IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Review of:)
U.S. Patent No. 9,006,224)
Issued: Apr. 14, 2015)
Application No.: 12/094,173)
PCT Filing Date: Nov. 20, 2006)

For: **Neuroendocrine Tumor Treatment**

FILED VIA E2E

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,006,224

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Par Pharmaceutical, Inc. ("Petitioner" or "Par") requests *inter partes* review of Claims 1-3 of United States Patent No. 9,006,224 (the "'224 patent"), titled "Neuroendocrine Tumor Treatment," which according to USPTO records is assigned to Novartis AG ("Patent Owner" or "Novartis").

I. OVERVIEW

The Board should grant *inter partes* review because the '224 patent claims nothing more than what was already well-known in the art. The '224 patent claims methods of treating advanced pancreatic neuroendocrine tumors with a rapamycin derivative known as everolimus. The prior art, however, already taught treating these exact tumors with rapamycin and its derivatives. And everolimus was identified as having better bioavailability and presenting a "clinical advantage" over rapamycin. Further, everolimus specifically was taught to be effective in a recognized rat model of these pancreatic tumors. Additionally, unlike rapamycin, both everolimus and temsirolimus (another rapamycin derivative) had been shown to be effective and well-tolerated in human cancer patients, and temsirolimus had been shown to be safe and effective in treating humans with advanced neuroendocrine tumors ("NETs"). Thus, it would have been obvious to use everolimus to treat advanced pancreatic NETs as recited in the claims.

II. REQUIREMENTS FOR PETITION FOR *INTER PARTES* REVIEW

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Par certifies that the '224 patent is available for *inter partes* review and that Par is not barred or estopped from requesting *inter partes* review of the challenged claims of the '224 patent.

B. Notice of Lead and Backup Counsel and Service Information

Pursuant to 37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), and 42.10(a), Par provides the following designation of Lead and Back-Up counsel.

LEAD COUNSEL	BACKUP COUNSEL
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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney for Par is attached. Par consents to electronic service.

C. Notice of Real-Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Par is a real-party-in-interest for this proceeding. Par identifies the following additional entities as real-parties-in-interest: Endo International PLC; Endo DAC; Endo Management Limited; Endo Luxembourg Holding Company S.a.r.l.; Endo

Luxembourg Finance Company I S.a.r.l.; Endo Luxembourg Finance Company II S.a.r.l.; Paladin Labs Canadian Holding Inc.; Paladin Labs Inc.; Luxembourg Endo Specialty Pharmaceuticals Holding I S.a r l.; Luxembourg Endo Specialty Pharmaceuticals Holding II S.a r l.; and Par Pharmaceutical Companies, Inc.

D. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

Novartis Pharm. Corp. et al. v. Par Pharm., Inc., 1:14-cv-1289-RGA (D. Del.). *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, 1:14-cv-1494-RGA (D. Del.). *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, 1:15-cv-78-RGA (D. Del.). *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, 1:15-cv-475-RGA (D. Del.). *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, 1:15-cv-1050-RGA (D. Del.). *Roxane Labs., Inc. v. Novartis AG*, IPR2016-1461 (filed July 19, 2016). Petitions for *Inter Partes* Review of U.S. Patent No. 5,665,772, Nos. IPR2016-00084, -01023, -01059, -01102, and -01103. According to USPTO records, U.S. Patent App. No. 14/608,644 claims priority to the '224 patent.

E. Fee for *Inter Partes* Review

The Director is authorized to charge the fee specified by 37 C.F.R. § 42.15(a) to Deposit Account No. 506269.

F. Proof of Service

Proof of service of this petition on the Patent Owner at the correspondence address of record for the '224 patent is attached.

III. IDENTIFICATION OF CLAIMS BEING CHALLENGED (37 C.F.R. § 42.104(B))

For the reasons herein, the Board should find claims 1-3 unpatentable on the following grounds:

Ground 1. Claims 1-3 are unpatentable under 35 U.S.C. § 103 because they are rendered obvious by Oberg 2004 (Ex. 1027) in combination with Boulay 2004 (Ex. 1005) and O'Donnell (Ex. 1029).

Ground 2. Claim 2 is unpatentable under 35 U.S.C. § 103 because it is rendered obvious by Oberg 2004 (Ex. 1027) in combination with Boulay 2004 (Ex. 1005) and O'Donnell (Ex. 1029), in further view of Tabernero (Ex. 1038).

Ground 3. Claims 1-3 are unpatentable under 35 U.S.C. § 103 because they are rendered obvious by Boulay 2004 (Ex. 1005), O'Donnell (Ex. 1029), and Duran (Ex. 1011).

Ground 4. Claim 2 is unpatentable under 35 U.S.C. § 103 because it is rendered obvious by Boulay 2004 (Ex. 1005), O'Donnell (Ex. 1029), and Duran (Ex. 1011), in further view of Tabernero (Ex. 1038).

IV. SUMMARY OF THE ARGUMENT

The '224 patent claims methods of treating advanced pancreatic NETs by administering to a human subject in need thereof a therapeutically effective amount

of everolimus[1] after failure of cytotoxic chemotherapy. Ex. 1001, '224 patent at 26:65-27:8. Treating advanced pancreatic NETs (such as islet cell tumors) by administering a therapeutically effective amount (including 10 mg/day) of everolimus after cytotoxic treatment fails would have been obvious at the time of the purported invention, November 21, 2005.

First (*i.e.*, Grounds 1 and 2), Oberg 2004 disclosed rapamycin as a treatment for advanced pancreatic NETs after cytotoxic treatment failed, and one of skill would have understood that suggestion to include rapamycin's other known active derivatives that had been reported to be administered to human cancer patients, such as everolimus. Ex. 1027, Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶¶ 79, 83-92, 104. Everolimus was first disclosed in 1992, and subsequent preclinical and clinical research touted its activity and identifying it as having a "clinical

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[1] The claims of the '224 patent use the term 40-O-(2-hydroxyethyl)-rapamycin. This compound is also known in the art as everolimus, RAD001, SDZ RAD, and RAD. *E.g.*, Ex. 1001, '224 patent at 11:50-51; Ex. 1033, Rao at 621; Ex. 1003, Ratain Decl. ¶ 72. Sometimes Novartis and its predecessor Sandoz refer to 40-O-(2-hydroxyethyl)-rapamycin as Compound A. '224 patent at 11:66-67. For ease of reference, this Petition will primarily use the term "everolimus" in referencing this compound.

advantage" over rapamycin. Ex. 1003, Ratain Decl. ¶¶ 72, 75-79. Further, everolimus would have been an obvious treatment choice because its efficacy in treating pancreatic NETs had been demonstrated in laboratory models and the prior art taught that everolimus was safe and effective in treating humans with solid tumors. Ex. 1005, Boulay 2004 at 254; Ex. 1029, O'Donnell at 803; Ex. 1003, Ratain Decl. ¶¶ 110-123. And although it would have been obvious to identify an appropriate dose, Tabernero explicitly taught using a unit dose of 10 mg/day of everolimus for treating solid tumors. Ex. 1038, Tabernero at 3007; Ex. 1003, Ratain Decl. ¶¶ 126-127, 152.

Second (*i.e.*, Grounds 3 and 4), Boulay 2004 demonstrated that everolimus was effective in treating pancreatic NETs in rats and would have suggested to one of ordinary skill to administer everolimus to humans with pancreatic NETs. A skilled artisan would have had a reasonable expectation that everolimus would be effective in pancreatic NETs because of the antitumor activity in this preclinical model. Ex. 1005, Boulay 2004 at 254; Ex. 1003, Ratain Decl. ¶ 112. Further, O'Donnell taught that everolimus was safe and effective for treating other tumors in humans. Ex. 1029, O'Donnell at 803; Ex. 1003, Ratain Decl. ¶¶ 119-123. One of ordinary skill would have tried, and reasonably expected to succeed, using everolimus to treat advanced pancreatic NETs in humans after cytotoxic treatment failed because Duran had demonstrated that another well-known rapamycin

derivative, temsirolimus,[2] was effective in treating advanced NETs. Ex. 1011, Duran at 3096; Ex. 1003, Ratain Decl. ¶¶ 129-131, 167.

To explain further, it was well-known as of November 2005 that rapamycin, an inhibitor of the protein mTOR, was a potent anti-tumor agent. Ex. 1003, Ratain Decl. ¶¶ 70-71, 83-92. Researchers had investigated the use of rapamycin in the treatment of a variety of cancers and tumor models, including two pancreatic cancer cell lines. *Id*. ¶¶ 70-71.

Because of rapamycin's promising results in that research, researchers investigated and identified rapamycin derivatives with similar anti-tumor and mTOR-inhibition properties, including everolimus and temsirolimus. *Id*. ¶¶ 72-82. As of November 2005, everolimus and temsirolimus were the two most studied rapamycin derivatives. *Id*. ¶ 75. Differing only at the C40 position (circled in red), these two rapamycin derivatives have identical binding sites for their biological targets, mTOR and FKBP12[3]:

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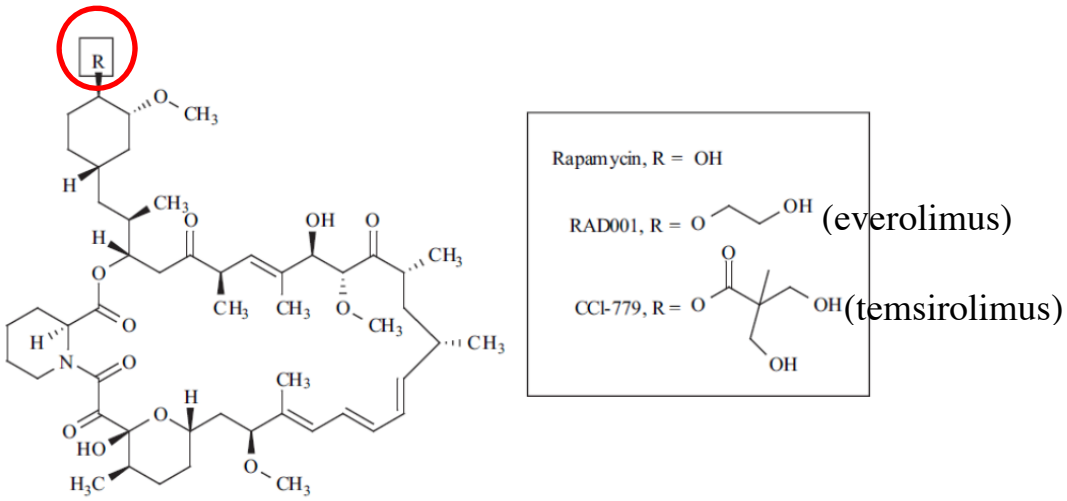
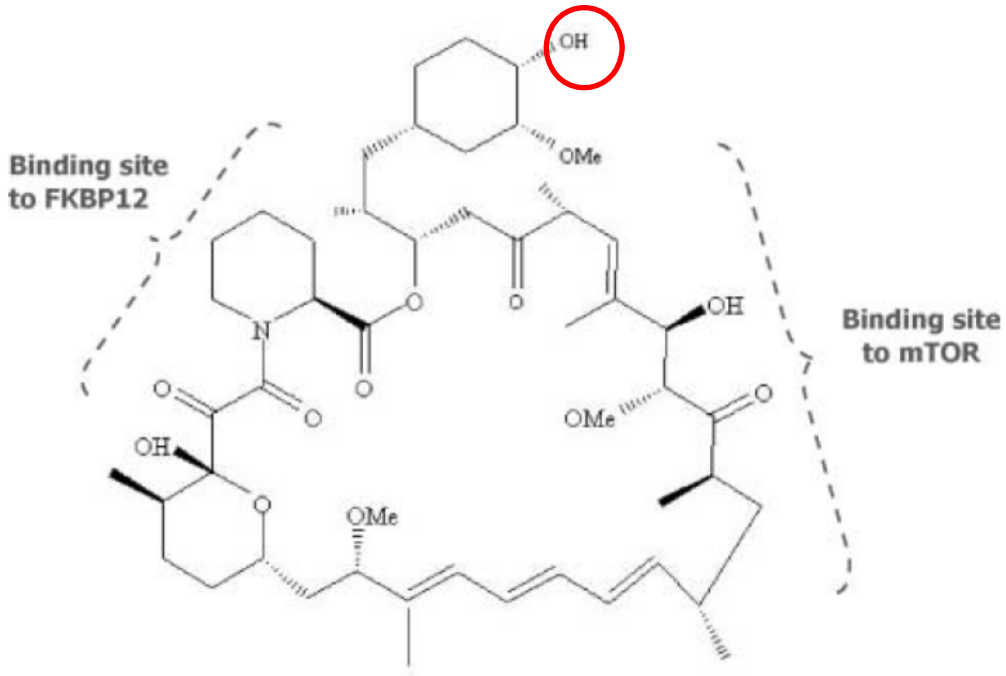
[2] Temsirolimus is also known as CCI-779 in the literature. Ex. 1033, Rao at 621; Ex. 1003, Ratain Decl. ¶ 73.

[3] By November 2005, it was known that rapamycin and its derivatives first bind to the protein FKBP12 and then that rapamcyin-FKBP12 complex interacts with mTOR to inhibit its activity. Ex. 1003, Ratain Decl. ¶ 83.





Id. ¶¶ 75, 91-92 (citing Ex. 1017, Huang 2002; Ex. 1039, Vignot at 528, Fig. 4). One of ordinary skill in November 2005 would have understood that both everolimus and temsirolimus have similar properties to each other and to rapamycin. Ex. 1003, Ratain Decl. ¶¶ 75-92.

Oberg 2004 suggested rapamycin (and therefore its known active derivatives) as a treatment for humans with advanced pancreatic NETs after the failure of chemotherapy. Ex. 1027, Oberg 2004 at 59; Ex. 1003, Ratain Decl. ¶¶ 100-104. Additionally, Boulay 2004 disclosed that everolimus was well-tolerated and effective in a rat model for pancreatic NETs that had been correlated to clinical efficacy in humans. Ex. 1005, Boulay 2004 at 254; Ex. 1003, Ratain Decl. ¶¶ 110-117. Specifically, Boulay 2004 reported that administering everolimus as a monotherapy to rats injected with pancreatic NET tumor cells showed statistically significant antitumor activity, and was "well tolerated, with no significant body weight loss or mortalities observed." Ex. 1005, Boulay 2004 at 254; Ex. 1003, Ratain Decl. ¶¶ 115-116. This model was reported to indicate likely clinical activity in pNET. Ex. 1003, Ratain Decl. ¶¶ 112.

A person of ordinary skill would have also known that both everolimus and temsirolimus are effective and well-tolerated in human cancer patients. Ex. 1029, O'Donnell at 803; Ex. 1003, Ratain Decl. ¶¶ 79-81; *see also* Ex. 1009, Dancey at 1105-1110; Ex. 1054, Dukart at 5:1-6:26; Ex. 1011, Duran at 3096. In particular, O'Donnell taught that everolimus exhibited anti-tumor effects and "was well tolerated with only mild degrees" of side effects. Ex. 1029, O'Donnell at 803; Ex. 1003, Ratain Decl. ¶ 120. And the prior art taught that everolimus was more bioavailable than rapamycin, with a "more favorable" pharmacokinetic profile,

proving a "clinical advantage." Ex. 1009, Dancey, at 1105-06; Ex. 1036, Schuler at 36-37, 41; Ex. 1003, Ratain Decl. ¶¶ 76-77. Further, Tabernero recommended that everolimus be administered in 10 mg daily doses as a monotherapy for treating advanced solid tumors. Ex. 1038, Tabernero at 3007.

In light of these teachings, a person of ordinary skill in the art seeking to treat patients with advanced pancreatic NETs after the failure of cytotoxic chemotherapy would have been motivated to combine the teachings of Oberg 2004, Boulay 2004, and O'Donnell to treat such tumors with everolimus as recited in the claims of the '224 patent. Ex. 1003, Ratain Decl. ¶¶ 132-138. Although one of ordinary skill would have been able to determine an appropriate dose using routine experimentation, a skilled artisan would have also incorporated the teaching of Tabernero that everolimus should be administered at 10 mg/day for the treatment of solid tumors, as recited in claim 2 of the '224 patent. Ex. 1038, Tabernero at 3007; Ex. 1003, Ratain Decl. ¶¶ 152-53, 159-160.

In addition, the prior art taught that everolimus had preclinical activity in a rat tumor model of pancreatic NETs, Boulay 2004 at 252-54, and clinical activity in treating humans with solid tumors, O'Donnell. A skilled artisan would have also been aware that the rapamycin derivative temsirolimus had been shown to have antitumor activity in humans with advanced neuroendocrine carcinomas, a subset of advanced NETs, who had previously been treated with cytotoxic chemotherapy.

Ex. 1011, Duran at 3096; Ex. 1003, Ratain Decl. ¶¶ 94, 130. Therefore, in seeking to treat humans with advanced pancreatic NETs, a skilled artisan would have been motivated to combine the teachings of Boulay 2004, O'Donnell, and Duran, and in doing so, would have reasonably expected that everolimus would be effective in treating humans with advanced pancreatic NETs after failure with cytotoxic chemotherapy. Ex. 1003, Ratain Decl. ¶¶ 139-142, 161-174. And, as stated above, although a person of ordinary skill would have been able to determine an appropriate dose, including 10 mg/day, a skilled artisan would have also incorporated Tabernero's teaching of a unit dose of 10 mg/day to treat solid tumors, which would include pancreatic NETs. Ex. 1038, Tabernero at 3007; Ex. 1003, Ratain Decl. ¶¶ 125, 169-170, 176-177.

As described in more detail below, because the combinations of Oberg 2004, Boulay 2004, O'Donnell, and Tabernero (*i.e.*, Grounds 1 and 2); and Boulay 2004, O'Donnell, Duran, and Tabernero (*i.e.*, Grounds 3 and 4) each teach all elements of the claims, and are combinations motivated by a known problem in the field at the time of the alleged inventions, these combinations render claims 1-3 of the '224 patent obvious. *See In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor."); *see also KSR Int'l Co. v. Teleflex*

Inc., 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.").

V. OVERVIEW OF THE '224 PATENT

The '224 patent claims methods of using everolimus to treat humans with advanced pancreatic NETs after the failure of cytotoxic chemotherapy. Ex. 1001, '224 patent. Specifically, claim 1 recites:

> 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.

Claim 2 recites a specific dose of everolimus:

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

And claim 3 recites a particular type of pancreatic NET:

> 3. The method of claim 1, wherein the tumor is [an] islet cell tumor.

Ex. 1001, '224 patent at 26:65-27:8.

The '224 patent describes the use of mTOR inhibitors, like rapamycin, everolimus, and temsirolimus, in the treatment of pancreatic NETs. *Id*. at 2:3-40. It further describes that rapamycin and its derivatives, such as everolimus and

temsirolimus, inhibit mTOR activity through a complex with FKBP12. *Id*. at 1:6-15. And it states that mTOR inhibitors have potent antiproliferative properties, which makes them useful for cancer chemotherapy, and particularly for advanced solid tumors. *Id*. at 2:35-40.

The '224 patent does not include any preclinical data evidencing the effect of any mTOR inhibitor on pancreatic NETs. *See generally* Ex. 1001, '224 patent; Ex. 1003, Ratain Decl. ¶¶ 31-37. Instead, the '224 patent includes several prophetic examples, including administering everolimus (Compound A) to cancer cell lines to "show interesting antiproliferative activity in combination with another chemotherapeutic agent," to determine "the immediate pharmacodynamic effect of the mTOR inhibitor," to determine that "Compound A [everolimus] is able to restore activity of endocrine agents, like estrogen inhibitors and/or aromatase inhibitors" in breast cancer tumors. *Id*. at 25:49-26:27.

Nor does the '224 patent include any clinical data evidencing the effect of any mTOR inhibitor on pancreatic NETs in humans. *See generally* Ex. 1001, '224 patent; Ex. 1003, Ratain Decl. ¶ 37. Instead, the '224 patent includes several prophetic clinical trial protocols, including administering everolimus (Compound

A) alone or in combination with Sandostatin LAR®[4] in patients having carcinoid or islet cell cancer, evaluating the effect of adding everolimus (Compound A) to patients with advanced midgut carcinoid tumors already receiving Sandostatin LAR®, and evaluating the effect of everolimus (Compound A) at a dosage of 10 mg/day in patients with measureable advanced pancreatic NETs (islet cell tumor) with or without Sandostatin LAR®. Ex. 1001, '224 patent at 26:28-64.

Boulay 2004 was submitted to the Patent Office during prosecution, but the Examiner never discussed or relied upon it. Ex. 1003, Ratain Decl. ¶ 49. Oberg 2004, O'Donnell, and Tabernero were neither submitted to the Patent Office nor considered by the Examiner during prosecution of the '224 patent.[5] *Id*.

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[4] The active ingredient of Sandostain LAR® is octreotide acetate, a somatostatin analog. Ex. 1003, Ratain Decl. ¶ 35. Octreotide acetate was approved to treat symptoms of VIPomas, a type of pancreatic NET. *Id*.. The use of somatostain analogs as a treatment for pancreatic NETs was well-known. Ex. 1027, Oberg 2004 at 59-60.

[5] Novartis submitted Oberg 2004 and Tabernero to the Patent Office in the continuation application 14/608,644, on an IDS dated April 1, 2015, two weeks before the '224 patent issued, but did not submit Oberg 2004 or Tabernero to the Patent Office during prosecution of the parent '224 patent. Ex. 1056, Apr. 1, 2015

VI. THE PERSON OF ORDINARY SKILL IN THE ART

The '224 patent claims methods of treating pancreatic NETs in human patients by administering the known rapamycin derivative everolimus. Ex. 1003, Ratain Decl. ¶ 20; Ex. 1001, '224 patent. Accordingly, a person of ordinary skill in the art in November 2005 would have had (1) a medical degree (e.g., MD) with several years of specific experience in medical oncology, which generally includes board certification, as well as knowledge of oncology drug development and clinical pharmacology; or (2) a Ph.D. in cancer biology, molecular biology, medicinal chemistry, or a related field with several years of experience in oncology drug development and clinical pharmacology, including evaluating cancer therapeutics in *in vitro* and/or *in vivo* assays, as well as familiarity with the practice of medical oncology. Ex. 1003, Ratain Decl. ¶ 21. This description is approximate, and a higher level of education or skill might make up for less experience, and

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IDS at NPL refs. 8, 18. The Examiner cited Oberg 2004 in connection with the continuation application as teaching the use of somatostatin analogues as effective in inducing NET regression. Ex. 1057, Dec. 18, 2015, Office Action at 6-7. The Examiner has not cited or addressed Tabernero in connection with the continuation application. Thus, although these references have been before the Office as prior art in a continuation application, the Office has not considered arguments substantially similar to those presented in the instant Petition for the '224 patent.

vice-versa. *Id*.

VII. CLAIM CONSTRUCTION

A. Applicable Law

In deciding whether to institute *inter partes* review, "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears."[6] 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, No. 15-446, slip op. at 13, 579 U.S. ____ (2016). This claim construction standard is different from—and broader than—that applied in district court. *Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1327-28 (Fed. Cir. 2015). Under the broadest reasonable interpretation, "claims should always be read in light of the specification and teachings in the underlying patent." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015). The "PTO should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review." *Id*. In addition, "[e]ven under the broadest reasonable interpretation, the Board's

[6] The district court, in contrast, affords a claim term its "ordinary and customary meaning . . . to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). Par expressly reserves the right to argue different or additional claim construction positions under this standard in district court.

construction cannot be divorced from the specification and the record evidence and must be consistent with the one that those skilled in the art would reach." *Id*. (quotation marks and citations omitted).

To the extent there is any ambiguity regarding the "broadest reasonable construction" of a claim term, the ambiguity should be resolved in favor of the broader construction, absent amendment by the patent owner. Final Rules, 77 Fed. Reg. 48680, 48699 (Aug. 14, 2012) ("[T]he broader standard serves to identify ambiguities in the claims that can then be clarified through claim amendments."). Consistent with the patent owner's responsibility to clarify ambiguous terms, "the Office may take into consideration inconsistent statements made by a patent owner about claim scope, such as those submitted under 35 U.S.C. 301(a), when applying the 'broadest reasonable interpretation' standard." *Id*. Thus, while not controlling, claim constructions offered by a patent owner in related litigation (under the narrower standard applicable in district court) are relevant to the "broadest reasonable construction" applicable here. *See, e.g., SAP Am., Inc. v. Versata Dev. Grp., Inc.*, No. CBM2012-00001 (P.T.A.B. Jan. 9, 2013), Paper 36 at 8-9 (adopting petitioner's proposed construction, in part, because it was "consistent with [p]atentee's proposed construction in the related district court proceeding").

B. Construction of Claim Terms

All claim terms—including those not specifically addressed in this section—

have been accorded their broadest reasonable interpretation consistent with the specification of the '224 patent as understood by one of ordinary skill in the art at the time of the alleged inventions. Par provides the broadest reasonable interpretations of the following terms:

1. "pancreatic neuroendocrine tumor"

The term "pancreatic neuroendocrine tumor," which is referred to as "pancreatic NET" in this petition, is recited in claim 1: "A method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject . . . ." Ex. 1001, '224 patent at claim 1.

A person of ordinary skill in the art at the time of the alleged inventions would understand that a NET is an abnormal growth of cells of the nervous or endocrine systems within or proximal to the pancreas. Ex. 1003, Ratain Decl. ¶ 53. The '224 patent specification states that "Pancreatic neuroendocrine tumors as indicated herein e.g. include islet cell tumors, APUDomas, insulinomas, glucagonomas, nonfunctioning pancreatic NETS, pancreatic NETs associated with hypercalcemia, gastrinomas, VIPomas, somatostatinomas, GRFomas." Ex. 1001, '224 patent at 8:13-17. Reading this statement in the context of the entire patent, a skilled artisan would have understood the term "pancreatic neuroendocrine tumors" as used in the claims to include these tumors. Ex. 1003, Ratain Decl. ¶¶ 55-56.

Accordingly, the broadest reasonable construction of the claim term "pancreatic neuroendocrine tumor" is "abnormal growth of cells of the nervous or endocrine systems in the pancreas, including, e.g., islet cell tumors, APUDomas, insulinomas, glucagonomas, nonfunctioning pancreatic NETS, pancreatic NETs associated with hypercalcemia, gastrinomas, VIPomas, somatostatinomas, and GRFomas." Ex. 1003, Ratain Decl. ¶ 57.

2. "advanced tumors"

The term "advanced tumors" also appears in claim 1, "A method for treating pancreatic neuroendocrine tumors . . . wherein the tumors are advanced tumors . . . ." Ex. 1001, '224 patent at claim 1.

A person of ordinary skill in the art at the time of the alleged inventions would have understood the claim term "advanced tumors" to have its ordinary and customary meaning in the art that is consistent with the specification. As used by those of skill in the field of oncology, an "advanced" tumor is a tumor that is unresectable or metastatic. Ex. 1003, Ratain Decl. ¶ 59; *see also* Ex. 1023, Moertel at 520 (describing the patients with advanced islet cell carcinoma as having been identified with "proof of unresectable or metastatic islet-cell carcinoma.").

This plain meaning is consistent with the '224 patent specification, which correlates "advanced" tumors with "metastatic or unresectable" tumors. Ex. 1001, '224 patent at 26:57-58 ("measurable advanced (metastatic or unresentable [*sic*,

unresectable)] pancreatic neuroendocrine tumors"); Ex. 1003, Ratain Decl. ¶ 59. An unresectable tumor is one that is unable to be completely removed by surgery. *Id*.

Accordingly, the broadest reasonable construction for "advanced tumors" is "tumors that are metastatic or unresectable." *Id*. ¶ 60.

3. "unit dose"

The term "unit dose" appears in claim 2: "wherein a unit dose of [everolimus] is 10 mg/day." Ex. 1001, '224 patent at 27:5-6.

A person of ordinary skill in the art at the time of the alleged inventions would have understood that the '224 patent uses the term "unit dose" consistent with its ordinary and customary meaning. Ex. 1003, Ratain Decl. ¶ 62. A person of ordinary skill would understand the term "unit dose" to refer to a single administration of the indicated dose. *Id*. The specification of the '224 patent does not use the term "unit dose," however the specification does indicate that daily doses may be "administered in divided doses up to four times a day." Ex. 1001, '224 patent at 10:27-36. The specification thus uses the term "divided dose[]" to include the administration of a daily dose in multiple units. Ex. 1003, Ratain Decl. ¶ 62.

Accordingly, the broadest reasonable construction of the claim term "unit dose" is "dose administered as a single unit." Ex. 1003, Ratain Decl. ¶ 63.

4. "islet cell tumor"

The term "islet cell tumor" appears in claim 3: "wherein the tumor is [an] islet cell tumor." Ex. 1001, '224 patent at 27:7-8.

A person of ordinary skill in the art at the time of the alleged inventions would have understood that the '224 patent uses the term "islet cell tumor" consistent with its ordinary and customary meaning. Ex. 1003, Ratain Decl. ¶¶ 65-66. The '224 patent specification indicates that islet cell tumors are equated with pancreatic NET, identifying islet cell tumors as a synonym: "pancreatic neuroendocrine tumors (islet cell tumor)." Ex. 1001, '224 patent at 26:58-59.

Accordingly, the broadest reasonable construction of the claim term "islet cell tumor" is "abnormal growth of cells of the nervous or endocrine systems within the pancreas." Ex. 1003, Ratain Decl. ¶ 67.

VIII. TECHNICAL BACKGROUND AND STATE OF THE ART AT THE TIME OF THE PURPORTED INVENTION

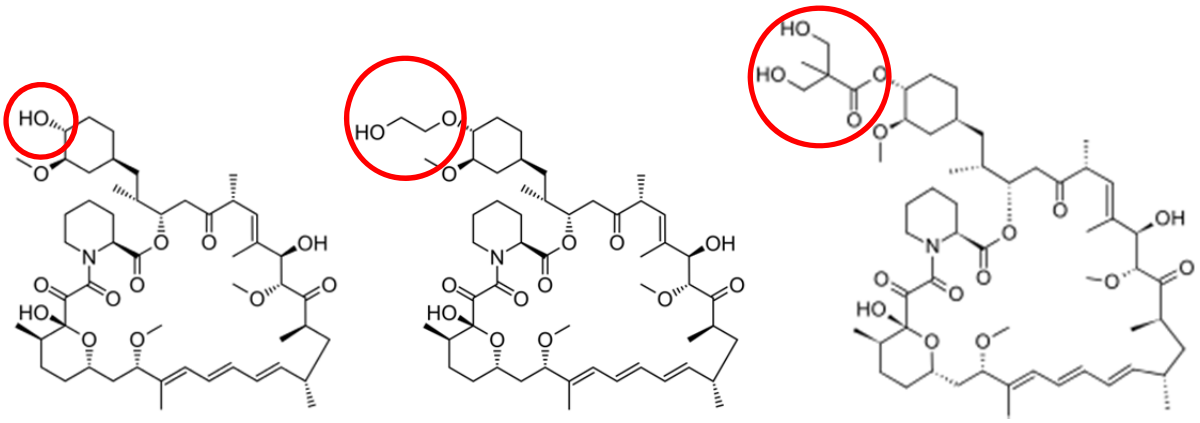
A. Rapamycin was well-known as a potent antitumor agent

Rapamycin was first discovered in a soil sample from Easter Island in the early 1970s, and scientists shortly identified its antifungal, antibiotic, and antitumor properties. Ex. 1003, Ratain Decl. ¶¶ 69-70; Ex. 1042, '171 patent at 2:7–4:14; Ex. 1013, Eng. Researchers have continued to study rapamycin in various cancer and tumor models. Ex. 1003, Ratain Decl. ¶¶ 70-71; *see also* Ex. 1044, '018 patent at 5:48-6:14 (describing the use of rapamycin in the treatment of

skin carcinomas and malignant central nervous system carcinomas); Ex. 1015, Guba. At least as early as 1999, rapamycin was identified as an antitumor agent in two pancreatic cancer cell lines, MiaPaCa-2 and Panc-2. Ex. 1014, Grewe. Additionally, rapamycin was identified as a treatment for NETs—a category that includes pancreatic NETs— in 2004. Ex. 1003, Ratain Decl. ¶ 71; Ex. 1027, Oberg 2004 at 60.

B. Rapamycin derivatives, like everolimus and temsirolimus, were known to have similar biological activity to rapamycin

Rapamycin's promising activity sparked interest among researchers in identifying rapamycin derivatives—compounds similar to rapamycin, but with small or minor modifications—with similar biological activity. *See, e.g.*, Ex. 1041, '803 patent; Ex. 1045,'036 patent; Ex. 1043, '883 patent; Ex. 1047, '730 patent at 1:47-3:6; Ex. 1049, '213 patent; Ex. 1003, Ratain Decl. ¶ 72. In 1992, Sandoz disclosed everolimus, a derivative formed by substituting the hydroxyl group at rapamycin's C40 position with a 2-hydroxyethyl group. Ex. 1048, '772 patent at 1:10-2:30; Ex. 1003, Ratain Decl. ¶ 72. That same year, American Home Products Corporation disclosed temsirolimus, a hydroxyester derivative of rapamycin also substituted at the C40 position. Ex. 1046, '718 patent; Ex. 1003, Ratain Decl. ¶¶ 73, 75. The chemical structures of rapamycin, everolimus, and temsirolimus are shown below, with the different groups at the C40 position circled in red:



Rapamycin Everolimus Temsirolimus

Ex. 1003, Ratain Decl. ¶ 75.

As of November 2005, everolimus and temsirolimus were the most well-studied rapamycin derivatives, both clinically and in the laboratory. Ex. 1012, Dutcher; Ex. 1017, Huang 2002; Ex. 1039, Vignot; Ex. 1033, Rao; Ex. 1003, Ratain Decl. ¶ 75.

Contemporary publications touted the properties of everolimus to those of ordinary skill. Specifically, it was reported that everolimus has slightly lower pharmacological properties than rapamycin *in vitro*, but comparable properties *in vivo* and was developed to overcome formulation problems with rapamycin. Ex. 1036, Schuler at 36-37, 38-40 (Tables 1-8), 41; Ex. 1003, Ratain Decl. ¶ 76. One of ordinary skill would also have known that everolimus has slightly increased bioavailability and a shorter half-life than rapamycin. Ex. 1009, Dancey, at 1105-06; Ex. 1003, Ratain Decl. ¶ 77. Everolimus was reported to have "more favorable pharmacokinetic properties" which "provide a clinical advantage, i.e., it should be

easier to handle and to monitor such a drug in clinical practice." Ex. 1036, Schuler at 41; Ex. 1003, Ratain Decl. ¶ 76. Everolimus was also known to be well-tolerated with mild side effects when administered to human patients with solid tumors. Ex. 1029, O'Donnell at 803; Ex. 1003, Ratain Decl. ¶ 79.

By November 2005, everolimus was also well-known as having promising immunosuppressant and antitumor activities. For example, the prior art taught that everolimus "is a new, orally active rapamycin-derivative that is immunosuppressive and that efficiently prevents graft rejection in rat models . . . and has therefore been selected for development." Ex. 1036, Schuler at 36, Abstract; Ex. 1005, Boulay 2004 at 252 ("[Everolimus], an orally bioavailable derivative of rapamycin, . . . demonstrates potent antiproliferative effects against a variety of mammalian cell types. . . . As a result of these properties, [everolimus] is being clinically developed both as an immunosuppressant . . . and as a novel therapeutic in the fight against human cancer."); Ex. 1003, Ratain Decl. ¶ 76. And Sandoz Ltd. described everolimus as having "particularly useful" properties for "proliferative disorders, e.g. tumors, hyper-proliferative skin disorder and the like." Ex. 1048, '772 patent at 3:22-4:10; *see also* Ex. 1036, Schuler at 36-37, 41 (describing selection of everolimus for clinical development and as having "more favorable" pharmacokinetic profile than rapamycin); Ex. 1003, Ratain Decl. ¶¶ 76-

77. Other publications agreed that everolimus shows promising anti-tumor activity. Ex. 1029, O'Donnell; Ex. 1003, Ratain Decl. ¶¶ 78-79.

By November 2005, temsirolimus was also well-known as having promising antitumor activities. The prior art reported that temsirolimus shows "promising" results as an anticancer agent for advanced stage kidney cancer and "a phase III randomized trial [] is underway." Ex. 1034, Sawyers at 344; Ex. 1003, Ratain Decl. ¶¶ 80-81. Temsirolimus was reported to be effective in reducing tumor mass when administered to mice engrafted with renal tumors, thus acting as an antineoplastic agent, "particularly for neoplasms which are refractory to standard therapy, or for whom standard therapy is not appropriate." Ex. 1054, Dukart at 2:5-7, 4:10-25; Ex. 1003, Ratain Decl. ¶ 80. Two phase I clinical trials using temsirolimus had been conducted human patients with solid tumors and lymphomas. Ex. 1054, Dukart at 5:1-6:26. Tumor size was reported to be reduced in patients with a variety of cancers, including renal carcinoma, soft tissue carcinoma, breast cancer, neuroendocrine cancer of the lung, cervical cancer, uterine cancer, head and neck cancer, glioblastoma, non-small cell lung cancer, prostate cancer, pancreatic cancer, lymphoma, melanoma, small cell lung cancer, ovarian cancer, and colon cancer. *Id*. It was further known that temsirolimus showed "promising" results as an anticancer agent for advanced stage kidney cancer. Ex. 1034, Sawyers at 344; Ex. 1003, Ratain Decl. ¶ 81.

C. The mechanism of action for the immunosuppressant and antitumor activity of rapamycin and its derivatives was well-characterized

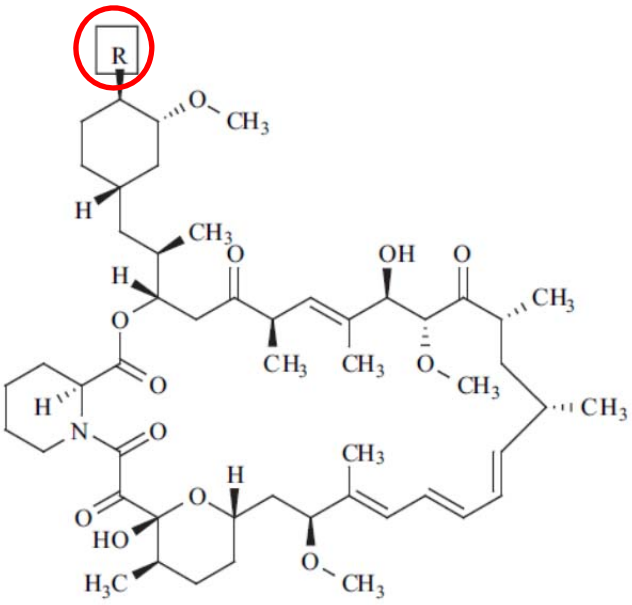
Before November 2005, researchers had made significant progress in identifying the mechanisms of action that made rapamycin and its derivatives—including everolimus and temsirolimus—biologically useful. It was known that rapamycin binds to the protein FKB12 (FK-Binding Protein 12), and that this FKBP12-rapamycin complex inhibited the activity of the mTOR protein. Ex. 1037, Tolcher at S41-42; Ex. 1005, Boulay 2004 at 252 ("[Everolimus], like rapamycin, binds with high affinity to a ubiquitous intracellular receptor, the immunophilin FKBP12. This complex specifically interacts with . . . mTOR . . ., inhibiting downstream signaling events."); Ex. 1003, Ratain Decl. ¶ 83.

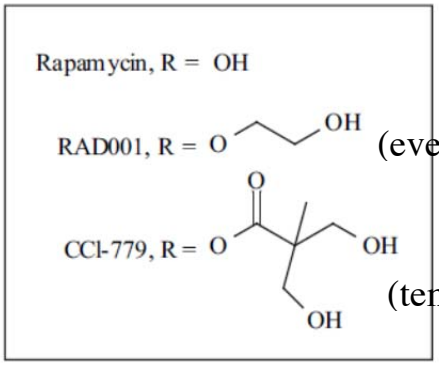
It was also known that mTOR played a role in the Akt/PI3 kinase signal transduction pathway, which mediates proliferative signals and thus was "an attractive target for chemoprevention drug development." Ex. 1037, Tolcher at S41-42; Ex. 1003, Ratain Decl. ¶ 84. Abnormalities in this AktPI3-mTOR pathway were known to be implicated in a number of different cancers, including pancreatic NETs. Ex. 1031, Perren at 1097, Abstract, 1101-02; Ex. 1009, Dancey at Table 1; Ex. 1003, Ratain Decl. ¶¶ 89, 96-97.

The FKBP12-rapamycin complex was known to inhibit the progression of the G1 phase of the cell cycle in osteosarcoma, liver, and T-cells, and interferes with mitogenic signaling pathways involved in G1 progression. Ex. 1006, Brown

at 756; Ex. 1003, Ratain Decl. ¶ 85. This activity—the FKBP12- rapamycin complex inhibition of mTOR—was known to be responsible for the antiproliferative properties of rapamycin and its derivatives, including everolimus. Ex. 1039, Vignot at Abstract; Ex. 1033, Rao at 622; Ex. 1005, Boulay 2004 at 252-53; Ex. 1003, Ratain Decl. ¶ 86.

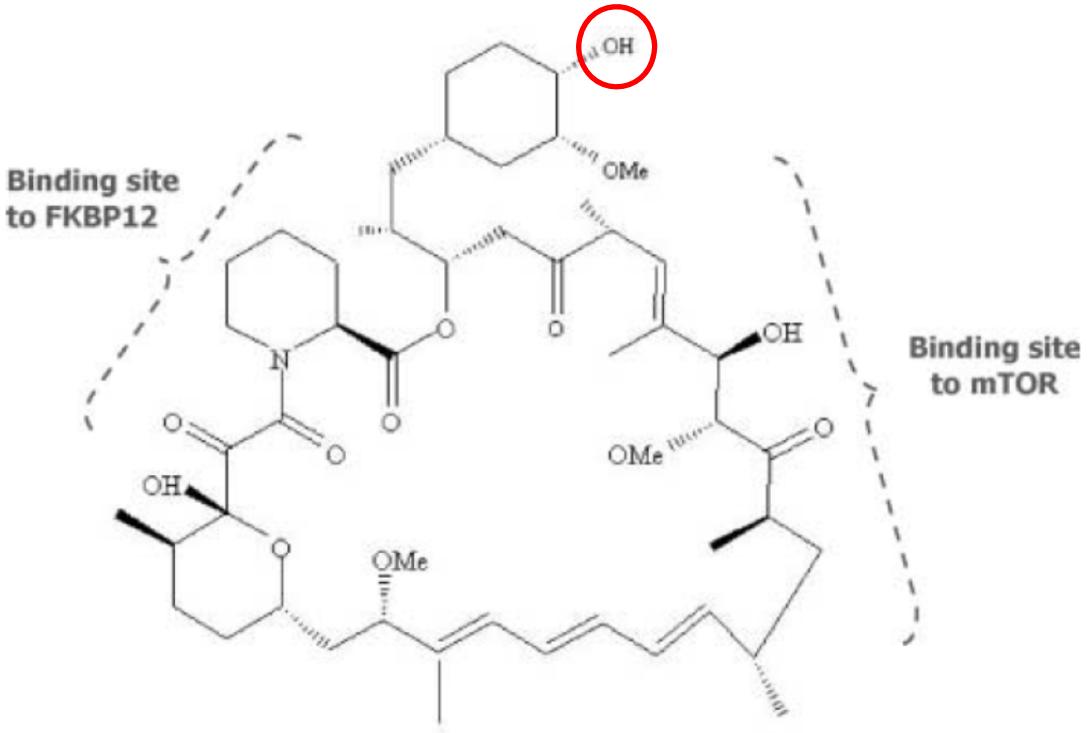
The mTOR and FKBP12-binding domains of rapamycin had been identified. *See, e.g.*, Ex. 1006, Brown; Ex. 1035, Schreiber at Fig. 5. Everolimus and temsirolimus were known to differ structurally from rapamycin only where circled in red below. This portion of the molecule is distanced from the mTOR and FKBP12-binding sites:





(everolimus)

(temsirolimus)



Ex. 1018, Huang 2003 at Fig. 1; Ex. 1033, Rao at Fig. 1; Ex. 1003, Ratain Decl. ¶ 91.

Thus, as of November 2005, a skilled artisan would have expected everolimus and temsirolimus each to have similar activity to their parent compound, rapamycin, in the mTOR signaling cascade. *See, e.g.*, Ex. 1018, Huang 2003 at Abstract; Ex. 1033, Rao at Abstract; Ex. 1003, Ratain Decl. ¶ 92. Further, a skilled artisan would have expected these mTOR inhibitors to be effective in tumor cells with hyperactivation of mTOR signaling, such as NETs. Ex. 1003, Ratain Decl. ¶¶ 88, 97-98; Ex. 1051, Wang 2002 at 140, Table 1, 144; Ex. 1028, Oberg & Ericksson at 755-56, Table 1.

IX. THE SCOPE AND CONTENT OF THE ASSERTED PRIOR ART

A. Oberg 2004 taught that humans with advanced pancreatic NETs should be treated with rapamycin as a monotherapy after cytotoxic therapy failed

Oberg 2004 (Ex. 1027) is prior art to the '224 patent under at least 35 U.S.C. § 102(b), because it published in April 2004, more than one year before the '224 patent's November 2005 priority date. *See* Oberg 2004; Ex. 1061, Bennett Decl. ¶¶ 44-53.

Oberg 2004 is a journal article disclosing the then-standard treatment protocols for NETs, a category that includes pancreatic NETs. *See, e.g.*, Oberg 2004 at 59; Ex. 1003, Ratain Decl. ¶¶ 100-108. Oberg 2004 reported the "clinical management of metastatic NE tumours." *Id*. at 57. A person of skill in the art thus would understand that Oberg 2004's description of treating NETs includes the treatment of advanced (*i.e.*, metastatic or unresectable) NETs. Ex. 1003, Ratain Decl. ¶¶ 101, 103.

Oberg 2004 graphically disclosed the therapy choices for treating NETs, including advanced NETs:

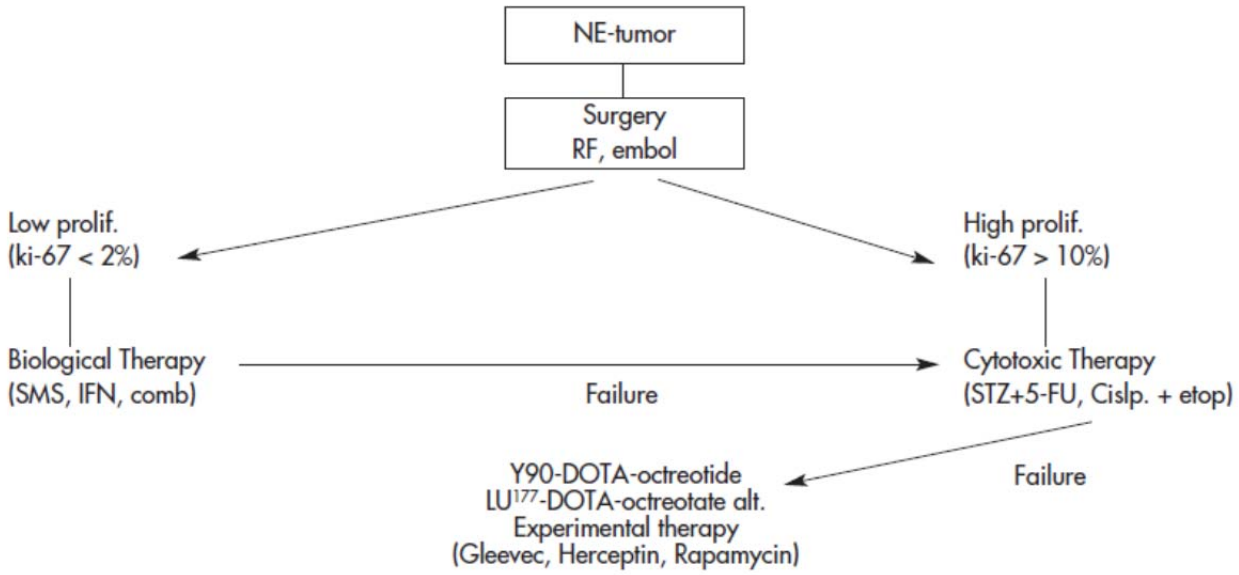


Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Oberg 2004 at Fig.1; Ex. 1003, Ratain Decl. ¶ 102. According to Oberg 2004, when treating NETs, surgery is the first option. Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶¶ 102-103. If the surgery is not successful or possible, then the tumor is unresectable and thus advanced. Ex. 1003, Ratain Decl. ¶ 59. For these advanced tumors, the next step is chosen based on whether the tumor is low-proliferative or high-proliferative. Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶ 103. Low-proliferative tumors are treated first with biological therapies, such as interferon (IFN) or somatostatin inhibitors (SMS), and then cytotoxic therapy (*e.g.*, cytotoxic chemotherapeutics) if they fail to respond to biological therapies. Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶ 103. High-proliferative tumors are treated with cytotoxic therapy. Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶ 103. For any advanced (*i.e.*, unresectable) NETs which receive but are non-responsive to

cytotoxic chemotherapies, experimental therapies are next recommended. Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶ 103. One of the disclosed experimental therapies is rapamycin. Oberg 2004 at Fig. 1, 60; Ex. 1003, Ratain Decl. ¶¶ 103-104.

Oberg 2004 expressly described rapamycin as "[a]nother interesting new compound" that "may block signal transduction through the m-TOR pathway. Clinical trials with this compound as a single agent or in combination with cytotoxic agents are planned." Oberg 2004 at 60; Ex. 1003, Ratain Decl. ¶ 104. Oberg 2004 thus taught that rapamcyin's mTOR-inhibition properties are the reason for its use in treating NETs. Oberg 2004 at 60; Ratain Decl. ¶ 104. The recommendation to use rapamycin as a therapy for advanced NETs, including advanced pancreatic NETs, was echoed in Wiedenmann 2004, which identifies rapamycin as a "new targeted therap[y] that offer[s] new hope" "in order to improve current, rather limited treatment options especially in metastatic NET disease." Ex. 1052, Wiedenmann 2004 at 97; Ex. 1003, Ratain Decl. ¶¶ 105-108.

Oberg 2004 only differs from claims 1 and 3 of the '224 patent in that it does not explicitly disclose the use of everolimus and discloses rapamycin as a monotherapy in the treatment of human patients with advanced pancreatic NETs after the failure of cytotoxic chemotherapy. Oberg 2004 also does not include an

explicit description of a 10 mg/day unit dose of everolimus as recited in claim 2 of the '224 patent.

B. Boulay 2004 taught that everolimus was well-tolerated and effective at treating pancreatic NETs in rat models

Boulay 2004 (Ex. 1005) is prior art to the '224 patent under at least 35 U.S.C. § 102(b), because it published in January 2004, more than one year before the '224 patent's November 2005 priority date. *See* Boulay 2004; Ex. 1061, Bennett Decl. ¶¶ 54-62.

Boulay 2004 disclosed that everolimus, "like rapamycin, binds with high affinity to . . . FKBP12" and that "[t]his complex specifically interacts with . . . mTOR" to "inhibit[] downstream signaling events." *Id*. at 252. Boulay 2004 disclosed that everolimus was being clinically developed for anti-cancer therapeutics in humans. *Id*. ("[Everolimus], an orally bioavailable derivative of rapamycin, . . . demonstrates potent antiproliferative effects against a variety of mammalian cell types. . . . As a result of these properties, [everolimus] is being clinically developed both as an immunosuppressant . . . and as a novel therapeutic in the fight against human cancer."); *see also id*. at 253; Ex. 1003, Ratain Decl. ¶ 110. Specifically, Boulay 2004 disclosed concurrent clinical trials of everolimus in humans with cancer. Boulay 2004 at 252, 260; Ex. 1003, Ratain Decl. ¶ 110.

Boulay 2004 also disclosed the use of everolimus as a monotherapy in treating rats with CA20948 tumors, which are a specific line of pancreatic NETs

used in laboratory studies. Boulay 2004 at Abstract; Ex. 1003, Ratain Decl. ¶¶ 111-112. Boulay 2004 described this treatment as causing "antitumor activity characterized by statistically significant inhibition of tumor growth as compared with vehicle controls." Boulay 2004 at 254; Ratain Decl. ¶ 113. Boulay 2004 disclosed that "[f]or all treatment schedules, [everolimus] was well tolerated" and elicited antitumor potency equivalent to that of the positive control, the cytotoxic agent 5-FU. Boulay 2004 at 254, 258; Ex. 1003, Ratain Decl. ¶¶ 115-116. Boulay 2004 disclosed that it is the "first full publication demonstrating significant antitumor efficacy of a rapamycin derivative in an animal model of pancreatic cancer." Boulay 2004 at 258; Ex. 1003, Ratain Decl. ¶ 117. Boulay 2004 disclosed that everolimus was "administered p.o. daily at 0.5 or 2.5 mg/kg (x6/week)," which indicates that the tumor-bearing rats in the study were given everolimus once per day by mouth at two different total doses (0.5 or 2.5 mg/kg) and that this once-daily treatment was administered six times over the course of a week. Ex. 1003, Ratain Decl. ¶ 114. Boulay 2004 further disclosed that everolimus was administered in doses of "0.5 mg/kg qd x6" and "2.5 mg/kg qd x6." Boulay 2004 at 254, Fig. 1 at legend. One of ordinary skill would understand a dose administered "qd" is a dose administered once per day in a single administration. Ex. 1003, Ratain Decl. ¶ 114. Boulay 2004 thus disclosed the administration of everolimus as a monotherapy in a daily unit dose.

Boulay 2004 only differs from claims 1 and 3 of the '224 patent in that it does not (1) report efficacy in human patients with advanced pancreatic NETs (although it does disclose concurrent clinical trials in humans with cancer), or (2) explicitly identify administration after the failure of cytotoxic chemotherapy. Boulay 2004 also does not include an explicit description of a 10 mg/day unit dose of everolimus as recited in claim 2 of the '224 patent, although it does disclose the daily administration of unit doses of everolimus.

C. O'Donnell taught that everolimus was well-tolerated and showed promise as an antitumor agent in human patients

O'Donnell (Ex. 1029) is prior art to the '224 patent under at least 35 U.S.C. § 102(b), because it published in June 2003, more than one year before the '224 patent's November 2005 priority date. *See* O'Donnell; Ex. 1061, Bennett Decl. ¶¶ 63-71.

O'Donnell disclosed the administration of various dosage levels of everolimus as a monotherapy to human patients with solid tumors. *Id*.; Ex. 1003, Ratain Decl. ¶ 119. O'Donnell disclosed that the treatments were "well tolerated" and only had "mild degrees" of side effects, and that "7/8 patients exhibited inhibition for at least 7 days." O'Donnell at 803; Ex. 1003, Ratain Decl. ¶¶ 120-121. O'Donnell disclosed that patients were administered everolimus "once weekly" at 4 dose levels: 5, 10, 20, and 30 mg. O'Donnell at 803. A person of ordinary skill in the art would have understood from this that everolimus was

administered in a single dose. Ex. 1003, Ratain Decl. ¶ 119. O'Donnell disclosed that other additional clinical studies had been initiated to explore everolimus's ability to treat human tumors. O'Donnell at 803; Ex. 1003, Ratain Decl. ¶ 123.

O'Donnell differs from claims 1 and 3 of the '224 patent only in that it does not (1) explicitly disclose the treatment of humans with advanced pancreatic NETs (although it does disclose clinical trials in humans with solid tumors), or (2) explicitly teach administration after the failure of cytotoxic chemotherapy. O'Donnell also does not include an explicit description of a 10 mg/day unit dose of everolimus as recited in claim 2 of the '224 patent, although it does disclose the administration of a unit dose of everolimus.

D. Tabernero taught that an appropriate dosage for humans taking everolimus for the treatment of advanced solid tumors was 10 mg/day

Tabernero (Ex. 1038) is prior art to the '224 patent under at least 35 U.S.C. § 102(a), because it was published in June 2005, before the '224 patent's November 2005 priority date. *See* Tabernero; Ex. 1061, Bennett Decl. ¶¶ 72-81.

Tabernero disclosed that everolimus was an mTOR-inhibitor, and further disclosed data from an investigation of everolimus's safety and recommended dosage levels for the treatment of cancer. *Id*. at 3007; Ex. 1003, Ratain Decl. ¶¶ 125-127. Tabernero disclosed that the safety and dosage levels were being investigated to develop everolimus further as an anti-tumor agent. Tabernero at 3007. Tabernero disclosed the treatment of human patients with advanced solid

tumors with everolimus in dosages of 20, 50, or 70 mg weekly, or 5 or 10 mg daily. Tabernero at 3007; Ex. 1003, Ratain Decl. ¶ 126. A person of ordinary skill in the art would have understood that in describing the doses as given "weekly" or "daily," that the doses were given once per day or once per week. Ex. 1003, Ratain Decl. ¶ 126. Tabernero disclosed that everolimus was effective at inhibiting mTOR in the studied tumors. Tabernero at 3007; Ex. 1003, Ratain Decl. ¶ 125. Tabernero recommended a unit dose of 10 mg/day of everolimus as a monotherapy for further phase II/phase III clinical trials for treatment of solid tumors, which would include pancreatic NETs. Tabernero at 3007; Ex. 1003, Ratain Decl. ¶ 127.

Tabernero differs from claim 2 of the '224 patent only in that it does not (1) explicitly identify the treatment of human patients with advanced pancreatic NETs, or (2) disclose administration after the failure of cytotoxic chemotherapy.

E. Duran taught the use of temsirolimus in the treatment of human patients with advanced neuroendocrine carcinomas

Duran (Ex. 1011) is prior art to the '224 patent under at least 35 U.S.C. § 102(a), because it published in June 2005, before the '224 patent's November 2005 priority date. *See* Duran; Ex. 1061, Bennett Decl. ¶¶ 82-91.

Duran disclosed the use of the rapamycin-derivative temsirolimus in the treatment of human patients with metastatic neuroendocrine carcinomas (NECs), a subset of advanced NETs. *Id*. at 3096; Ex. 1003, Ratain Decl. ¶¶ 94, 129-130. Duran explicitly identified that NECs include "islet cell carcinomas," a subset of

islet cell tumors. Duran at 3096; Ex. 1003, Ratain Decl. ¶ 129. Of the twenty-three patients who received temsirolimus treatment, eleven had previously undergone chemotherapy treatment. Duran; Ex. 1003, Ratain Decl. ¶ 130. Duran disclosed that temsirolimus "appears to have antitumor activity in NECs." Duran at 3096; Ex. 1003, Ratain Decl. ¶ 130.

Duran differs from claims 1 and 3 of the '224 patent in that it identifies the use of temsirolimus instead of everolimus in the treatment of patients with advanced NETs or islet cell tumors. Duran also does not include an explicit description of a 10 mg/day unit dose of everolimus as recited in claim 2 of the '224 patent.

X. CLAIMS 1-3 WOULD HAVE BEEN OBVIOUS OVER THE PRIOR ART

For the specific reasons explained below, a person of ordinary skill in the art would have found claims 1-3 of the '224 patent obvious in November 2005.

A. Legal Background

A patent claim is unpatentable if it is obvious in view of the prior art. 35 U.S.C. § 103. A finding of unpatentability requires that a claim be anticipated or obvious from the perspective of a skilled artisan at the time the invention was made. *Id*. In analyzing obviousness in light of the prior art, it is important to understand the scope of the claims, the level of skill in the relevant art, the scope and content of the prior art, the differences between the prior art and the claims,

and any secondary considerations of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. There may also be a specific teaching, suggestion, or motivation to combine a prior art reference with another prior art reference. *E.g.*, *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665 (Fed. Cir. 2000). Such a teaching, suggestion, or motivation to combine the prior art references may be explicit or implicit in the prior art. *Id.*

A patent is obvious when it "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement," as long as there is reason to combine the elements. *KSR*, 550 U.S. at 417-18 (internal quotation marks omitted). Similarly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.* at 417.

"[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the

elements in the manner claimed." *KSR*, 550 U.S. at 420. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id*. at 421.

The obviousness inquiry takes "an expansive and flexible approach" to determine the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. *Id*. at 407, 415. It considers "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id*. at 418. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id*. at 421. Thus a patent is obvious when it "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement," as long as there is reason to combine the elements. *Id*. at 417-18. For instance, "[c]ombining two embodiments disclosed adjacent to each other in a prior art patent does not require a leap of inventiveness." *Boston Sci. Scimed, Inc. v. Cordis Corp*., 554 F.3d 982, 991 (Fed. Cir. 2009). Similarly, "if a technique has been used to improve one device, and a

person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. The specific motivations for the combinations of the relied-upon references are discussed in the below section. The specific motivations to combine the references are discussed in the Grounds below.

B. Ground 1: Claims 1-3 would have been obvious in view of Oberg 2004, Boulay 2004, and O'Donnell

1. Claim 1

Claim 1 claims "[a] method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need thereof a therapeutically effective amount of [everolimus] as a monotherapy and wherein the tumors are advanced tumors after failure of cytotoxic chemotherapy." Ex. 1001, '224 patent.

A person of ordinary skill in the art seeking to treat humans with advanced pancreatic NETs after the failure of cytotoxic chemotherapy would have looked to the teachings of Dr. Kjell Oberg. Before November 2005, Dr. Oberg was one of the preeminent clinical researchers on NETs. Ex. 1058, Oberg Biography; Ex. 1003, Ratain Decl. ¶ 132. He was one of the founders of the European Nueroendocrine Tumor Society ("ENETS"), whose primary aims was to "establish guidelines for the diagnosis and therapy of gastroenteropancreatic neuroendocrine tumors." Ex. 1058, Oberg Biography; Ex. 1059, ENETS Info; Ex. 1003, Ratain

Decl. ¶ 132. By November 2005, Dr. Oberg had also published numerous articles on NET treatment. Ex. 1058, Oberg Biography; Ex. 1003, Ratain Decl. ¶ 132.

Oberg 2004 taught the use of rapamycin as a monotherapy for the treatment of human patients with advanced pancreatic NETs after the failure of cytotoxic therapy. Ex. 1027, Oberg 2004; Ex. 1003, Ratain Decl. ¶ 133. Oberg 2004 depicted the then-standard treatment for NETs, which includes pancreatic NETs:

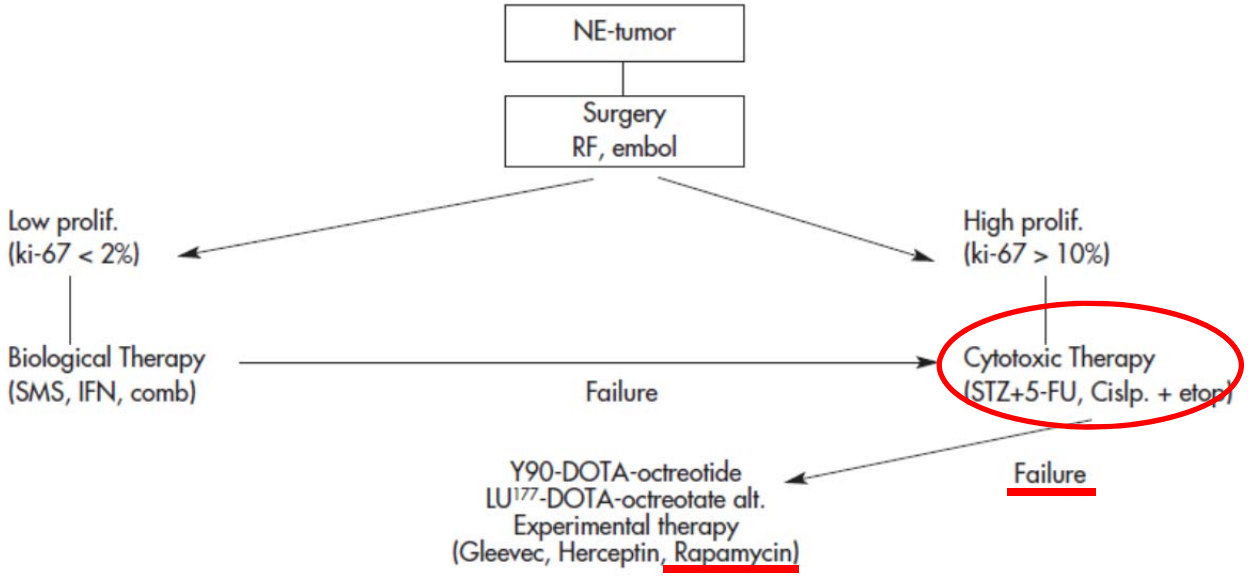


Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Ex. 1027, Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶¶ 133, 146. Oberg 2004 stated that NETs should be treated with cytotoxic therapy (*e.g.*, cytotoxic chemotherapeutics) for unresectable (*i.e.*, advanced) high proliferative tumors and unresectable (*i.e.*, advanced) low proliferative tumors that did not respond to biological therapies. Ex. 1027, Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶ 133. If cytotoxic therapies failed to treat any advanced NET, Oberg taught the use of

various experimental therapies, including rapamycin. Ex. 1027, Oberg 2004 at Fig. 1; Ex. 1003, Ratain Decl. ¶¶ 133, 146.

Oberg described rapamycin as "[a]nother interesting new compound" that "may block signal transduction through the m-TOR pathway. Clinical trials with this compound as a single agent or in combination with cytotoxic agents are planned." Ex. 1027, Oberg 2004 at 60. A person of ordinary skill in the art would have understood from Oberg 2004 that rapamycin's mTOR-inhibition properties are the reason for its usefulness in treating advanced NETs. Ex. 1003, Ratain Decl. ¶ 146. Because Oberg 2004 taught that it is rapamycin's ability to inhibit mTOR that made it a useful treatment for advanced NETs, a person of ordinary skill in the art would have understood that Oberg 2004's teachings would extend to other rapamycin derivatives known to be mTOR inhibitors, such as everolimus and temsirolimus. Ex. 1003, Ratain Decl. ¶ 135. In fact, there were no reported data of rapamycin administered to cancer patients, in contrast to its known active derivatives, everolimus and temsirolimus. *Id*. ¶¶ 104, 135. As such, a skilled artisan would have understood Oberg 2004's reference to rapamycin to include the derivatives with known clinical safety and efficacy in cancer patients. *Id*.

By November 2005, everolimus and temsirolimus were the most studied rapamycin derivatives for their clinical efficacy in various cancers. Ex. 1029, O'Donnell; Ex. 1054, Dukart; Ex. 1009, Dancey; Ex. 1038, Tabernero; Ex. 1011,

Duran; Ex. 1003, Ratain Decl. ¶¶ 75, 135-136. And everolimus was known to have a "clinical advantage" over rapamycin and be more bioavailable. Ex. 1003, Ratain Decl. ¶¶ 76-77. A person of ordinary skill in the art seeking to treat human patients with advanced pancreatic NETs after the failure of cytotoxic chemotherapy using the "experimental drug" specifically suggested by Oberg 2004 would have also looked to rapamycin derivatives with similar antitumor and mTOR-inhibition properties to rapamycin, especially those that had demonstrated safety and efficacy in human cancer patients or those shown to be effective in treating pancreatic NETs in preclinical models. Ex. 1003, Ratain Decl. ¶¶ 137-138, 149-151.

Specifically, a skilled artisan would have looked to other rapamycin derivatives to use as a treatment for pancreatic NETs as taught in Oberg 2004, and Boulay 2004 reference disclosed data showing that the use of everolimus in a rat pancreatic NET model was effective and well-tolerated as a monotherapy. Ex. 1005, Boulay 2004; Ex. 1003, Ratain Decl. ¶¶ 111-113, 137.

Boulay 2004 disclosed the successful use of everolimus as a monotherapy in a rat model of pancreatic NETs. Ex. 1005, Boulay 2004 at 252-54; Ex. 1003, Ratain Decl. ¶¶ 111-113. Specifically, rats with CA20948 pancreatic NETs were given daily doses of 0.5 or 2.5 mg/kg of everolimus. Ex. 1005, Boulay 2004 at 252. The treatments were "well tolerated, with no significant body weight loss or

mortalities observed," and resulted in statistically significant antitumor activity. *Id*. at 254.

A skilled artisan would have been motivated by Boulay 2004 to substitute rapamycin with everolimus for the treatment of humans with pancreatic NETs as taught in Oberg 2004 because of the encouraging data on its effectiveness in this rat model of pancreatic NET. Ex. 1003, Ratain Decl. ¶¶ 112, 137. And a skilled artisan would have been had a reasonable expectation that everolimus would be effective in humans because O'Donnell taught that the use of everolimus in human cancer patients was effective and safe. Ex. 1029, O'Donnell; Ex. 1003, Ratain Decl. ¶¶ 120-121, 138. O'Donnell disclosed the use of various dosage levels of everolimus in the treatment of human patients with solid tumors and taught that the treatments were "well tolerated" and only had mild side effects. Ex. 1029, O'Donnell; Ex. 1003, Ratain Decl. ¶¶ 120-121, 138. O'Donnell disclosed that other additional clinical studies had been initiated to explore everolimus's ability to treat human tumors. Ex. 1029, O'Donnell; Ex. 1003, Ratain Decl. ¶ 123.

As discussed, a skilled artisan would have been motivated to combine the teachings of Oberg 2004, Boulay 2004, and O'Donnell, and this combination "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement." *KSR*, 550 U.S. at 417, 420 ("[A]ny need or problem known in the

field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."); *see also Beattie*, 974 F.2d at 1312.

Here, cancer patients with advanced pancreatic NETs need additional treatment after chemotherapy fails. Ex. 1003, Ratain Decl. ¶ 99. Oberg 2004 taught using rapamycin as a monotherapy to treat advanced pancreatic NETs after the failure of cytotoxic chemotherapy; Boulay 2004 taught that everolimus was effective as a monotherapy in treating pancreatic NETs in mammals; and O'Donnell taught that everolimus was safe and effective in humans for the treatment of solid tumors. A person of ordinary skill in the art would have had a reasonable expectation of success in using everolimus as a monotherapy instead of rapamycin as taught in Oberg 2004 because Boulay 2004 demonstrated that everolimus was effective in treating pancreatic NETs in mammals. If everolimus was effective in the preclinical model for pancreatic NETs, a skilled artisan would reasonably have expected that it would be effective in treating humans with pancreatic NETs. Ex. 1003, Ratain Decl. ¶ 112. Accordingly, claim 1 would have been obvious over this combination. *Id*. ¶¶ 149-151.

2. Claim 2

Claim 2 depends from claim 1 and further recites "wherein a unit dose of [everolimus] is 10 mg/day." The limitations of claim 2 are obvious for all the reasons discussed above for claim 1.

O'Donnell disclosed that everolimus was administered as a unit dose weekly at 5, 10, 20, and 30 mg for treatment of solid tumors, but did not explicitly disclose a unit dose of 10 mg/day. Ex. 1029, O'Donnell. Boulay 2004 further disclosed that everolimus in a unit dose of 0.5 or 2.5 mg/kg daily resulted in antitumor activity in the rat pancreatic NET model, but it too did not explicitly disclose a unit dose to a human of 10 mg/day. Ex. 1005, Boulay 2004 at 253, 254. Other reports indicated that everolimus was administered at 5-10 mg/day in clinical studies. Ex. 1039, Vignot at Table 1; Ex. 1003, Ratain Decl. ¶ 152.

Regardless, the dose recited in claim 2 would have been obvious because the '224 patent does not set forth any human clinical or laboratory data showing that a daily unit dose of 10 mg is optimal compared to any other dose of everolimus. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (finding claim limitation regarding dosage obvious when the patent "sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent" to distinguish any "concerns for

dose-related GI problems"); Ex. 1003, Ratain Decl. ¶ 153; *see generally* Ex. 1001, '224 patent.

Further, identifying an appropriate and effective dose for the treatment of tumors (*e.g.*, dose titration) is a standard exercise requiring nothing more than routine experimentation. Ex. 1003, Ratain Decl. ¶ 153. Identifying such a dose "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007), quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Thus, a person of ordinary skill in the would have been motivated to identify an appropriate dose of everolimus to effectively treat humans with advanced pancreatic NETs, including a unit dose of 10 mg/day. Ex. 1003, Ratain Decl. ¶ 153. As such, claim 2 would have been obvious over this combination.

3. Claim 3

Claim 3 depends from claim 1 and further recites "wherein the tumor is [an] islet cell tumor." The limitations of claim 1 are obvious for all the reasons discussed above.

With respect to claim 3, an islet cell tumor is a subset of pancreatic NETs and thus teachings in the art directed to the treatment of NETs and pancreatic NETs would apply equally to islet cell tumors. Ex. 1003, Ratain Decl. ¶¶ 156-157. As such, claim 3 would have been obvious over this combination.

C. Ground 2: Claim 2 would have been obvious in view of Oberg 2004, Boulay 2004, O'Donnell, and Tabernero

Claim 2 depends from claim 1 and further recites "wherein a unit dose of [everolimus] is 10 mg/day," and would have been obvious over the above-discussed Oberg 2004 combination, in further view of Tabernero.

The only limitation present in claim 2 but not in claim 1, is the 10 mg/day unit dose limitation. Ex. 1001, '224 patent. Although dose titration to identify effective doses is a routine skill known to a skilled artisan, a skilled artisan would have also searched for available everolimus dosage information. Ex. 1003, Ratain Decl. ¶¶ 143, 152, 159 . Tabernero expressly recommended a unit dose of 10 mg/day of everolimus for treating humans with advanced solid tumors. Ex. 1038, Tabernero. Specifically, after examining the safety and proper dosage levels of everolimus as an antitumor agent for advanced solid tumors, Tabernero disclosed that a unit dose of 10 mg/day was well-tolerated and effective and recommended that dosage for further clinical trials with everolimus as a single agent (*i.e.*, as a monotherapy). Ex. 1038, Tabernero; Ex. 1003, Ratain Decl. ¶ 159.

Tabernero expressly identified a recommended daily unit dose for treating advanced solid tumors and taught that this unit dose was well-tolerated and effective. A skilled artisan would therefore have had a reasonable expectation of success in achieving an effective therapy for advanced pancreatic NETs after failure of cytotoxic chemotherapy in administering a unit dose of 10 mg/day of

everolimus in combining Oberg 2004, Boulay 2004, and O'Donnell with Tabernero. Ex. 1003, Ratain Decl. ¶¶ 143, 160. Accordingly, claim 2 is obvious over this combination.

D. Ground 3: Claims 1-3 would have been obvious in view of Boulay 2004, O'Donnell, and Duran

1. Claim 1

A skilled artisan seeking to treat advanced pancreatic NETs in humans after the failure of cytotoxic chemotherapy would have identified Boulay 2004, which disclosed that everolimus treatment was successful as a monotherapy in a rat pancreatic NET model. Ex. 1005, Boulay 2004; Ex. 1003, Ratain Decl. ¶¶ 112, 141. A skilled artisan would have known that everolimus would be safe and effective in human cancer patients. Ex. 1003, Ratain Decl. ¶¶ 119-121. O'Donnell taught that everolimus treatment was well-tolerated and effective in treating human cancer patients with solid tumors. Ex. 1029, O'Donnell; Ex. 1003, Ratain Decl. ¶¶ 119-123. Duran further taught that the related mTOR inhibitor and similar rapamcyin derivative, temsirolimus, had been shown to be safe and effective as a monotherapy in treating human patients with advanced NET previously treated with cytotoxic chemotherapy. Ex. 1011, Duran; Ex. 1003, Ratain Decl. ¶¶ 129-131, 142. Because temsirolimus was known to have similar anti-tumor properties as everolimus and was known to be an mTOR inhibitor like both rapamycin and everolimus and was known to be effective in humans with NETs, a skilled artisan

would have a reasonable expectation that everolimus would also be safe and effective as a monotherapy in treating human patients with advanced NET previously treated with chemotherapy. Ex. 1003, Ratain Decl. ¶¶ 75, 82, 87-88, 91-92, 142. Thus, the prior art taught that everolimus was effective as a monotherapy in a rat model of pancreatic NET (Boulay 2004), everolimus was safe and effective as a monotherapy in treating solid tumors in human patients (O'Donnell), and the related rapamycin derivative temsirolimus was safe and effective as a monotherapy in treating advanced NET in humans after failure of chemotherapy (Duran). A skilled artisan would have been motivated to administer everolimus after failure of cytotoxic chemotherapy because such therapy was the "gold standard" but associated with low success rates. Ex. 1003, Ratain Decl. ¶ 166. As such, a skilled artisan would have been aware of the need for additional treatment options after chemotherapy failed. *Id*. ¶¶ 99, 166.

A skilled artisan would have had a reasonable expectation of success in administering everolimus as a monotherapy to human patients with advanced pancreatic NETs after the failure of cytotoxic chemotherapy in light of the teachings of Boulay 2004, O'Donnell, and Duran. Ex. 1003, Ratain Decl. ¶ 167. Accordingly, claim 1 of the '224 patent would have been obvious in view of this combination.

2. Claim 2

Claim 2 depends from claim 1 and further recites "wherein a unit dose of [everolimus] is 10 mg/day." The limitations of claim 2 are obvious for all the reasons discussed above for claim 1.

O'Donnell disclosed that everolimus was administered to humans in weekly unit doses at 5, 10, 20, and 30 mg for treatment of solid tumors but did not explicitly disclose a unit dose of 10 mg/day. Ex. 1029, O'Donnell. Boulay 2004 further disclosed that everolimus administered in daily unit doses of 0.5 or 2.5 mg/kg resulted in antitumor activity in the rat pancreatic NET but did not explicitly disclose a unit dose to a human of 10 mg/day. Ex. 1005, Boulay 2004 at 253, 254. Other clinical reports disclosed everolimus administered at 5-10 mg/day. Ex. 1039, Vignot at Table 1; Ex. 1003, Ratain Decl. ¶ 169.

Regardless, the dose recited in claim 2 would have been obvious because the '224 patent does not set forth any human clinical or laboratory data showing that a daily unit dose of 10 mg is optimal compared to any other dose of everolimus. *Merck*, 395 F.3d at 1374 (finding claim limitation regarding dosage obvious when the patent "sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent" to distinguish any "concerns for dose-related GI problems"); Ex. 1003, Ratain Decl. ¶ 170; *see generally* Ex. 1001, '224 patent.

Further, identifying an appropriate and effective dose for the treatment of tumors (*e.g.*, dose titration) is a standard exercise requiring nothing more than routine experimentation. Ex. 1003, Ratain Decl. ¶ 169. Identifying such a dose "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Pfizer*, 480 F.3d at 1368, quoting *Peterson*, 315 F.3d at 1330. Thus, a person of ordinary skill in the art would have been motivated to identify an appropriate dose of everolimus to effectively treat humans with advanced pancreatic NETs, including a unit dose of 10 mg/day. As such, claim 2 would have been obvious over this combination.

3. Claim 3

Claim 3 depends from claim 1 and further recites "wherein the tumor is [an] islet cell tumor." The limitations of claim 1 are obvious for all the reasons discussed above.

With respect to claim 3, an islet cell tumor is a subset of pancreatic NETs and thus teachings in the art directed to the treatment of NETs and pancreatic NETs would apply equally to islet cell tumors. Ex. 1003, Ratain Decl. ¶ 173. Indeed, Duran explicitly identified islet cell carcinomas as included within NEC. Ex. 1011, Duran at 3096. As such, claim 3 would have been obvious over this combination.

E. Ground 4: Claim 2 of the '224 patent is invalid as obvious in view of Boulay 2004, O'Donnell, Duran, and Tabernero

Claim 2 depends from claim 1 and further recites "wherein a unit dose of [everolimus] is 10 mg/day," and would have been obvious over the above-discussed Boulay 2004 combination, in further view of Tabernero.

The only limitation present in claim 2 but not in claim 1, is the 10 mg/day unit dose limitation. Ex. 1001, '224 patent. Although dose titration to identify effective doses is a routine skill known to a skilled artisan, a skilled artisan would also search for available dosage information. Ex. 1003, Ratain Decl. ¶¶ 143, 169, 176. Tabernero expressly recommended a unit dose of 10 mg/day of everolimus for treating human tumors. Ex. 1038, Tabernero. Specifically, after examining the safety and proper dosage levels of everolimus as an antitumor agent, Tabernero disclosed that a unit dose of 10 mg/day was well-tolerated and effective and recommended that dosage for further clinical trials with everolimus as a single agent (*i.e.*, as a monotherapy). Ex. 1038, Tabernero; Ex. 1003, Ratain Decl. ¶ 176.

Tabernero expressly identified a recommended daily unit dose for treating advanced solid tumors and taught that it was well-tolerated and effective. A skilled artisan would therefore have had a reasonable expectation of success in achieving an effective therapy for advanced pancreatic NETs after failure of cytotoxic chemotherapy in administering a unit dose of 10 mg/day in combining the

teachings of Boulay 2004, O'Donnell, and Duran with Tabernero. Ex. 1003, Ratain Decl. ¶¶ 143, 177. Accordingly, claim 2 is obvious over this combination.

XI. SECONDARY CONSIDERATIONS FAIL TO OVERCOME THE STRONG EVIDENCE OF OBVIOUSNESS

To overcome Par's strong *prima facie* obviousness showing set forth in the four proposed grounds above, Novartis may attempt to come forward with secondary considerations of nonobviousness. Secondary considerations can include (i) long-felt need, (ii) unexpected results, (iii) skepticism of the invention, (iv) teaching away from the invention, and (vii) coping by others. *Graham*, 383 U.S. at 15-17. Par is unaware of any secondary considerations that would support a finding of nonobviousness for claims 1-3. Ex. 1003, Ratain Decl. ¶ 178. Moreover, even where relevant secondary considerations are present, they may not make claims nonobvious, particularly where—like here—a strong *prima facie* case exists. *See, e.g.*, *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

Novartis may allege that the method claims of the '224 patent satisfied a long-felt but unmet need for treating pancreatic NETs. But other treatments were available as of November 2005 for the treatment of pancreatic NETs, as identified in Oberg 2004. Ex. 1027, Oberg 2004 at 57-60. Thus, "others had previously solved" any "long-felt need" allegedly met by the '224 patent. *In re PepperBall Techs., Inc.*, 469 F. App'x 878, 882-83 (Fed. Cir. 2012).

Further, sales of everolimus for the treatment of pancreatic NETs do not support any objective indicia of the non-obviousness of the '224 patent claims. The '224 patent claims require administering everolimus, a compound whose use remains subject to separate patent coverage even today. Ex. 1048, '772 patent at claim 10. As a result, "no entity other than [Novartis] could have successfully brought [the claimed methods] to market." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013). Because of this barrier to market entry, any argument that commercial sales of Novartis's Afinitor® (everolimus) product evidence non-obviousness is weak at best, especially in view of the strong *prima facie* case discussed above. *Merck*, 395 F.3d at 1376-77; *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed. Cir. 2000).

Finally, if Novartis alleges that copying by ANDA applicants supports nonobviousness, such an argument has been dismissed as "not probative of nonobviousness" in the ANDA context. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Par expressly reserves the right to supplement its argument regarding secondary considerations based on Novartis's allegations.

XII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION UNDER 325(D) IN FAVOR OF IPR PETITION 2016-01461

As Par was finalizing its petition, Roxane filed a petition challenging the patentability of claims 1 and 2 of the '224 patent. *Roxane Labs., Inc. v. Novartis*

AG, No. IPR2016-01461 (filed July 19, 2016). Par respectfully submits that the Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny this Petition challenging all three claims of the '224 patent because it does not present "the same or substantially the same prior art or arguments previously . . . presented." 35 U.S.C. § 325(d). This is so for at least two reasons. First, in its petition, Roxane relied on different primary references with different teachings, different arguments, and substantively different testimony from a different expert than those included in Par's Petition. *Roxane*, IPR2016-0461, Paper 1 at 34-45; Ex. 1003. For example, Roxane's petition does not rely on Oberg 2004, Boulay 2004, O'Donnell, or Duran as Par does in this Petition. In fact, the only prior art the two petitions have in common in their grounds is Tabernero, but Par relies on this reference only as teaching the limitation of claim 2 while Roxane relies on this reference as supporting unpatentability of claim 1 as well. The arguments and evidence advanced in the two petitions are substantively different with little overlap.

Additionally, Roxane challenged only claims 1 and 2 of the '224 patent, whereas Par challenges claims 1, 2, and 3 in the instant Petition. As such, Par's Petition cannot present "the same or substantially the same prior art or arguments." Because dependent claim 3 merely limits the method of claim 1 to a particular type of tumor and is unpatentable for the same reasons as claim 1, the public interest, as

well as Par's own interests, is better served by fully resolving the patentability of all the claims of this patent now. Further, the prior art and arguments included in Roxane's petition have not been "previously presented." Roxane filed its petition mere days before Par, and the Board will have the opportunity to analyze and consider the merits of both petitions simultaneously. The Board has made no substantive findings regarding the prior art or arguments included in Roxane's petition.

Par is willing to coordinate schedules and procedural aspects so as to minimize the burden on the Board in considering these two substantively different petitions concerning the same patent. However, because Par challenges all claims rather than a subset and has presented substantively different art, arguments, and evidence supporting the unpatentability of the claims of the '224 patent, the Board should fully consider Par's Petition on its merits. *Rackspace US, Inc. v. Personal Web Techs., LLC*, No. IPR2014-00057 (P.T.A.B Apr. 15, 2014), Paper 9 at 23-25 (declining to exercise discretion under 325(d) because of different art, claims, and arguments despite multiple proceedings on same patent).

XIII. CONCLUSION

For the reasons set forth above, Par respectfully requests *inter partes* review of Claims 1-3 of the '224 patent.

Respectfully submitted,

Dated: July 22, 2016

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CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of this Petition for *Inter Partes* Review of U.S. Patent No. 9,006,224 and all Exhibits and other documents filed together with this Petition were served on the official correspondence address for U.S. Patent No. 9,006,224 shown in PAIR and Novartis Pharmaceutical Corporation's current litigation counsel:

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Petition complies with the word count limitation of 37 C.F.R. § 42.24(a)(1)(i) because the Petition contains 12,329 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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