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Paper 12
Date: October 5, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICAL LLC,
Petitioner,

v.

NOVARTIS AG,
Patent Owner.

IPR2016-01479[1]
Patent 9,006,224 B2

Before CHRISTOPHER L. CRUMBLEY, ROBERT A. POLLOCK, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

CRUMBLEY, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

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[1] This proceeding as initially filed named Par Pharmaceutical, Inc. as the sole Petitioner. Argentum Pharmaceutical LLC was joined as a party to this proceeding via a Motion for Joinder in IPR2017-01063; West-Ward Pharmaceuticals International Limited was joined as a party via a Motion for Joinder in IPR2017-01078. Subsequently, Par and West-Ward separately requested termination of their participation in the proceeding pursuant to settlement. Argentum Pharmaceutical LLC is the sole remaining Petitioner.

I. INTRODUCTION

In this *inter partes* review, instituted pursuant to 35 U.S.C. § 314, Argentum Pharmaceutical LLC ("Argentum") challenges the patentability of claims 1–3 of U.S. Patent No. 9,006,224 B2 (Ex. 1001, "the '224 patent"), owned by Novartis AG ("Novartis").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision, issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73, addresses issues and arguments raised during trial. For the reasons discussed below, we determine that Argentum has not shown by a preponderance of the evidence that claims 1–3 of the '224 patent are unpatentable.

A. Procedural History

On July 22, 2016, Par Pharmaceutical, Inc. ("Par") filed a Petition requesting an *inter partes* review of claims 1–3 of the '224 patent. Paper 1 ("Pet."). Novartis filed a Preliminary Response. Paper 7. On February 14, 2017, we instituted an *inter partes* review of the challenged claims. Paper 8 ("Dec."). Subsequent to institution, Argentum and West-Ward Pharmaceuticals International Limited ("West-Ward") filed separate petitions and motions for joinder with the instant proceeding. IPR2017-01063, Papers 1, 3; IPR2017-01078, Papers 1, 3. On September 25, 2017, we granted both motions for joinder, joining Argentum and West-Ward as petitioners to this *inter partes* review. Paper 33. As we noted at the time, both Argentum and West-Ward stated that their petitions include the same

grounds and arguments[2] as those in the Par proceeding, and both parties rely on the same evidence including the same expert witness testimony. *Id*. at 5.

Following institution, Novartis filed a Patent Owner Response (Paper 17, "PO Resp.") and Argentum filed a Reply (Paper 21, "Reply"). We granted Novartis authorization to file a Surreply (Paper 26, "Surreply") to address alleged new arguments made in Argentum's Reply, and permitted Argentum to file a short Response (Paper 29).

Argentum relies upon the declaration testimony of Dr. Mark J. Ratain (Ex. 1003), and with its Reply submitted a Supplemental Declaration of Dr. Ratain (Ex. 1119). Novartis took cross-examination of Dr. Ratain via deposition following the submission of each declaration, and filed the transcripts (Exs. 2040, 2111). Novartis filed observations on the cross-examination of Dr. Ratain (Paper 34) and Argentum filed a response to the observations (Paper 42).

Novartis relies upon the declaration testimony of Dr. Matthew H. Kulke. Ex. 2041. Argentum took cross-examination of Dr. Kulke via deposition and submitted the transcript. Ex. 1070.

Novartis filed a Motion to Exclude certain evidence submitted by Argentum (Paper 35, "Mot. Exclude"), after which Argentum filed an Opposition (Paper 41, "Opp. Exclude") and Novartis filed a Reply (Paper 43, "Reply Exclude").

[2] For this reason, although we cite to Par's Petition in this decision because it is of record in this proceeding, we attribute all the contentions made therein to Argentum as the sole remaining Petitioner.

Oral argument was requested by both parties. Papers 31, 36. Argument was heard on November 1, 2017, and a transcript has been entered into the record. Paper 49 ("Tr.").

On January 23, 2018, Par and Novartis filed a joint motion to terminate Par as a petitioner due to settlement (Paper 50), which we granted on February 6, 2018 (Paper 52).

On February 14, 2018, counsel for Argentum contacted the Board via e-mail, requesting that the Board hold the Final Written Decision in abeyance in order to facilitate ongoing settlement discussions with Novartis. Ex. 3002. We notified the parties that, in light of the parties' request and because the proceedings involve joinder, pursuant to 35 U.S.C. § 316(a)(11) and 37 C.F.R. § 42.100(c) we would adjust the time for issuing a Final Written Decision. Counsel for West-Ward[3] e-mailed a similar request on February 15, 2018. Ex. 3003. West-Ward continued to provide updates to the Board via e-mail to notify us that settlement negotiations were ongoing and to request that we continue to hold this Decision in abeyance.

On October 2, 2020, West-Ward and Novartis jointly requested to terminate West-Ward as a petitioner due to settlement (Paper 57), which we granted (Paper 60). Argentum is the sole remaining Petitioner in this proceeding.

[3] West-Ward updated its Mandatory Notices on January 8, 2019, notifying us that it changed its name to Hikma Pharmaceuticals International Limited. IPR2017-01078, Paper 11. Because the majority of the filings in this case were made prior to the name change, for clarity of this Decision we will refer to the company using its prior name, West-Ward.

B. Related Proceedings

Claims 1 and 2 of the '224 patent were challenged by a different petitioner in IPR2016-01461; the Board denied institution of trial in that proceeding.

We are informed that the '224 patent has been asserted in two patent infringement actions in the United States District Court for the District of Delaware: *Novartis Pharm. Corp. et al. v. Roxane Labs., Inc*., No. 15-474-RGA, and *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.,* No. 15-475-RGA. Pet. 3; Paper 4, 2–3.

While this *inter partes* review was pending, the District Court entered a decision in the former case, finding no invalidity of claim 1 the '224 patent, on December 14, 2017. *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505 (D. Del. 2017) ("District Court Decision"). That decision also found that certain claims of a related patent, U.S. Patent No. 8,410,131 ("the '131 patent") were not invalid. *Id*. West-Ward appealed the District Court's decision as to the '131 patent to the United States Court of Appeals for the Federal Circuit, but did not appeal the District Court's decision regarding the '224 parent at issue here. On May 13, 2019, the Federal Circuit affirmed. *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019) ("Federal Circuit Decision").

C. The '224 Patent

The '224 patent, titled "Neuroendocrine Tumor Treatment," issued April 14, 2015, from U.S. Patent Application No. 12/094,173. Ex. 1001, codes (54), (45), (21). The patent describes treating neuroendocrine tumors using mTOR (mammalian target of rapamycin) inhibitors, including rapamycin and its derivatives. *Id*. at 1:2–5, 1:17–43. One specifically listed

rapamycin derivative is 40-O-(2-hydroxyethyl)-rapamycin, also known as everolimus. *Id*. at 1:46–47, 11:50–51.

The ’224 patent discloses that mTOR inhibitors have activity as immunosuppressants, and have also been found useful for the treatment of solid tumors, particularly advanced solid tumors, including pancreatic neuroendocrine tumors (PNETs). *Id*. at 2:35–67. PNETs are particularly lethal, having a 5-year patient survival rate of 55.3%; the ’224 patent states that most such tumors are malignant at the time of diagnosis, and 60% or more present with liver metastases. *Id*. at 3:1–10. The ’224 patent concludes that there is an unmet need for treatment of PNETs in patients whose disease has progressed following one or more courses of chemotherapy. *Id.* at 3:9–12.

The ’224 patent describes a method of treatment using mTOR inhibitors, specifically with everolimus (also called “compound A”). *Id*. at 11:66–67. The patent proposes a clinical study in which patients with advanced PNETs are treated with 10 mg/day of everolimus after failure of cytotoxic chemotherapy. *Id*. at 26:56–60.

D. The Challenged Claims

Claim 1 is independent and illustrative of the challenged claims:

> 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.

Ex. 1001, 26:66–27:4. Claim 2 specifies a unit dose of 10 mg/day, and claim 3 requires that the tumor be an islet cell tumor. *Id.* at 27:5–8.

E. The Instituted Grounds

We instituted an *inter partes* review of all claims challenged in the Petition on the following grounds of unpatentability, each alleging obviousness of the claims under 35 U.S.C. § 103(a)[4]:

Claim(s) Challenged	References
1–3	Öberg 2004,[5] Boulay 2004,[6] and O'Donnell[7]
2	Öberg 2004, Boulay 2004, O'Donnell, and Tabernero[8]
1–3	Boulay 2004, O'Donnell, and Duran[9]

[4] The relevant sections of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, took effect on March 16, 2013. Because the application from which the '224 patent issued was filed before that date, our citations to Title 35 are to its pre-AIA version.

[5] K. Öberg, *Treatment of neuroendocrine tumors of the gastrointestinal tract*, 27 ONCOLOGIA 57 (2004) (Ex. 1027).

[6] A. Boulay et al., *Antitumor efficacy of intermittent treatment schedules with the rapamycin derivative RAD001 correlates with Prolonged Inactivation of Ribosomal Protein S6 Kinase 1 in Peripheral Blood Mononuclear Cells*, 64 CANCER RES. 252 (2004) (Ex. 1005).

[7] A. O'Donnell et al., *A phase I study of the oral mTOR inhibitor RAD001 as a monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamics (PD) endpoints in patients with solid tumors*, 22 PROC. AM. SOC'Y OF CLINICAL ONCOLOGY 200(803ab) (2003) (Ex. 1029).

[8] J. Tabernero et al., *A phase I study with tumor molecular pharmacodynamics (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors,* 23 J. CLINICAL ONCOLOGY 3007 (2005) (Ex. 1038).

[9] I. Duran et al., *A Phase II Trial of Temsirolimus in Metastatic Neuroendocrine Carcinomas (NECs)*, 23 SUPPLEMENT TO J. CLINICAL ONCOLOGY 3096 (2005) (Ex. 1011).

Claim(s) Challenged	References
2	Boulay 2004, O'Donnell, Duran, and Tabernero

II. ANALYSIS

A. Legal Standards

To prevail in challenging Novartis's claims, Argentum must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex, Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations.[10] *See Graham v. John Deere Co.,* 383 U.S. 1, 17–18 (1966). The level of ordinary skill in the art may be reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Claim Construction

In an *inter partes* review based on a petition filed prior to November 13, 2018, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the

[10] The record does not contain evidence or argument regarding objective evidence of non-obviousness.

patent in which they appear. 37 C.F.R. § 42.100(b) (2016).[11] Under that standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Only those terms which are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); *see also U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (holding claim construction is not necessary when it is not "directed to, or has been shown reasonably to affect, the determination of obviousness").

In its Petition, Argentum proffered constructions for four claim terms: "pancreatic neuroendocrine tumor," "advanced tumors," "unit dose," and "islet cell tumor." Pet. 18–21. Novartis's Preliminary Response addressed only the construction of "advanced tumors," agreeing that the term should be construed to refer to a tumor that is unresectable or metastatic. Prelim. Resp. 7–8. Novartis also asked that we state that "advanced" does not mean "after failure of cytotoxic chemotherapy," though this is not a construction any petitioner asserted. *Id*. at 9–11.

[11] An amendment to this rule does not apply here because the Petition was filed prior to November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018) (now codified at 37 C.F.R. § 42.100(b) (2019)).

In our Institution Decision, we agreed with the parties that the broadest reasonable interpretation of "advanced" tumors, when viewed in light of the '224 patent specification, is "metastatic or unresectable." Dec. 6. But we declined to incorporate in our construction a requirement that "advanced" does not means "after failure of cytotoxic chemotherapy," as Novartis requested. *Id*. We did not consider it necessary to construe any other terms from the challenged claims. During the instituted trial, neither party asked that we revisit the construction of "advanced," or argued that we should render any further constructions. In view of the complete record, we reaffirm our prior construction of "advanced tumor," and do not consider further constructions of any claim term to be necessary.

C. Obviousness over Öberg 2004, Boulay 2004, and O'Donnell

Argentum contends that claims 1–3 are unpatentable under 35 U.S.C. § 103(a) as having been obvious over the combined teachings of Öberg 2004, Boulay 2004, and O'Donnell. Pet. 40–47. Argentum relies upon the Declaration of Mark J. Ratain, M.D. (Ex. 1003) to support its positions.

1. The Prior Art

Öberg 2004 discusses methods of treatment for neuroendocrine tumors of the gastrointestinal tract and pancreas. Ex. 1027, 57. Öberg 2004 specifically discusses treatment of metastatic tumors, which Dr. Ratain testifies would fall within the skilled artisan's understanding of advanced tumors. *Id*.; *see also* Ex. 1003 ¶ 101. Included in Öberg 2004 is the following figure, which discloses an algorithm for the therapy of neuroendocrine tumors:

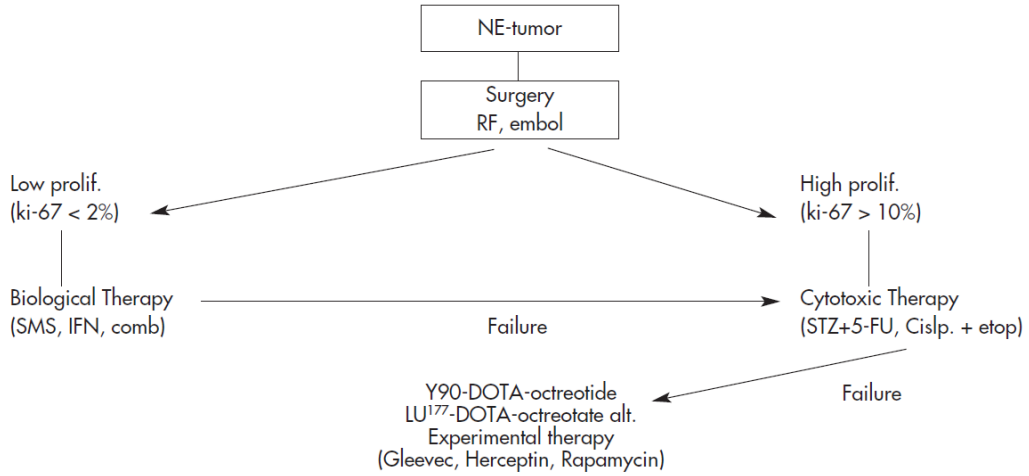

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Figure 1 of Öberg 2004, shown above, discloses an algorithm for therapy of neuroendocrine (NE) tumors beginning with surgery, radiotherapy, or embolization as a first therapy, followed by (in the case of high-proliferative tumors) cytotoxic therapy and, after failure of cytotoxic therapy, experimental therapies such as rapamycin. Ex. 1027, 60. Öberg 2004 discusses rapamycin as an "interesting new compound" and suggests clinical trials with rapamycin as a single agent or in combination with cytotoxic chemotherapy. *Id*. According to Argentum, "Öberg 2004 only differs from claims 1 and 3 of the '224 patent in that it does not explicitly disclose the use of everolimus," and, as to claim 2, it does not include a specific reference to the 10 mg/day unit dose required by that claim. Pet. 31–32.

Boulay 2004 is a study of the efficacy of treatment with "rapamycin derivative RAD001" (everolimus) in the CA20948 synergenic rat pancreatic tumor model. Ex. 1005, 252. According to Dr. Ratain, CA20948 is a rat tumor line used as a model for PNET in laboratory studies, and a person of ordinary skill in the art would have recognized that activity in the model

would support clinical development to treat human PNETs. Ex. 1003 ¶ 112. Boulay 2004 also notes that everolimus was a rapamycin derivative being clinically developed at that time, for use in treatment of human cancer. Ex. 1005, 252. Boulay concludes that everolimus "displays significant antitumor activity in the synergenic CA20948 rat pancreatic tumor model," and is "well tolerated, with no significant body weight loss or mortalities observed." *Id*. at 253–54.

O'Donnell is the abstract of a poster presented at the 2003 Annual Meeting of the American Society of Clinical Oncology, describing a phase I study of everolimus. Ex. 1029, 200. The study was a dose escalation study, performed "to identify the optimal biologically effective dose based on toxicity" in patients having solid tumors. *Id*. O'Donnell concluded that dosages of 5, 10, 20, and 30 mg weekly were "well tolerated" with only mild degrees of side effects. *Id*.

2. The Proposed Combination

Argentum contends that a person of ordinary skill in the art, seeking to treat patients with PNET after failure of cytotoxic chemotherapy, would have looked to Öberg 2004's disclosure of rapamycin as an "interesting new compound," and would have understood these teachings to extend to other rapamycin derivatives known to be mTOR inhibitors. Pet. 42. Dr. Ratain testifies that, by 2005, there was a "significant body" of data on the administration of everolimus to humans, but no reported clinical data on rapamycin. Ex. 1003 ¶ 135. Dr. Ratain concludes that a person of ordinary skill in the art would have had reason to administer a rapamycin derivative, such as everolimus, with similar biological activity to rapamycin. *Id*. According to Argentum, that reason would have been further strengthened by Boulay 2004's disclosure of everolimus' activity in treating a rat

pancreatic tumor model, and O'Donnell's disclosure that administration of everolimus to human cancer patients was effective and safe. Pet. 43–44. Argentum also contends that this treatment would have had a reasonable expectation of success, particularly in view of Boulay 2004's disclosure of the effectiveness in the rat model. *Id*. at 45.

With respect to the unit dosage specified in claim 2, Argentum concedes that O'Donnell and Boulay 2004 do not specify 10 mg/day. Pet. 46. Nevertheless, Argentum contends that determining the optimal dosage would have required nothing more than routine experimentation, and Novartis has not shown any particular effectiveness of 10 mg/day as compared to other dosages. *Id*. at 46–47.

3. Reason to Select Everolimus

Novartis contends that the combined art fails to render the claims obvious, because Argentum "provides no credible reason why a [person of ordinary skill in the art] would have been motivated to select **everolimus** over other prior art compounds to treat advanced PNETs after failure of cytotoxic chemotherapy." PO Resp. 23–24. Novartis contends that, at the time of the invention, numerous compounds were being developed to treat cancer generally, and many of those compounds were in more advanced stages of clinical development than everolimus. *Id*. at 24. For example, Novartis observes that small molecule tyrosine kinase inhibitors (*e.g*., gefitinib, erlotinib, SU101, sorafenib, imatinib mesylate, and sunitinib malate), and anti-receptor antibodies (*e.g*., cetuximab and trastuzumab) had reached at least Phase III clinical trials in human cancers, and sorafenib had completed Phase II clinical trials in NETs (including advanced PNETs). *Id.* (citing Ex. 2041 ¶113; Ex. 2043, 361–66; Ex. 1037, S42–S43; Ex. 2061, 1248; Ex. 2072, 2270; Ex. 2051, 7484). Novartis asserts that a person of

ordinary skill in the art would have favored any of these various compounds over everolimus, given the limited state of knowledge as to its efficacy at the time. *Id*. at 25.

Novartis argues that unless Argentum can prove that the skilled artisan would have selected everolimus from among the possible treatments available, its obviousness case must fail. PO Resp. 23. To support this proposition, Novartis cites *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 861 (Fed. Cir. 2015), as holding that "[i]n cases involving a new method of treatment using a known compound, the Board should consider whether the prior art as a whole would have motivated a [person of ordinary skill in the art] to select the claimed compound over other prior art compounds." PO Resp. 23. We disagree with Novartis' interpretation of *Insite Vision*.

The Federal Circuit's decision in appeal from the related District Court case is instructive on this point. In that case, just as in this one, Novartis argued that claim 1 of the '224 patent was nonobvious because the skilled artisan would not have been motivated to select everolimus over other prior art compounds. District Court Decision, 287 F. Supp. 3d at 527. The District Court accepted that argument as one basis for finding that the claims were not invalid. *Id*. But the Federal Circuit found this conclusion to be in error. Federal Circuit Decision, 923 F.3d at 1059 ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.") (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)). While the Federal Circuit found that such considerations may be appropriate when evaluating a "lead compound" obviousness challenge, the combination asserted in the District Court (and mirrored here) does not involve such an analysis. *Id*. at 1060. The Federal

Circuit concluded that the proper inquiry in cases such as the present one is whether a person of ordinary skill in the art would have been motivated to modify the prior art to arrive at the claimed method of treatment. *Id*. "This question was answered affirmatively when the district court found that a person of ordinary skill 'would have been motivated to pursue everolimus as one of several potential treatment options.'" *Id*.

Judged by the correct standard, the evidence leaves little doubt that a person of ordinary skill in the art would have been motivated to pursue everolimus as a potential treatment option for advanced PNETs after failure of cytotoxic chemotherapy. Novartis does not seriously contend otherwise, focusing its arguments instead on whether the motivation to pursue everolimus was greater than the motivation to pursue other possible treatments. Not only does Öberg 2004 discusses rapamycin as an "interesting new compound" that suggests clinical trials with rapamycin in combination with cytotoxic chemotherapy, it specifically provides a treatment algorithm that shows rapamycin among the potential "experimental therapies" following failure of cytotoxic chemotherapy. Ex. 1027, 60, Fig 1. And O'Donnell specifically demonstrates that administration of everolimus to human cancer patients was safe. Ex. 1029, 200. We credit Dr. Ratain's testimony that by 2005, there was a "significant body" of data on the administration of everolimus to humans, but no reported clinical data on rapamycin. Ex. 1003 ¶ 135. Given the difference in information on everolimus and rapamycin, we find that the skilled artisan would have been motivated to pursue everolimus as an alternative to the rapamycin disclosed in Öberg 2004.

4. Reasonable Expectation of Success

Even if a person of ordinary skill would have had reason to pursue everolimus, however, our inquiry does not end there. Argentum must also prove that the 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." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). 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).

Again, review of the District Court's decision in the related case, as well as the Federal Circuit's decision on appeal, is instructive.[12] The District Court found that, as of 2001, there were no clinical trials of everolimus and that another rapamycin derivative, temsirolimus,[13] had only undergone

[12] We recognize that the Federal Circuit Decision applies to the '131 patent, and was rendered on a different factual basis than the prior art at issue before us. For example, the critical date for the '131 patent is approximately four years earlier than that of the '224 patent, requiring a different evaluation of the state of the art. In addition, we recognize that a district court's decision regarding whether a patent would have been obvious is rendered under a different standard of proof—clear and convincing evidence—than is required here. Therefore, the court's determination on reasonable expectation of success is not directly determinative of our decision here. Nevertheless, we find the court's analysis of the caselaw, and what factual inquiries are relevant to the question of reasonable expectation of success, instructive.

[13] Temsirolimus, also known as CCI779 or 40-(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate)-rapamycin (Ex. 1001, 2:11–12), differs from everolimus by the substituent groups attached to the rapamycin backbone. Both the district court defendant and Argentum have relied on

Phase I study. District Court Decision, 287 F. Supp. 3d at 512. The court also noted that everolimus and temsirolimus differ in pharmacological properties relevant to treatment (*id.* at 517), and that PNETs were known to differ from carcinoids in behavior, incidence, molecular genetics, and responses to pharmacotherapies. *Id*. at 519. Noting the high rate of failure for potential cancer treatments, especially among hard-to-treat cancers like PNET, the court found that this would have diminished any expectation that everolimus would be effective in PNETs. *Id*. at 529.

Reviewing the District Court's findings as to the '131 patent, the Federal Circuit affirmed. Federal Circuit Decision, 923 F.3d 1051, 1061 (Fed. Cir. 2019) ("We conclude that the district court did not clearly err in finding that West-Ward's asserted prior art combination . . . failed to provide clear and convincing evidence of a reasonable expectation of success."). Among the District Court's findings noted by the appeals court were the fact that the phase I data resulted from small sample sizes and studies that were designed to test safety, not efficacy. *Id*. The court also noted that the studies in the prior art did not disclose the number of patients enrolled who had advanced RCC, as well as the findings regarding the pharmacological differences between temsirolimus and everolimus. *Id*. The court concluded that "[t]he district court reviewed the above evidence, determined that the molecular biology of advanced RCC was not fully understood, recognized the limitations in the temsirolimus phase I data, and found that such data did not provide a person of ordinary skill with a reasonable expectation of success. . . . We hold that the district court did not err." *Id*. at 1062.

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clinical trials of temsirolimus as relevant to the reasonable expectation of success in treating patients with everolimus.

We are presented with similar facts in the case at hand. O'Donnell, the only prior art clinical trial of everolimus presented to us, was a Phase I trial designed to test dosages, not efficacy. Ex. 1029, 803. While Öberg 2004 does disclose the promise of rapamycin, we agree with the District Court that at the time of the invention the mTOR pathway was insufficiently understood, such that a person of ordinary skill in the art would not have reasonably expected rapamycin's "promise," as reported in Öberg 2004, to translate to everolimus. Ex. 1027, 60. And in regard to Boulay 2004, Novartis argues that the record lacks sufficient evidence to support Argentum's contention that the CA20948 rat pancreatic tumor model described therein was applicable to the treatment of PNETs. Ex. 1005, 253. On this point, again we agree with the District Court. District Court Decision, 287 F. Supp. 3d at 526 ("I find that Defendant has failed to establish by clear and convincing evidence that CA20948 is a PNET model."). Upon evaluating the full record before us, we find that the CA20948 tumor model line originated from a pancreatic adenocarcinoma, which is distinct from a neuroendocrine tumor (NET). Ex. 2038, 197–99; Ex. 2041 ¶¶ 132–134. We credit and rely on Dr. Kulke's testimony that pancreatic adenocarcinomas and PNETs were known to differ in their origin, incidence, clinical behavior, molecular genetics, and responses to pharmacotherapies. Ex. 2041 ¶¶ 57, 135–136.

Argentum does not dispute the distinction between CA20948 and PNETs, but instead argues that tests performed on CA20948 would nevertheless be understood to be applicable to PNETs. Reply 17–18. Argentum's primary support for this argument derives from the De Jong reference, which discloses the use of the CA20948 pancreatic tumor line in a study of the treatment of neuroendocrine tumors. Ex. 1010, Abstract. As

Novartis correctly observes, however, the De Jong study involved radiation-based treatment of tumors using radioactive somatostatin-analogues. PO Resp. 33; Ex.1010, 356–58. Both neuroendocrine tumors and CA20948 express somatostatin receptors; it is this commonality that made CA20948 useful as a model for NETs in De Jong's study of radiation treatment. Ex. 2041 ¶¶ 139, 141. But just because some features of a cell line make it useful in studies of tumors where those features are relevant, it does not necessarily follow that the cell line is relevant to *all* studies of those tumors. *See* Tr. 14:15–25. As Dr. Kulke credibly explains, the person of ordinary skill in the art would not have understood from the De Jong radiation treatment study that CA20948 could be used as a model for NETs in a pharmacotherapy study. Ex. 2041 ¶ 143–146. For these reasons, we agree with the District Court that Argentum has not proven CA20948 to be a PNET model; nor is there reason to believe that a person of ordinary skill in the art would have considered CA20948 to be applicable to studying the treatment of PNETs with mTOR inhibitors, much less such treatment after the failure of cytotoxic chemotherapy.

We also agree with the District Court's evaluation of the state of the art, and its finding that at the time of the invention "the molecular mechanisms underlying PNETs and the mTOR pathway's role in human cancers were not completely understood." District Court Decision, 287 F. Supp. 3d at 520 (citing Ex. 2027, 317; Ex. 1033, 632–33). At the time of the invention, no mTOR inhibitor had been approved to treat cancer in humans, and we credit Dr. Kulke's testimony that it was unclear whether mTOR inhibitors would be an effective approach to cancer treatment. Ex. 2041 ¶71. Publications report that as of 2004 it was "unclear what role mTOR kinase activity plays" (Ex. 1005, 253), and "a number of unresolved

questions regarding the function and the mechanism of action of mTOR" remained as of 2005 (Ex. 2027, 314, 317). Given the complexity of the cell signaling pathways and the incomplete understanding of the activity of mTOR inhibitors, we find that the relevant art at the time of the invention remained highly unpredictable.

In addition to the foregoing, we also find the Federal Circuit's recent decision in *OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019), analogous to the case at hand and helpful guidance for resolution of these issues. In *OSI Pharmaceuticals*, the Federal Circuit reversed the Board's determination that certain claims to methods for treating non-small cell lung cancer (NSCLC) with the drug erlotinib were unpatentable as having been obvious, concluding that substantial evidence did not support the Board's finding of reasonable expectation of success. 939 F.3d at 1377.

The Federal Circuit found that the Board had "misinterpreted the asserted references to teach more than substantial evidence supports." *Id*. at 1377–78. The Board had found that the prior-art reference Gibbs provided "a clear inference" that "erlotinib has anti-cancer activity against non-small cell lung cancer." *Id*. at 1383. On review, the Court noted that Gibbs "is a review article that collects, reviews, and analyzes other research studies." *Id*. And looking to the underlying references cited in Gibbs, the Court found that none of those references discussed erlotinib's effect on NSCLC. *Id*. at 1383–84.

The Board had also found that the combination of Gibbs with prior-art reference Schnur, or Schnur with OSI's Form 10-K, "would have provided a person of ordinary skill with a reasonable expectation of success in using erlotinib to treat NSCLC in a mammal." *Id*. at 1384. The Court disagreed, finding that once properly read, the asserted combinations of prior art "do

not provide substantial evidence supporting the Board's findings of reasonable expectation of success." *Id*. The Court noted that Schnur "fails to disclose any in vitro or in vivo efficacy data for erlotinib or otherwise suggest the use of erlotinib to treat NSCLC." *Id*. The combination of Gibbs and Schnur, the Court explained, thus at most taught only that erlotinib "has good anticancer activity in some cancers, not including NSCLC." *Id*. The Court found "significant" the lack of efficacy data "or other indication of success" because of (1) the "highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II," and (2) the undisputed fact "that a drug's success in treating one type of cancer does not necessarily translate to success in treating a different type of cancer." *Id*.

Given these facts, the Court concluded that:

> These references provide no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this. Indeed, given a 99.5% failure rate and no efficacy data or any other reliable indicator of success, the only reasonable expectation at the time of the invention was failure, not success. It is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references.

Id.

We are presented with similar facts here. The parties do not dispute that PNETs were understood to be a particularly fatal and difficult-to-treat form of cancer. Ex. 1001, 3:1–10 (PNETs have 5-year patient survival rate of 55.3%). *Id*. at 3:1–10. This is especially so of PNETs in patients who have previously failed cytotoxic chemotherapy. For example, Moertel reported that while positive response rates for first-line therapies of PNETs

ranged from 30–69 percent, in patients where first-line therapy had failed the second-line treatment was successful only 17% of the time, and those responses were transient. Ex. 1023, 519. *See also* Ex. 2001 ¶¶ 75–77; Ex. 2012, 518; Ex. 2011, 4767. Although Dr. Ratain points out that these studies tested the efficacy of second-line cytotoxic therapies, not second-line molecularly targeted therapies like mTOR inhibitors (Ex. 1119 ¶¶ 28–33), this distinction does not change the fact that at the time of the invention, no second-line therapy had demonstrated in clinical trials a significant chance of success in treating advanced PNETs.

Even aside from the particular challenges to treatment posed by PNETs, we find that oncology drugs in general were known to have a low rate of success, with only 5% progressing from first-in-human trials to regulatory approval, a lower rate than almost all other types of drugs. Ex. 2023, 711–12, Fig. 1. Oncology drugs were also less likely to be successful in phase II trials than other types of drugs. *Id*. at 712 ("[T]he highest rate of attrition at this phase is in the oncology field: more than 70% of oncology compounds fail in [phase II]."). And the rate of success in trials is further lowered for drugs that have a novel mechanism of action, such as mTOR inhibitors at the time of the invention. *Id*. at 713; Ex. 2041 ¶¶ 164, 266 ("As of November 2005, everolimus was a compound with a novel mechanism of action . . . because no mTOR inhibitor had regulatory approval or had published Phase III clinical trial results for the treatment of any type of cancer.").

Also analogous to the facts presented in *OSI Pharmaceuticals* is the fact that, at the time of the invention, there was no efficacy data for the treatment in question, or any other reliable indicator of success. As discussed above, the only clinical trial of everolimus in the record is

O'Donnell, which discloses a Phase I study. Ex. 1029, 200. But Phase I trials were intended to study the toxicity of a drug, not its efficacy. Ex. 2041 ¶ 160, n.17. And more broadly, there had been no pharmacotherapy at all that had been shown to have clinical efficacy against advanced PNETs after failure of cytotoxic chemotherapy. Ex. 1063, 79–80; Ex. 2041 ¶ 276. While Phase II clinical trials had been conducted on temsirolimus, another mTOR inhibitor related to everolimus, those trials concluded that temsirolimus had "little activity" and did not warrant further evaluation in advanced NETs. Ex. 2028, 1148, 1150–51. Although Argentum presents evidence as to the efficacy of everolimus in treating the CA20948 rat pancreatic tumor model, as discussed above we agree with the District Court's finding that this is not a PNET model and would have been of limited relevance in predicting the efficacy of treating PNETs, especially advanced PNETs after failure of cytotoxic chemotherapy.

In sum, the record as a whole leads us to the conclusion that, at best, there was hope that everolimus could be successful in treating advanced PNETs after failure of cytotoxic chemotherapy. But as the Federal Circuit put it, "hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art." *OSI Pharms.*, 939 F.3d at 1384. For these reasons, we cannot conclude that the combined prior art or other evidence of record proves by a preponderance of the evidence that a person of ordinary skill in the art would have had a reasonable expectation of using everolimus to treat advanced PNETs after failure of cytotoxic chemotherapy, as required by the claims. And it follows that Argentum has failed to prove by a preponderance of the evidence that claims 1–3 would have been obvious over the combined disclosures of Öberg 2004, Boulay 2004, and O'Donnell.

D. Obviousness over Öberg 2004, Boulay 2004, O'Donnell, and Tabernero

Argentum also contends that, even if the dosage limitation of claim 2 is not obvious as being routine experimentation in light of Öberg 2004, Boulay 2004, and O'Donnell, Tabernero explicitly teaches such a dosage. Pet. 48.

Tabernero is a presentation abstract regarding a Phase I study of the use of everolimus in patients with advanced solid tumors. Ex. 1038. Tabernero discloses that everolimus inhibits mTOR, a protein kinase involved in "the regulation of cell growth, proliferation, and survival." *Id*. Tabernero recommends further Phase II–III development of everolimus, at a dosage of 10 mg daily, as a single agent tumor treatment. *Id*.

Our determination above, that the record does not support a finding of reasonable expectation of success in treating advanced PNETs after failure of cytotoxic chemotherapy by combining Öberg 2004, Boulay 2004, and O'Donnell, also determines the outcome on this ground. First, Argentum does not contend that Tabernero provides a reasonable expectation of successfully treating advanced PNETs, only relying on the dosage presented in the reference as teaching the claimed dosages. Second, as discussed above, phase I trials such as those disclosed in Tabernero assess the relationship between dosage and safety, not efficacy. Third, there is no evidence that the patients in Tabernero presented with PNETs, let alone advanced PNETs. We cannot conclude from Tabernero that there would have been a reasonable expectation of success as to the efficacy of a dosage of 10 mg in treating advanced PNETs after failure of cytotoxic chemotherapy. On this point, we note that the District Court also found that "[a]lthough Tabernero provided a [person of ordinary skill in the art] 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." District Court Decision, 287 F. Supp. 3d at 528–29.

E. Obviousness over Boulay 2004, O'Donnell, and Duran

Argentum also contends that claims 1–3 would have been obvious over the combined disclosures of Boulay 2004, O'Donnell, and Duran. Pet. 49–52. The disclosures of Boulay 2004 and O'Donnell relied upon by Argentum are set forth above.

Duran discusses the administration of the rapamycin derivative temsirolimus to patients having metastatic neuroendocrine carcinomas (NECs), which Dr. Ratain testifies are a subset of advanced NETs. Ex. 1011, 3096; Ex. 1003 ¶ 129. Specifically, Duran notes islet cell carcinomas as a subset of the treated NECs. Ex. 1011, 3096. Of the 23 patients in the study, 11 had undergone prior chemotherapy. *Id*. Duran concludes that temsirolimus appears to have antitumor activity in NECs. *Id*.

Argentum contends that Duran teaches that temsirolimus, which is related to everolimus, had been shown to be safe and effective as monotherapy in patients with advanced NET previously treated with cytotoxic chemotherapy. Pet. 49. This, combined with Boulay 2004's teaching that everolimus was successful in a rat pancreatic tumor model, and O'Donnell's disclosure that everolimus was tolerated and effective in humans, allegedly would have led a person of ordinary skill in the art to administer everolimus to a patient having advanced NETs after failure of cytotoxic chemotherapy. *Id*. at 49–50. Relying on the testimony of

Dr. Ratain, Argentum contends that such a treatment would have had a reasonable expectation of success. *Id*. at 50 (citing Ex. 1003 ¶ 167).

With respect to claim 2, Argentum again contends that the dosage limitation would have been the result of routine experimentation. Pet. 51–52. As with the prior ground, Novartis does not address claim 2 separately or contend that the proper dosage would not have been determined via routine experimentation.

Having reviewed Duran, we cannot conclude that its addition to the ground of unpatentability in place of Öberg 2004 remedies the problem with the Öberg 2004, Boulay 2004, and O'Donnell ground discussed above, namely the lack of a reasonable expectation of success in treating advanced PNET following failure of cytotoxic chemotherapy. Duran discloses treatment with temsirolimus, which as discussed above is pharmacologically different than either everolimus or rapamycin. Ex. 1011, 3096; *see also* District Court Decision, 287 F. Supp. 3d at 528 (noting the "clinically-relevant differences in everolimus and temsirolimus"). We also note that Duran reported only "interim" results, and its trial was an uncontrolled, single-arm study. Ex. 1011, 3096 ("study accrual is ongoing"). Based on these findings, we agree with the District Court that "[a]t most, a [person of ordinary skill in the art] would have concluded that Duran disclosed preliminary data supporting the notion that temsirolimus may be effective to treat metastatic neuroendocrine carcinomas." District Court Decision, 287 F. Supp. 3d at 528. And we note that, in a follow-up publication, Duran noted that temsirolimus had "little activity" and "did not warrant further single-agent evaluation." Ex. 2028, 1148. We conclude, on this record, that the combined disclosures of the prior art would not have provided a reasonable expectation of success in treating advanced PNET with

everolimus following failure of cytotoxic chemotherapy. For this reason, Argentum's proposed ground of unpatentability based on obviousness over Duran, Boulay 2004, and O'Donnell fails.

F. Obviousness over Boulay 2004, O'Donnell, Duran, and Tabernero

As with the prior ground involving Öberg 2004, Argentum contends that even if Boulay 2004, O'Donnell, and Duran do not teach or suggest claim 2's dosage limitation of 10 mg/day, this dosage is explicitly set forth by Tabernero. Pet. 53. Again, Novartis does not address this ground separately or contend that Tabernero does not disclose this dosage of everolimus.

Our conclusion above, that a person of ordinary skill in the art would not have had a reasonable expectation of success in achieving the method of claim 1 based on Boulay 2004, O'Donnell, and Duran, also applies to this ground of unpatentability. As explained above regarding Boulay 2004, O'Donnell, and Duran, the addition of Tabernero to the combination does not remedy the lack of a reasonable expectation of success. Argentum has not carried its burden of proof on this ground.

G. *Motion to Exclude*

Novartis filed a Motion to Exclude seeking exclusion of certain evidence filed by Argentum. First, Novartis asks us to exclude the Declarations of Dr. Ratain (Exs. 1003, 1119) under Federal Rule of Evidence (FRE) 702, because Dr. Ratain is allegedly not an expert in the technology of the '224 patent. Mot. Exclude 2–6. Second, Novartis requests exclusion of a number of Argentum's exhibits because they were allegedly not relied upon in the Petition or Reply. *Id*. at 6–8. Third, Novartis "provisionally" moves to exclude "any evidence that does not appear in instituted Grounds 1–4 that [Argentum] may rely upon to establish

any element of their *prima facie* case." *Id*. at 8–9. Finally, Novartis asks that, under FRE 106 we consider certain portions of Dr. Kulke's testimony (Exs. 1070, 1095, 1119) that were not cited by Argentum in its papers. *Id*. at 9–14.

Addressing Novartis' last argument first, Argentum argues that Novartis uses FRE 106 as a pretext to discuss various portions of Dr. Kulke's testimony in a "thinly veiled second sur-reply." Opp. Exclude 2–3. According to Argentum, FRE 106 permits the introduction of additional evidence that, in fairness, ought to be considered; it is not a basis for excluding evidence. *Id*. (citing *Mobile Tech, Inc. v. Invue Sec. Prods. Inc.*, IPR2016-00892, Paper 35 at 68–69 (PTAB Sept. 28, 2017) (noting that FRE 106 "provides a basis for including, rather than excluding, evidence."). Because the portions of Dr. Kulke's testimony cited by Novartis are already in the record, Argentum argues that Novartis is using its Motion as simply an opportunity to further discuss its own expert's testimony. Opp. Exclude 2–3.

We agree. If Argentum had submitted only certain portions of Dr. Kulke's testimony into the record before us, Novartis would be entitled to rely on FRE 106 to request that the Board admit other portions of his testimony that, in fairness, should be considered. But that is not what Novartis requests here; nor could it, given that Exhibits 1070, 1095, and 1119 were already admitted in their entirety. And in any event, Novartis' request would not have been proper as part of a motion to exclude. Upon reviewing the Motion, it is clear that Novartis is using its FRE 106 arguments as a vehicle for introducing additional citations to, and discussion of, Dr. Kulke's testimony that were not introduced in the multiple other opportunities for merits briefing that Novartis had during this trial. For this

reason, we have not considered the citations to Dr. Kulke's testimony on pages 9–14 of the Motion.

On Novartis' "provisional" motion to exclude "any evidence" that does not appear in the instituted grounds, Argentum notes that Novartis has failed to satisfy any of the requirements of a motion to exclude, such as specifically identifying the evidence to be excluded and showing that the moving party previously served objections to that evidence. Opp. Exclude 10–11. Novartis attempts to justify its "provisional" motion by citing to Federal Circuit decisions such as *In re NuVasive, Inc.*, 841 F.3d 966, 972–73 (Fed. Cir. 2016) and *Genzyme Therapeutic Prods. LP v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1368 (Fed. Cir. 2016) as "encourag[ing] patent owners to move to exclude reliance on evidence outside of the instituted grounds, lest they risk waiving objections to such misuse." Reply Exclude 5. Even if this is a proper interpretation of these Federal Circuit cases, however, they do not grant Novartis the ability to circumvent our Rules by filing a vague "provisional" motion to exclude. We deny Novartis' Motion on this basis.

Novartis' remaining bases for its Motion—that Dr. Ratain's testimony and certain exhibits not cited in the briefs should be excluded—are moot given our determination on the merits. We have found that Argentum has not shown by a preponderance of the evidence that claims 1–3 of the '224 patent are unpatentable even if Dr. Ratain's testimony and the other exhibits are considered; excluding this evidence would not alter the result. As such, we dismiss as moot Novartis' Motion to Exclude on these bases.

III. CONCLUSION

Based on our review of the entirety of the record developed at trial, Argentum has not proven by a preponderance of the evidence that any of the challenged claims are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–3 of U.S. Patent No. 9,006,224 B2 have not been proven unpatentable;

FURTHER ORDERED that Novartis' Motion to Exclude (Paper 35) is *denied-in-part* and *dismissed-in-part*; and

FURTHER ORDERED that, because this Decision is final, a party to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
1–3	103(a)	Öberg 2004, Boulay 2004, O'Donnell		1–3
2	103(a)	Öberg 2004, Boulay 2004, O'Donnell, Tabernero		2
1–3	103(a)	Boulay 2004, O'Donnell, Duran		1–3
2	103(a)	Boulay 2004, O'Donnell, Duran, Tabernero		2
Overall Outcome				**1–3**

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