experience any clinical benefit. (*See* JTX-15; JTX-24). Although a phase II temsirolimus study was underway, data from that study was not yet available. (*See* JTX-16).

Everolimus and temsirolimus also differ in pharmacological properties relevant to treatment, such as binding affinities for FKBP-12 (Tr. 523:18-524:4 (citing JTX-25 at p. 38)) and elimination half-lives (Tr. 526:24-527:20 (citing JTX-22 at p. 703)). Such pharmacological differences, along with the high failure rates of cancer drugs in phase II and phase III clinical trials, and the fact that the molecular biology of advanced RCC was not firmly established (particularly with respect to the role of HIF-1), diminish the relevance of the temsirolimus phase I clinical trials to everolimus. Therefore, despite (1) the existing temsirolimus phase I data, (2) the everolimus dosing disclosures in the '772 and '973 patents, and (3) existing knowledge of the mTOR pathway, Defendant has failed to establish by clear and convincing evidence that a POSA would have reasonably expected everolimus to effectively treat advanced RCC as of February 2001.

Finally, Defendant argues that the prior art's lack of clinical data for everolimus to treat advanced RCC "does not render the asserted claims nonobvious when the'131 Patent itself does not cure those deficiencies." (D.I. 91 at 39 (citing *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005)). The holding in *Merck* is not as broad as Defendant asserts. In *Merck*, the patentees claimed methods for treating and preventing osteoporosis using a once-weekly dosing regimen. *Merck*, 395 F.3d at 1366-67. Two prior art articles disclosed all elements of the claimed invention, differing from the invention "only in terms of a minor [5mg] difference in dosage." *Id.* at 1375. Neither the patent nor the prior art articles explained how their disclosed once-weekly dosing regimens would avoid the adverse side effects associated with the traditional

daily dosing regimen of the drug at issue. *Id.* at 1374. Since the patent set "forth no human or clinical or laboratory data showing the safety and tolerability of the [claimed] treatment methods," the court concluded that "the claimed invention adds nothing beyond the teachings of th[e prior art] articles." *Id.* Contrary to Defendant's assertions here, the *Merck* court did not hold that a patentee may never rely on the absence of clinical data in the prior art when the asserted patent does not contain clinical data. *Merck* dealt with the scenario where the prior art disclosed all elements of the claimed invention, with only a minor difference in a dosage, and the patent provided no reason for the departure from the prior art dosage. Here, no prior art reference discloses the use of everolimus to treat advanced RCC. The prior art does not disclose all elements of the asserted claims, and the holding in *Merck* does not apply.

3. Level of Ordinary Skill in the Art

The parties agree that the POSA would have a medical degree and/or Ph.D. in biology, biochemistry, pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, and would collaborate with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry. (Tr. 62:6-20, 425:19-426:8). They dispute whether a POSA would have experience with the mTOR pathway and rapamycin and its analogs. (*Id.* at 62:10-16; 426:13-21). Both parties' experts testified, however, that their opinions would not change if the Court were to adopt the opposing expert's definition of a POSA. (*Id.* at 63:1-4; 428:18-21). Given the incomplete knowledge of the molecular biology of advanced RCC and the variety of treatment avenues for advanced RCC being pursued as of the priority date, I find that a POSA would not necessarily have experience with the mTOR pathway and rapamycin and its analogs.

Therefore, the POSA would have a medical degree and/or Ph.D. in biology, biochemistry,

pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, and would collaborate with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry.

4. Secondary Considerations

During trial, the parties agreed that there are no secondary considerations of nonobviousness relevant to the '131 patent. (*Id.* at 639:15-22). As there are no relevant secondary considerations, they play no part in the obviousness analysis.

Considering the evidence as a whole, Defendant has not shown by clear and convincing evidence that claims 1-3 of the '131 patent are invalid as obvious.

III. VALIDITY OF THE '224 PATENT

A. Findings of Fact

1. The POSA has a medical degree and/or Ph.D. in biology, biochemistry, pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, and, if necessary, collaborates with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry.

2. The priority date for claim 1 of the '224 patent is November 21, 2005. (D.I. 68-1 at 5).

3. Duran, Dancey, Tabernero, von Wichert, and U.S. Patent Publication No. 2004/0147541 ("the '541 publication") are prior art.

4. Duran, Dancey, and Tabernero, in view of what was known in the art, do not teach a POSA the administration of a therapeutically effective amount of everolimus as a monotherapy to inhibit the growth of advanced PNETs after the failure of cytotoxic chemotherapy.

5. Duran, Dancey, and Tabernero, in view of von Wichert and what was known in the art, do not teach a POSA the administration of a therapeutically effective amount of everolimus as a monotherapy to inhibit the growth of advanced PNETs after the failure of cytotoxic chemotherapy.

6. Duran, Dancey, and Tabernero, in view of '541 publication and what was known in the art, do not teach a POSA the administration of a therapeutically effective amount of everolimus as a monotherapy to inhibit the growth of advanced PNETs after the failure

of cytotoxic chemotherapy.

7. Administration of a therapeutically effective amount of everolimus as a monotherapy to treat advanced PNETs after the failure of cytotoxic chemotherapy would not have been obvious to a POSA.

B. Conclusions of Law

Defendant contends that administration of a therapeutically effective amount of everolimus as a monotherapy to treat patients with advanced PNETs after the failure of cytotoxic chemotherapy would have been obvious to a POSA. The essence of Defendant's obviousness argument is that the prior art teaches that mTOR inhibitors were demonstrated to be safe and effective to treat advanced PNETs in phase II and preclinical models, including after the failure of cytotoxic chemotherapy, and that everolimus would have been an obvious substitute for temsirolimus because both drugs are mTOR inhibitors with shared properties. Therefore, according to Defendant, the invention as a whole, including all limitations, would have been obvious to a POSA.

1. Scope and Content of the Prior Art

i. Background

The vast majority of new oncology drugs fail during development: only 5% progress from the first in-human trials to FDA approval, and 70% fail during phase II trials. (Tr. 721:8-24; PTX-80 at pp. 711-12). Drugs that demonstrate promising phase I results often fail at phase II. (*See, e.g.*, PTX-226 at p. 235 (noting partial responses to CI-980 treatment in phase I study of patients with colon cancer); PTX-207 at p. 573 (CI-980 treatment failed to demonstrate clinical activity in phase II study in colon cancer patients)). Even at phase III, 59% of cancer treatments fail. (Tr. 838:22-839:1; PTX-80 at p. 712). Therefore, a POSA would not rely on promising phase I results as a reasonable predictor of treatment success at phase II or phase III.

Neuroendocrine tumors arise from endocrine cells and are slow-growing tumors that include PNETs and carcinoids. (JTX-48). PNETs arise in the pancreas whereas carcinoids arise outside the pancreas, and these two tumor types were known to differ in clinical behavior (PTX-192 at p. 1133), incidence (JTX-63 at p. 57), molecular genetics (*id.*), and responses to pharmacotherapies (PTX-208 at p. 311). Due to these differences, PNETs and carcinoids were usually evaluated separately in clinical trials. (PTX-158 at p. 1545; PTX-159 at p. 233).

As of November 2005, the only FDA-approved treatment for advanced PNETs was streptozocin, a cytotoxic chemotherapy. (Tr. 661:8-17). Since cytotoxic chemotherapies had demonstrated high rates of tumor recurrence or progression in addition to significant toxicities, there was a need for effective treatments for advanced PNETs, particularly after the failure of cytotoxic chemotherapy. (JTX-91 at p. 47; Tr. 661:18-662:19). Advanced PNET patients who had previously failed cytotoxic chemotherapy were particularly difficult to treat, and showed significantly worse outcomes than chemotherapy-naïve advanced PNET patients. (Tr. 663:4-18; PTX-170 at p. 518; PTX-217 at p. 1142 (1992 study stating, "No agent appears to be active as second line therapy of" advanced PNETs)). This was true even in studies where patients received second-line cytotoxic chemotherapy with a mechanism of action that differed from that of the primary cytotoxic chemotherapy previously administered. (Tr. 664:6-666:23; PTX-170 at p. 518; PTX-261 at pp. 521-22; PTX-217 at p. 1141).

As of the priority date, the molecular mechanisms underlying PNETs and the mTOR pathway's role in human cancers were not completely understood. (*See, e.g.*, JTX-45 at p. 317 ("[T]he antitumor activity of rapamycin may depend on the function of cell-cycle regulatory proteins as well as upstream cellular signaling through mTOR."); JTX-53 at p. 73 (concluding that study results will aid in designing future studies aimed at "the identification of key growth factor

pathways involved in the formation of [PNET] tumors"); JTX-87 at pp. 632-33 ("The challenge for the future will be to dissect further the molecular signaling pathways modulated by rapamycin in order to appreciate fully the molecular mechanisms underpinning sensitivity or resistance to mTOR inhibition.")). mTOR had been recognized as an important target for anticancer therapeutics development. (JTX-45 at p. 313; JTX-87 at p. 621; JTX-69 at pp. 198-99). It was just one of multiple components in various pathways identified as targets for cancer therapeutics. For example, receptor tyrosine kinases, including receptor tyrosine kinases in the mTOR pathway, were viewed as promising. (Tr. 356:7-357:6, 675:2-677:4; 676:10-21, PTX-167 at p. 7484; JTX-69 at pp. 199-200). The P70S6 kinase pathway, the ras/raf-1 pathway, protein kinase C, mTOR inhibitors, PI3K inhibitors, AKT inhibitors, and receptor tyrosine kinase inhibitors were among the options for therapeutic targets to treat advanced PNET. (Tr. 675:2-677:4; JTX-5 at p. 368). Several receptor tyrosine kinase inhibitors were in phase III clinical trials for human cancers. (Tr. 677:24-678:11).

Labeling it an "experimental therapy," Oberg proposed rapamycin as one of several new compounds to treat neuroendocrine tumors, noting that rapamycin may block signal transduction through the mTOR pathway. (JTX-63 at p. 60). Oberg also noted that clinical trials of rapamycin as a monotherapy or a combination therapy were planned. (*Id.*). Among the other compounds Oberg identified were the peptide receptor radionuclide therapies ^{90}Y-DOTA-octreotide and ^{177}LU-DOTA-octreotate, which the prior art characterized as "very promising, especially in patients with inoperable or metastatic gastroenteropancreatic (GEP) tumors." (*Id.* at p. 60; JTX-68 at p. 596).

Reviewing the clinical development of mTOR inhibitors, Rao noted ongoing phase I and phase II clinical trials of mTOR inhibitors to treat a variety of cancers, though none of these trials

involved patients with neuroendocrine tumors. (JTX-87 at pp. 628-30). Increased selectivity and lower toxicity than classic cytotoxic chemotherapy agents were two of the perceived advantages of mTOR inhibitors. (*Id.* at p. 621). Rao deemed preliminary everolimus combination therapy results "exciting in that they suggest that combinations of signal transduction inhibitors may be useful to overcome drug resistance." (*Id.* at p. 632). After noting that drug-drug interactions are a consideration with rapamycin analogs and the "excessive hematological toxicity" observed in an everolimus-gemcitabine combination therapy, Rao cautioned that "combination studies require careful evaluation of toxicities." (*Id.*). Rao stated that the results of ongoing mTOR combination therapy clinical trials would "provide important directions for future clinical testing." (*Id.*).

Some prior art references discuss rapamycin and its analogs as a class of drugs, noting that they are all mTOR inhibitors and demonstrate similar cell-line sensitivity patterns of inhibition. (*See, e.g.*, *id.* at p. 621; JTX-50 at p. 112). Despite these similarities, however, rapamycin, temsirolimus, and everolimus were known to have clinically relevant biological differences. These included differences in half-life, oral bioavailability, FKBP-12 binding affinity, and effects on cellular metabolism. (Tr. 750:16-753:5, 401:19-23; JTX-25 at p. 38; JTX-45 at pp. 318-20; PTX-184 at p. 514). As of the priority date, no clinical data had compared the anticancer efficacy of everolimus with rapamycin in humans. (Tr. 359:10-360:17, 682:17-19, 712:5-713:21).

ii. Asserted Prior Art References

(a) Duran

Duran is a June 2005 publication that reports the interim results of an uncontrolled phase II temsirolimus study in patients with metastatic neuroendocrine carcinomas. (JTX-48). Metastatic neuroendocrine carcinomas are advanced neuroendocrine tumors that encompass several tumor types, including NETs, PNETs, and carcinoids. (Tr. 362:1-19). Patients were

eligible to enroll in the study if "they demonstrated 35% increase in tumor volume, clinical deterioration or new tumor focus in the last 6 months." (JTX-48). Of the 23 patients enrolled at the time, 15 were evaluable for response, and 10 had achieved prolonged stable disease, including one patient with tumor rescission and two patients demonstrating a clinical benefit. (*Id.*). Duran concluded, "Temsirolimus appears to have antitumor activity in [neuroendocrine tumors], study accrual is ongoing." (*Id.*). It is not disputed that Duran did not expressly disclose the number of enrolled patients with advanced PNETs. (*See id.*). Nor did it disclose whether any of the patients evaluable for response had advanced PNETs or had advanced PNETs after the failure of cytotoxic chemotherapy. (Tr. 367:5-8). Duran also did not disclose the tumor types for the 10 patients that achieved prolonged stable disease. (*Id.* at 367:9-12).

Plaintiffs assert that a POSA would not rely on the preliminary findings reported in Duran because interim observations are subject to change, and because it is unclear from the initial results whether the observed effects are due to temsirolimus or the natural progression of advanced neuroendocrine tumors. (D.I. 93 at 37-38 (citing JTX-58 at p. 463; PTX-193 at pp. 937-38)). Defendant counters that a POSA would have expected the Duran study to include patients with PNETs since 25% of all neuroendocrine tumors are PNETs. (D.I. 92 at 20 (citing Tr. 684:16-24)). Although Duran disclosed promising preliminary results of cancer treatment with temsirolimus, a POSA would have recognized the limitations of an uncontrolled study and would have waited for the final results before relying on this study to predict neuroendocrine tumor responses to mTOR inhibitors, especially considering differences in properties between everolimus and temsirolimus. (*See, e.g.*, JTX-25 at p. 38; JTX-22 at pp. 702-03).

(b) Dancey

Dancey is an April 2005 review describing the mechanisms of action, clinical data, and existing and potential clinical uses for mTOR inhibitors. (JTX-45). Dancey discloses that rapamycin and its derivatives were known to inhibit cell proliferation by inducing G1 phase arrest and to induce apoptosis in some models while demonstrating limited normal tissue toxicity. (JTX-45 at p. 316). Additionally, Dancey teaches that "activity, metabolism, and toxicity profiles would be expected to overlap" for rapamycin, temsirolimus, and everolimus given their structural similarities, but that pharmacokinetic differences in these drugs may also lead to differences in clinical activity and toxicity. (*Id.* at p. 319). Pharmacological differences between temsirolimus and everolimus include variation in terminal half-life and bioavailability in some patient populations. (*Id.* at pp. 318-19, 320, Table 1). "Significant interindividual pharmacokinetic variability of everolimus and rapamycin has been reported." (*Id.* at p. 319). As Dancey also notes, several questions remained regarding the molecular biology underlying rapamycin's antitumor activity and its relation to the mTOR pathway. Dancey explains that it was known that rapamycin does not inhibit all cellular activities of mTOR (*id.* at p. 314), but "the mechanism by which rapamycin inhibits mTOR is unclear" (*id.* at p. 316), and "the means by which rapamycin induces antiproliferative effects are not completely understood" (*id.* at p. 317). Therefore, "mTOR function in normal and malignant cells [would] require[] further elucidation." (*Id.* at p. 314).

Some cancers were resistant to mTOR inhibitors in clinical models. (*See, e.g.*, *id.* at p. 317 ("Mutations or defects of mTOR-regulated proteins . . . also render cells insensitive to rapamycin."); JTX-87 at p. 624 ("Pre-clinical and early clinical results demonstrate that only a subset of tumors will respond to rapamycin-based therapies."); PTX-43 at p. 357 (reporting no efficacy of mTOR inhibitor temsirolimus in phase II study of brain cancer patients); PTX-93 at

p. 1047 (reporting insufficient efficacy in phase II temsirolimus study of skin cancer to warrant further evaluation)). Although Dancey does not discuss advanced PNETs, it discloses that temsirolimus and everolimus were under evaluation for treatment of some of the same tumor types in ongoing phase II clinical trials, and that temsirolimus was under phase II evaluation for neuroendocrine tumors. (JTX-45 at p. 320, Table 1). Dancey also notes that existing preclinical studies suggest that rapamycin, temsirolimus, and everolimus would have similar antitumor effects, but cautioned, "Results from clinical trials will be required to determine whether apparent similarities/differences seen in nonclinical trials will correlate with clinical outcomes." (*Id.* at p. 318). Phase II everolimus clinical data was not yet available, and limited preliminary phase I everolimus clinical data suggested that everolimus combinations may necessitate dosing and schedule modifications from the usual doses and schedules of individual drugs when those drugs are used in combination therapies. (*Id.* at p. 322). Preliminary phase II data in temsirolimus had demonstrated objective response rates of 7-10% in patients with advanced RCC and advanced breast cancer, and an objective response rate of 44% in mantle cell lymphoma. (*Id.* at p. 321).

Dancey concludes that existing clinical trial results demonstrate that mTOR inhibitors are generally well-tolerated, and may induce prolonged stable disease, but rapamycin and its analogs do not inhibit all cellular activity of mTOR, and they "may not be the sole, or even the optimal, means of mTOR inhibition." (*Id.* at p. 324). Development of rapamycin and its analogs as cancer treatments would thus require additional basic science and clinical research. (*Id.*). Dancey notes that the rapamycin-insensitive functions of mTOR "suggest that direct inhibitors of the mTOR kinase domain will display substantially broader anticancer activities than rapamycin." (*Id.*). Therefore, although Dancey provides a hypothesis that rapamycin may be an effective therapy to treat cancer, it cautions that rapamycin may not be successful, and that further experimentation

will be required to determine whether rapamycin and its analogs represent viable cancer treatments.

(c) Tabernero

Tabernero is a June 2005 publication that reports the results of an uncontrolled phase I clinical dose-finding study for everolimus in patients with advanced solid tumors. (JTX-31). Of the 33 patients enrolled, one colon cancer patient demonstrated a partial response, and two patients (breast cancer and renal cell cancer) demonstrated disease stabilizations. (*Id.*). The Tabernero abstract concluded that everolimus, "at the doses and schedules studied, results in intratumoral inhibition of mTOR signaling," and recommended a daily everolimus dose of 10mg as a monotherapy for further phase II and phase III development. (*Id.*). It is not disputed that Tabernero did not report results in any patient with advanced PNET. (Tr. 306:1-4). Nor does Tabernero disclose whether patients had failed cytotoxic chemotherapy. (*Id.* at 722:19-723:14; *see* JTX-31).

Defendant argues that Tabernero would have included patients that failed cytotoxic chemotherapy because advanced solid tumor patients for whom an effective cytotoxic chemotherapy was available would not generally enroll in a phase I study until the standard cytotoxic chemotherapy had proven ineffective. (Tr. 372:11-24). Plaintiffs counter that a POSA would not have expected Tabernero to include only patients who had previously failed cytotoxic chemotherapy because conventional agents were not effective in some cancers, such as RCC. This would justify the study of new agents in phase I studies in patients with disease resistant to conventional treatment. (*Id.* at 722:23-723:14; *see also* JTX-21 at 885). Defendant's argument is inferential and, in light of Plaintiffs' counterargument, not very convincing. I find that Defendant has failed to establish by clear and convincing evidence that Tabernero would have

included patients who previously failed cytotoxic chemotherapy.

Therefore, Tabernero would have provided a POSA with an oral daily dose range for everolimus for future development in anticancer studies.

(d) von Wichert

Von Wichert studied the role of insulin-like growth factor-I ("IGF-I") in human neuroendocrine tumor cells and teaches that rapamycin monotherapy can inhibit the growth of the human BON cell line in vitro. (JTX-71 at pp. 4578-79). More specifically, BON cells secrete IGF-1, which promotes tumor growth. (D.I. 91 at 53 (citing JTX-71 at Abstract)). Von Wichert also discloses that IGF-I anchorage-independent growth of BON cells is mediated in part by a pathway involving mTOR, PI3K, and mitogen-activated protein kinase 1 activity, though mitogen-activated protein kinase 1 was less important for such growth. (JTX-71 at Abstract). According to Dr. Yu, anchorage-independent growth resembles natural tumor growth in the body, and the PI3K activity observed by von Wichert implicates the mTOR pathway. (Tr. 331:1-24; D.I. 91 at 53 (citing JTX-71 at Abstract)). It is not disputed that von Wichert did not conduct any in vivo testing, and did not test everolimus. (Tr. 401:5-22, 754:6-9; *see* JTX-71). The parties dispute whether the BON cell line is a model for human PNET, and whether the von Wichert experiments were designed to test efficacy. (D.I. 91 at 53; D.I. 92 at 24; D.I. 93 at 46-47).

Defendant asserts that the BON cell line is a human PNET cell line (Tr. 333:3-5), and that von Wichert teaches that "human PNET growth depends on the mTOR pathway and would be sensitive to mTOR inhibition" (D.I. 91 at 53; Tr. 332:18-333:2). Plaintiffs counter that as of November 2005, the BON cell line was not a model for human PNETs due to confusion in the prior art over the origin of the BON cell line and differences between PNET hormone secretion and BON cell hormone secretion. (D.I. 93 at 46).

First, Plaintiffs assert that as of the priority date, there was no consensus about the nature of the BON cell line. Some described BON cells as tumors of the pancreas (*see, e.g.*, JTX-60 at p. 667), while others characterized them as originating from a "metastatic carcinoid tumor of the pancreas" (JTX-52 at p. 303; PTX-183 at p. 577 ("human pancreatic carcinoid (BON) tumors")), and von Wichert described them as both "human BON carcinoid tumor cells" and "established from a human pancreatic carcinoid tumor" (JTX-71 at Abstract, p. 4573). According to Plaintiffs' expert Dr. Kulke, a POSA would be confused by description of a tumor as simultaneously a pancreatic and a carcinoid tumor because carcinoids were known to be tumors arising outside of the pancreas. (Tr. 742:17-743:5). Defendant's expert Dr. Yu acknowledged that as of the priority date, the generally accepted definition of a carcinoid tumor was a "neuroendocrine tumor[] not arising in the pancreas," and that PNETs and carcinoids were classified as different subsets of neuroendocrine tumors. (*Id.* at 403:17-404:10). Dr. Yu also conceded that the Evers reference described the origin of the BON cell line and disclosed that the BON cell line was obtained from a peripancreatic lymph node, not the pancreas itself. (*Id.* at 402:19-403:4; JTX-52 at p. 304).

According to Defendant, any confusion would not have prevented a POSA from relying on BON as a model for PNET because all of the prior art references referring to BON cells as carcinoid acknowledge that BON cells arise from the pancreas (D.I. 92 at 23), and several additional "prior art references relied on BON cells as representative of PNET biology" (D.I. 91 at 54 (citing JTX-39 at p. 1599; JTX-47 at p. 736 ("[t]he human NE pancreatic tumor cell lines QGP1 and BON"); JTX-56 at p. 791 ("[t]he pancreatic cell line BON, derived from a human pancreatic neuroendocrine tumor"); JTX-57 at p. 91 (describing BON as a "NE pancreatic tumor cell line[]"); JTX-60 at p. 667 ("the human neuroendocrine pancreatic cell line BON"))). As further support, Defendant also offers Dr. Kulke's reference in a 2010 paper to von Wichert as

applying to "pancreatic NET cell lines." (DTX-149 at pp. 70; Tr. 803:21-804:24).

Second, Plaintiffs argue that as of the priority date, a POSA would not have considered the BON cell line a model for PNETs because BON cell hormone secretion was not consistent with PNET hormone secretion. (D.I. 93 at 46-47). BON cells were reported to secrete serotonin, which was consistent with carcinoids (Tr. 406:17-407:7; JTX-52 at p. 307; PTX-183 at p. 577), but very rare in PNETs (Tr. 407:8-12; JTX-91 at p. 38). It had also been reported that BON cells did not secrete other hormones typically secreted by PNETs. (Tr. 405:19-406:16; JTX-52 at p. 306). Defendant does not directly respond to this argument.

Considering the evidence as a whole, I find that Defendant has failed to establish by clear and convincing evidence that a POSA would have considered the BON cell line a model for PNETs as of the priority date. Although the prior art consistently described BON cells as pancreatic, it also described BON cells as carcinoid. Dr. Yu admitted that, as of the priority date, the generally accepted definition of carcinoid tumors was limited to tumors arising outside the pancreas. The Kulke reference characterizing BON cells as PNETs carries no weight because it is a post-art reference. (DTX-149). Defendant also failed to address the observed differences in hormone secretion between BON cells and PNETs, and why a POSA would consider them immaterial in determining whether the BON cell line was a model for PNET.

Finally, Plaintiffs maintain that regardless of whether the BON cell line is a PNET model, the experiments disclosed in von Wichert were in vitro studies not designed to determine the efficacy of rapamycin in humans. (D.I. 93 at 47; Tr. 741:13-742:4; JTX-71 at p. 4573). According to Plaintiffs, none of Defendant's references using the BON cell line reported experiments designed to determine the therapeutic efficacy of a compound against neuroendocrine tumors. (D.I. 93 at 47-48). For example, Ahnert-Hilger, John, and Lemmer studied hormone secretion

(JTX-39 at Abstract; JTX-56 at Abstract; JTX-60 at Abstract), Jonas studied somatostatin receptor binding to somatostatin analogs (JTX-57 at Abstract), and Detjen studied interferon's molecular mechanism of action (JTX-47 at Abstract). (D.I. 93 at 48). Defendant does not argue that Ahnert-Hilger, John, Lemmer, or Jonas studied efficacy. Defendant counters, however, that because "Detjen used BON cells to study the molecular mechanisms of interferon-alpha to inhibit the growth of neuroendocrine tumors," the reference used BON cells to understand the efficacy of interferon-alpha to treat PNETs. (D.I. 92 at 24).

I agree with Plaintiffs. The Detjen reference contradicts Defendant's assertion. It describes the aim of the study as "[t]o characterize the antiproliferative effects at a molecular level" of in vivo interferon treatment for human neuroendocrine tumors. (JTX-47 at Abstract). Although Detjen confirms that interferon inhibits anchorage-independent growth of human neuroendocrine tumor cells (*id.* at pp. 740, 741 Figs. 5-6), it draws conclusions about the mechanism of action for interferon's inhibition of the growth of human neuroendocrine tumor cells, rather than assessing interferon's therapeutic efficacy (*id.* at p. 746 ("In summary, the current study provides a detailed analysis of the direct, cell cycle-regulatory effects of [interferon] in an in vitro model of [neuroendocrine] tumor disease.")).

Even assuming that BON cells are an appropriate model for PNETs, and that Detjen used BON cells to assess the efficacy of interferon-alpha to treat PNETs, Defendant has failed to provide evidence that the efficacy of interferon-alpha to treat PNETs is relevant to the efficacy of rapamycin and its analogs to do the same. Von Wichert was designed to investigate the role of IGF-I in neuroendocrine tumor growth, not to determine the therapeutic efficacy of rapamycin to treat PNETs. (JTX-71 at p. 4573). Von Wichert describes a primary contribution of the disclosed experiments to the scientific literature as "demonstrat[ing], for the first time, the existence of an

autocrine IGF-I loop regulating neuroendocrine secretion in a carcinoid tumor cell line," and it concludes that "the IGF-I signaling pathway is a potential novel target for the treatment of hypersecretion syndromes and growth of these tumors." (*Id.* at p. 4573). As Plaintiffs point out, von Wichert concluded with the recommendation to target IGF-I or the IGF-I receptor tyrosine kinase as a novel target for carcinoid tumors and is silent on the use of rapamycin or its analogs as a novel therapy. (*Id.* at pp. 4580-81; D.I. 93 at 48). Therefore, I find that von Wichert's in vitro data at most provide a basis for the hypothesis that rapamycin is a plausible therapy to treat neuroendocrine tumors, and that a POSA would recognize that this hypothesis would require further in vivo experiments and clinical development.

(e) '541 Publication

The '541 publication discloses everolimus as a preferred compound for the treatment of solid tumors, as a monotherapy or in combination with a chemotherapeutic agent. ('541 publication at Abstract, [9-10]). The '541 publication further discloses that everolimus monotherapy inhibits tumor growth in CA20948 rat pancreatic tumors in vivo—in one experiment, CA20948 tumor growth was reduced by 68-77% of treated rats relative to controls. (*Id.* at [88]). The '541 publication also discloses an experimental design for a future clinical dose-finding study for everolimus monotherapy in patients with advanced solid tumors not responsive to standard therapies. (*Id.* at [99-112]). An efficacy study with the same design is to follow if the dose-finding study is successful. (*Id.*). It is not disputed that the '541 publication does not explicitly discuss advanced PNETs (*see id.*) or that CA20948 is a rat cell line (Tr. 384:15-18; '541 publication at [87]).

Plaintiffs assert that the CA20948 cell line is chemotherapy-naïve (Tr. 739:21-740:1) and arises from the exocrine pancreas, and is therefore not a proper model for PNETs, which arise in

the endocrine pancreas. (D.I. 93 at 49 (citing JTX-61); Tr. 386:1-9, 739:14-20). The parties do not dispute that the Longnecker reference (JTX-61) discusses the origin of the CA20948 cell line, describes it as a pancreatic adenocarcinoma, and notes that it shows characteristics of acinar cell differentiation. (Tr. 385:2-8; *see also* JTX-61 at p. 202). Acinar cells and pancreatic adenocarcinomas are cells and tumors of the exocrine pancreas. (Tr. 385:16-386:9). Plaintiffs contend that PNETs and pancreatic adenocarcinomas are distinct classes of tumors known to arise in functionally distinct portions of the pancreas. (*Id.* at 728:16-729:1, 730:13-20). Plaintiffs further assert that because pancreatic adenocarcinomas and PNETs exhibit different clinical behavior (*id.* at 381:24-382:7, 656:9-657:2) and responses to pharmacotherapies (*id.* at 736:21-737:7; PTX-193 at pp. 937-38), and are typically evaluated separately in phase II and phase III clinical trials (Tr. 383:10-15), a POSA would not have extrapolated results from the CA20948 model to PNETs. (D.I. 93 at 50). Plaintiffs also maintain that, unlike PNETs, CA20948 cells were known to produce digestive enzymes. (*Id.* at 49 (citing Tr. 731:14-23; JTX-61 at p. 201)).

Defendant does not dispute these differences, but counters that a POSA would have viewed the CA20948 cells as a preclinical PNET model because CA20948 tumors express somatostatin receptors, which are characteristic of neuroendocrine tumors. (Tr. 317:1-4; D.I. 92 at 24). Defendant offers Plaintiffs' admission that most human pancreatic adenocarcinomas lack somatostatin receptors as evidence that the CA20948 cell line does not model pancreatic adenocarcinoma. (D.I. 92 at 24 (citing D.I. 93 at 51 n.16); *see also* JTX-84 at pp. 294-95). Citing the Li reference, Defendant contends that NETs, but not pancreatic adenocarcinomas, respond to somatostatin analogs. (D.I. 92 at 24 (citing JTX-84 at p. 293)). Defendant also argues that De Jong used CA20948 as a PNET model because, after finding that radiolabeled somatostatin analogs inhibited CA20948 tumor growth, the De Jong experiments subsequently tested the same

somatostatin analogs in human patients with NETs, including PNETs, and "observed positive responses in PNET patients." (D.I. 91 at 56; JTX-46 at pp. 358-59, 362).

Although Plaintiffs acknowledge that CA20948 tumor cells express somatostatin receptors, and that most human adenocarcinoma tumors do not express somatostatin receptors, Plaintiffs maintain that somatostatin receptors were known to be expressed in many human tissues and tumor cells, including some pancreatic adenocarcinomas, carcinoids, PNETs, and other tumors. (D.I. 93 at 51 (citing Tr. 394:5-9, 734:7-735:2; JTX-41 at p. 1089; JTX-84 at p. 294)). Additionally, the prior art disclosed that somatostatin inhibited the growth of some pancreatic adenocarcinoma cell lines. (Tr. 395:6-20, 734:13-735:2 (citing JTX-84 at pp. 294-95)). Further, the De Jong clinical trial enrolled patients with multiple tumor types, including tumors other than neuroendocrine tumors, to test a somatostatin analog. (JTX-46 at p. 362 Table III; Tr. 398:12-399:3, 735:10-21). Therefore, Plaintiffs argue, somatostatin receptor expression is not exclusive to neuroendocrine tumors, and somatostatin receptor expression and response to somatostatin therapy alone would not lead a POSA to consider the CA20948 cell line a model for PNETs. (D.I. 93 at 51). As further support, Plaintiffs point to Dr. Yu's admission that De Jong did not expressly describe CA20948 as a PNET cell line. (D.I. 93 at 50-51; Tr. 400:3-7).

Considering all of the evidence, I find that Defendant has failed to establish by clear and convincing evidence that CA20948 is a PNET model. Although the CA20948 cell line expresses somatostatin receptors, other prior art references had reported somatostatin receptor expression in a wide variety of tissues, including some pancreatic adenocarcinomas. (Tr. 734:7-735:2; JTX-84 at pp. 294-95). The Longnecker reference reporting the origins of the CA20948 cell line describes it as an "azaserine-induced adenocarcinoma[.]" (JTX-61 at p. 202). That De Jong tested the same somatostatin analogs in the CA20948 cell line and patients with neuroendocrine tumors, including

PNETs, does not establish that the CA20948 cell line is a PNET model.

Therefore, I find that the '541 publication discloses a hypothesis that everolimus monotherapy may be effective to treat advanced solid tumors in humans, and that it proposed an experimental design that could be used to test that hypothesis.

2. Comparing Prior Art and Claimed Subject Matter

Defendant again cites *Merck* to argue that the lack of clinical data in the prior art for the use of everolimus to treat advanced PNETs "cannot render the [asserted] claim [of the '224 patent] nonobvious, however, when the '224 patent itself does not cure those deficiencies." (D.I. 91 at 60 (citing 395 F.3d at 1374)). This argument fails here for the same reasons that it did with respect to the '131 patent.

Defendant's expert, Dr. Yu, opines that a POSA would have been motivated to administer a therapeutically effective amount of everolimus as a monotherapy to treat advanced PNETs after the failure of cytotoxic chemotherapy. (Tr. 304:9-16). Dr. Yu stated that a POSA would have been motivated to combine the prior art references Duran, Dancey, and Tabernero because they all deal with using mTOR inhibitors to treat cancer. (*Id.* at 303:9-18). Specifically, Dr. Yu asserted that Duran, Dancey, and Tabernero in combination (1) showed that mTOR inhibition is effective to treat advanced PNET after the failure of cytotoxic chemotherapy, (2) demonstrated that everolimus would be a safe and effective substitute for temsirolimus due to the drugs' shared mTOR inhibition mechanism of action, and (3) provided a safe and effective dose of everolimus to treat patients with advanced solid tumors, including advanced PNETs after the failure of cytotoxic chemotherapy. (*Id.* at 303:14-304:8). According to Dr. Yu, this prior art, combined with the teachings of von Wichert that mTOR inhibitor rapamycin was effective to inhibit tumor growth in a preclinical PNET model, provide additional support for a POSA to believe that a

therapeutically effective amount of everolimus could be administered as a monotherapy to treat patients with advanced PNET after the failure of cytotoxic chemotherapy. (*Id.* at 341:23-342:10). Dr. Yu further opined that a POSA would be able to combine the '541 publication's teachings of an effective daily dose of everolimus monotherapy in a preclinical PNET model with Duran, Dancey, and Tabernero to practice the elements of claim 1 of the '224 patent. (*Id.* at 315:2-22, 327:13-22). Therefore, according to Defendant, these references can be combined to suggest all limitations of claim 1 of the '224 patent.

The parties do not dispute that a POSA would have recognized the need for effective treatments for advanced PNETs after the failure of cytotoxic chemotherapy, as prior efforts to develop effective treatments had been unsuccessful. (D.I. 91 at 43 (citing JTX-63 at Fig. 1); D.I. 93 at 30; Tr. 663:4-21, 287:16-19). Nor do the parties dispute that there were no phase II or phase III clinical results for everolimus as of November 2005. (Tr. 359:19-360:17).

For all asserted combinations, Defendant argues that a POSA would have been motivated to combine the references because the prior art would have motivated a POSA to select everolimus (an mTOR inhibitor) when searching for a treatment for advanced PNETs, and all of the references concern the use of mTOR inhibitors to treat pancreatic cancer. (*Id.* at 303:14-18, 341:13-22, 327:3-12). Plaintiffs disagree and assert that a POSA would not have been motivated to select everolimus over other prior art compounds. (D.I. 93 at 32). As support, Plaintiffs offer Dr. Yu's admission that, as of the priority date, scientists were actively pursuing many signaling pathways for cancer therapies, and his concession that a POSA would have considered options other than the mTOR pathway to treat cancer. (Tr. 351:6-13; 354:10-14). Plaintiffs further argue that the prior art would have provided no motivation to select everolimus because there was no anticancer efficacy data for everolimus (*id.* at 712:5-713:21, 718:11-14, 359:8-360:17), there was no clinical anticancer

data for rapamycin (*id.* at 359:10-14, 682:17-19), no mTOR inhibitor had been FDA approved to treat any cancer (*id.* at 358:19-22), and some cancers were known to be resistant to mTOR inhibitors (JTX-87 at p. 624). Plaintiffs assert that an mTOR inhibitor would have been just one of many potential therapeutic targets within or outside the mTOR pathway that a POSA would have considered when developing a treatment for advanced PNETs. (Tr. 675:2-677:4). Other options would include protein kinase C, PI3K inhibitors, and receptor tyrosine kinase inhibitors, among others. (*Id.*). Therefore, Plaintiffs assert, since Dr. Yu did not compare what was known about the mTOR pathway with what was known about other signaling pathways, Defendant has failed to carry its burden to establish that a POSA would have been motivated to select everolimus to treat advanced PNETs. (D.I. 93 at 33).

Given the incomplete knowledge of the molecular biology of PNETs and the mTOR pathway, along with the high number of potential therapeutic targets both within and outside the mTOR pathway, I find that Defendant has failed to establish by clear and convincing evidence a motivation to select everolimus.

Even if Defendant had established such a motivation, however, Defendant has failed to prove by clear and convincing evidence that any one of the asserted prior art combinations would give a POSA a reasonable expectation of success of administering a therapeutically effective amount of everolimus as a monotherapy to treat advanced PNETs after the failure of cytotoxic chemotherapy.

i. Combination 1: Duran, Dancey, and Tabernero

I find that Defendant has not shown by clear and convincing evidence that the combination of Duran, Dancey, and Tabernero would have provided a POSA a reasonable expectation of success in using everolimus to treat advanced PNETs.

In light of clinically-relevant differences in everolimus and temsirolimus (*see, e.g.*, JTX-25 at p. 38; JTX-22 at pp. 702-03), the uncontrolled, single-arm design of the Duran study, the interim nature of the Duran results, and the lack of disclosure of the disease characteristics of the evaluable patients (*see* JTX-48), a POSA would not have concluded based on Duran that everolimus would have been effective to treat advanced PNETs after the failure of cytotoxic chemotherapy. At most, a POSA would have concluded that Duran disclosed preliminary data supporting the notion that temsirolimus may be effective to treat metastatic neuroendocrine carcinomas.

Defendant asserts that Dancey's disclosure that preclinical data demonstrated shared properties and overlapping activity and toxicity profiles of rapamycin, everolimus, and temsirolimus would have led a POSA to reasonably expect similar results with everolimus and temsirolimus. Defendant ignores Dancey's caution that preclinical similarities between temsirolimus and everolimus would not necessarily correlate with clinical outcomes, and that Dancey does not mention PNETs. (JTX-45 at p. 318). Even if a POSA could reasonably expect everolimus and temsirolimus to have similar antitumor effects, the combination of Duran and Dancey fails to provide a reasonable expectation that everolimus would be effective to treat advanced PNETs due to the lack of disclosure in Duran of the disease characteristics of the evaluable patients.

Although Tabernero provided a POSA with a safe daily oral everolimus dose in advanced solid tumors for further anticancer clinical development, the reported results provide no indication that everolimus would be effective against advanced PNETs after the failure of cytotoxic chemotherapy. There is no indication that any patient evaluated in Tabernero had advanced PNET or that any patient had failed first-line cytotoxic chemotherapy. (JTX-31). Since some cancers

were known to be resistant to mTOR inhibitors (JTX-87 at p. 624), a POSA would not reasonably have expected that results from an uncontrolled, phase I everolimus study in a variety of advanced solid tumors would yield similar results in advanced PNETs specifically. The high failure rates of oncology drugs at phase II and phase III clinical trials (Tr. 721:8-722:11, 838:22-839:1; PTX-80 at pp. 711-12) would have further diminished any expectation that everolimus would be effective in PNETs. Therefore, even in combination, Duran, Dancey, and Tabernero do not disclose the effective use of any mTOR inhibitor to treat advanced PNETs after the failure of cytotoxic chemotherapy.

Defendant has thus failed to prove by clear and convincing evidence that the combined teachings of Duran, Dancey, and Tabernero render claim 1 of the '224 patent obvious.

ii. *Combination 2: Duran, Dancey, and Tabernero in View of von Wichert*

Defendant has failed to prove that the BON cell line in von Wichert was a model for PNETs as of the priority date. Having found that von Wichert merely discloses the hypothesis, subject to further testing, that rapamycin may be effective to treat neuroendocrine tumors, I conclude that von Wichert adds little to the combination of Duran, Dancey, and Tabernero. Therefore, Defendant has failed to prove by clear and convincing evidence that claim 1 of the '224 patent is rendered obvious by Duran, Dancey, and Tabernero in view of von Wichert. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007) ("[A]n invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." (citation omitted)).

iii. *Combination 3: Duran, Dancey, and Tabernero in View of the '541 Publication*

Based on preclinical reports that everolimus demonstrated some inhibition of CA20948 tumor growth in a variety of cancers, the '541 publication taught a hypothesis that everolimus monotherapy may be effective to treat advanced solid tumors in humans, and it proposed an approach for further research to test that hypothesis. ('541 publication at [89, 99-112]). Defendant failed to establish, however, that the CA20948 rat pancreatic cell line was a model for PNETs as of the priority date. Therefore, I conclude that Defendant has failed to prove that the '541 publication, in combination with Duran, Dancey, and Tabernero, renders claim 1 of the '224 patent obvious.

3. Level of Ordinary Skill in the Art

The parties agree that the POSA would have a medical degree and/or Ph.D. in biology, biochemistry, pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, experience conducting preclinical, clinical and/or laboratory research relating to cancers of the neuroendocrine system, including PNETs, and would collaborate as needed with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry. (Tr. 257:22-258:15, 653:3-9). They dispute whether a POSA would have experience with the mTOR pathway and rapamycin and its analogs. (*Id.* at. 257:22-258:15; 652:24-653:18). Both parties' experts testified, however, that their opinions would not change if the Court were to adopt the opposing expert's definition of a POSA. (*Id.* at 258:20-259:6; 653:19-22). Given the incomplete knowledge of the molecular biology of advanced PNETs and the variety of treatment avenues for advanced PNETs being pursued as of the priority date, I find that a POSA would not necessarily have experience with the mTOR pathway and rapamycin and its analogs.

Therefore, the POSA would have a medical degree and/or Ph.D. in biology, biochemistry,

pharmaceutical sciences, molecular biology, cancer biology, or other biological sciences, would have experience conducting preclinical, clinical and/or laboratory research relating to cancers of the neuroendocrine system, including PNETs, and would collaborate with others having skills and expertise in areas such as pharmacology, drug formulation, and biochemistry.

4. Secondary Considerations

Defendant argues that secondary considerations do not support finding the '224 patent nonobvious because there was no long-felt need for a treatment for advanced PNET, no failure of others to develop such a treatment, and Plaintiffs failed to demonstrate unexpected results. (D.I. 91 at 60). Plaintiffs disagree. (D.I. 93 at 52).

i. Long-Felt Need

Plaintiffs argue that as of November 21, 2005, a long-felt need existed for new therapies to treat advanced PNETs after the failure of cytotoxic chemotherapy. (D.I. 93 at 53; Tr. 760:23-762:9; PTX-193 at p. 938; PTX-217 at p. 1142). As early as 1992, scientists recognized that second-line therapy outcomes were poor for advanced PNET patients who had previously failed first-line cytotoxic chemotherapy. (PTX-261 at pp. 521-22 (reporting less favorable survival times and times to disease progression in patients treated with second-line therapy and who had previously failed cytotoxic chemotherapy than in patients treated only with first-line therapy)). Dr. Yu agreed that as of November 2005, thirteen years later, there was still a need for new therapies to treat advanced PNETs after the failure of cytotoxic chemotherapy. (Tr. 831:23-832:4).

Dr. Yu asserted, however, that sunitinib and temsirolimus met any need that existed as of November 2005. (*Id.* at 832:10-13). As evidence, Defendant cites abstracts reporting interim results of sunitinib phase II trials demonstrating some clinical activity of sunitinib in advanced PNET patients. (D.I. 91 at p. 49; DTX-81; DTX-82). The primary author of these abstracts, Dr.

Kulke, also noted, however, that despite the results reported in the abstracts, additional studies to explore the clinical benefit of sunitinib in neuroendocrine tumor patients were warranted. (Tr. 785:17-24; DTX-81). Defendant's assertion is also contradicted by Dr. Yu's admission that although he was a board-certified medical oncologist specializing in pancreatic cancer as of June 2005 (Tr. 250:14-21), he did not prescribe sunitinib to treat advanced PNETs until after its FDA approval for that use in 2011 (*id.* at 832:22-833:8). Outside of the clinical trial setting, Dr. Yu provided no evidence that sunitinib was used to treat advanced PNETs prior to its FDA approval. (*Id.* at 833:9-18). Even if sunitinib was one treatment option for advanced PNETs as of November 2005, Dr. Yu and Dr. Kulke agreed that absent a cure, it is always preferable to have more than one treatment option, suggesting that sunitinib alone would not have satisfied the need for advanced PNET treatments. (*Id.* at 782:23-783:8, 833:19-834:3).

Nor did Dr. Yu prescribe temsirolimus to any patients based on the results of Duran. (*Id.* at 834:17-20). The final results of the Duran study, published in 2006, concluded that temsirolimus appeared to have little activity and did not warrant further study, and no phase III trial for temsirolimus monotherapy or combination therapy was conducted in patients with advanced PNETs. (*Id.* at 835:3-18 JTX-49 at p. 1148). Considering all of the evidence presented, I agree with Plaintiffs that there was a long-felt need for new therapies for the treatment of advanced PNETs after the failure of cytotoxic chemotherapy as of the priority date.

ii. Failure of Others

Plaintiffs assert that the failure of other drugs to treat advanced PNETs further supports finding claim 1 of the '224 patent nonobvious. (D.I. 93 at 55). More specifically, drugs such as topotecan and paclitaxel, which had demonstrated promising results to treat other solid tumors, failed to demonstrate efficacy against advanced PNETs. (Tr. 762:11-763:8, PTX-158 at p. 1543

(paclitaxel); PTX-159 at p. 234 (topotecan)). Defendant does not dispute that other drugs had failed to treat advanced PNETs (Tr. 831:14-22), but argues that this evidence "merely shows that a failed approach fails when tried again," treating all cytotoxic chemotherapies as equivalent treatments because they are all DNA-damaging (D.I. 91 at 63). Defendant's argument oversimplifies oncology research and ignores the evidence that a POSA would not abandon an approach to treatment based on the failure of one drug or combination because a large number of potential treatment options with differing mechanisms of action were available. (Tr. 666:15-668:10; PTX-59; PTX-262; PTX-265; PTX-266; PTX-269; PTX-271). Defendant also argues that since sunitinib and temsirolimus met the need for advanced PNET treatments, others had not failed. (D.I. 91 at 63). Defendant has not demonstrated that sunitinib and tesmsirolimus met the long-felt need for advanced PNET treatments. Therefore, the failure of others to develop a treatment for advanced PNETs after the failure of cytotoxic chemotherapy supports finding claim 1 of the '224 patent nonobvious.

iii. Unexpected Results

Unexpected results may be demonstrated by showing "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citation omitted). To assess unexpected results, courts must compare the claimed invention to the closest prior art. *Kao Corp v. Unilever U.S. Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). In this analysis, "'differences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—i.e., a new property dissimilar to the known property." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Differences in degree may be probative, however, when they represent "a marked

superiority in an expected property." *Id.*

Plaintiffs offer the RADIANT-3 study as representative of the claimed invention. (D.I. 93 at 56). Defendant disagrees, arguing that the RADIANT-3 study does not adequately represent the claimed invention because it does not embody the "everolimus monotherapy" or the "after the failure of cytotoxic chemotherapy" limitations of claim 1 of the '224 patent. (D.I. 91 at 61-62). Defendant points out that patients in the RADIANT-3 study remained on best supportive care, and the study did not compare progression-free survival for patients who failed cytotoxic chemotherapy with progression-free survival for those who had not. (D.I. 92 at 27-28). The statistical analyses in the RADIANT-3 study take into account that patients remained on best supportive care, and provide support for the authors' conclusion that everolimus demonstrated a clinical benefit irrespective of prior chemotherapy status. (JTX-4 at pp. 518, 519 Fig. 1; Tr. 767:21-768:12). I therefore conclude that the RADIANT-3 study sufficiently represents the limitations of claim 1 of the '224 patent.

Assuming RADIANT-3 is representative of claim 1, Defendant appears to offer Duran 2006 as the closest prior art, asserting that the results from the RADIANT-3 study are not unexpectedly better than the temsirolimus results in Duran 2006. (D.I. 91 at 61-62). The RADIANT-3 study reported a progression-free survival of 11 months in patients treated with everolimus, which Defendant argues is not substantially better than the 10.6 month progression-free survival in temsirolimus patients reported in Duran 2006. (D.I. 92 at 28; JTX-4 at p. 518; JTX-49 at p. 1151). Defendant also offers what it asserts are comparable partial response rates in advanced PNET patients in Duran 2006 (6.7%) and the RADIANT-3 study (5%). (D.I. 92 at 28; JTX-4 at p. 520; JTX-49 at p. 1151, Table 2).

Plaintiffs argue that the RADIANT-3 phase III clinical trial that demonstrated the efficacy

of everolimus to treat advanced PNETs and led to FDA approval of their Afinitor product for that indication produced unexpected results. (D.I. 93 at 56). As support, Plaintiffs offer the prior art's lack of clinical data for rapamycin, the failure of temsirolimus, the low success rates of oncology drugs, and the poor outcomes for PNET patients who had previously received cytotoxic chemotherapy. (Tr. 769:3-23). Plaintiffs also cite the lack of any effective treatment for advanced PNETs after the failure of cytotoxic chemotherapy as of November 2005. (*Id.* at 661:8-662:16, 663:4-23). Although these arguments are probative for purposes of the general obviousness inquiry, they fail to compare the RADIANT-3 study to the closest prior art. Therefore, they are not relevant to the unexpected results analysis.

Plaintiffs contend that Duran 2006 and the RADIANT-3 study cannot be compared due to differences in their designs. (*Id.* at 772:9-773:24, 836:2-838:9). To bolster this argument, Plaintiffs note that the FDA would not permit investigators to draw comparisons of the progression-free survival across both studies. (D.I. 93 at 58; Tr. 774:1-12). Although Plaintiffs maintain that the RADIANT-3 study and Duran 2006 are not comparable, Plaintiffs have not identified the closest prior art to the RADIANT-3 study.

Whether the FDA would permit a comparison of the RADIANT-3 and Duran 2006 studies is not dispositive of whether they are comparable for purposes of unexpected results. Adopting Plaintiffs' assertion that Duran 2006 and the RADIANT-3 study are not comparable does not excuse Plaintiffs from identifying the closest prior art to compare with the claimed invention for purposes of the unexpected results analysis. Crediting Plaintiffs' incomparability arguments and ignoring Duran 2006 leaves only Plaintiffs' arguments relevant to the general obviousness inquiry, which are insufficient to establish unexpected results. Since Plaintiffs have failed to identify the closest prior art, let alone compare the RADIANT-3 study to any piece of prior art, they have failed

to carry their burden to establish unexpected results by a preponderance of the evidence.

Therefore, I conclude that secondary considerations of long-felt need and failure of others support finding asserted claim 1 of the '224 patent nonobvious.

IV. CONCLUSION

Defendant failed to prove by clear and convincing evidence that the asserted claims of the '131 and '224 patents are invalid as obvious.