United States Court of Appeals for the Federal Circuit

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG,
Plaintiffs-Appellees

v.

WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED,
Defendant-Appellant

2018-1434

Appeal from the United States District Court for the District of Delaware in No. 1:15-cv-00474-RGA, Judge Richard G. Andrews.

Decided: May 13, 2019

CHRISTINA A. L. SCHWARZ, Venable LLP, New York, NY, argued for plaintiffs-appellees. Also represented by NICHOLAS N. KALLAS, SHANNON KEOUGH CLARK, LAURA KATHERINE FISHWICK, SUSANNE FLANDERS, JARED LEVI STRINGHAM.

DAVID ZIMMER, Goodwin Procter LLP, Boston, MA, argued for defendant-appellant. Also represented by KEITH A. ZULLOW, CINDY CHANG, STEVEN J. BERNSTEIN, MICHAEL

B. COTTLER, New York, NY; NATASHA ELISE DAUGHTREY, Los Angeles, CA; WILLIAM M. JAY, Washington, DC.

Before STOLL, PLAGER, and CLEVENGER, *Circuit Judges*.

STOLL, *Circuit Judge*.

West-Ward Pharmaceuticals International Ltd ("West-Ward")[1] appeals the decision of the United States District Court for the District of Delaware holding that claims 1–3 of U.S. Patent No. 8,410,131 would not have been obvious in view of the prior art. We conclude that the district court did not err in its nonobviousness determination and affirm.

BACKGROUND

Novartis Pharmaceuticals Corp. and Novartis AG (collectively, "Novartis") own the '131 patent, which claims methods of using the compound everolimus to treat advanced renal cell carcinoma ("RCC"). Everolimus is the active ingredient in Novartis's Afinitor product. West-Ward's predecessor in interest filed an Abbreviated New Drug Application ("ANDA") seeking to manufacture and sell generic versions of Afinitor, and Novartis filed this patent infringement suit in response. After a bench trial, the district court ruled that West-Ward failed to prove by clear and convincing evidence that claims 1–3 of the '131 patent are invalid as obvious. *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505, 518 (D. Del. 2017) ("Decision"). West-Ward appeals the district court's nonobviousness ruling.

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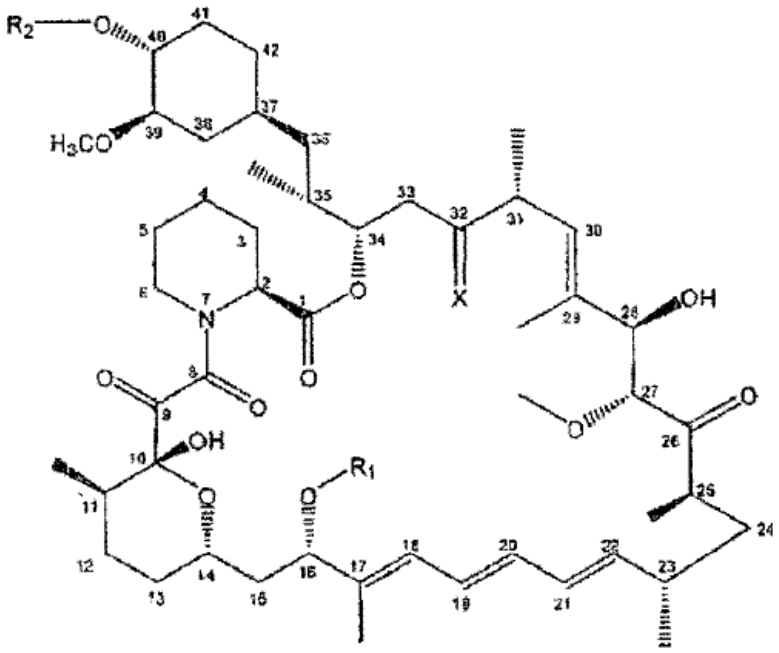
[1] On January 9, 2019, appellant West-Ward filed an amended certificate of interest notifying this court that it is now known as Hikma Pharmaceuticals International Ltd. We refer to appellant as West-Ward in this opinion.

I. Advanced RCC and the '131 Patent

Advanced RCC is a cancer of the kidneys that has spread to other parts of the body. As of February 19, 2001—the priority date of the '131 patent—advanced RCC carried a poor prognosis and was known to be unpredictable and difficult to treat. At that time, the only FDA-approved drug for treating advanced RCC was the immunostimulant interleukin-2, which was associated with poor response rates and toxicity in patients. Interferon alpha, another immunostimulant, was also administered to some patients in practice and was likewise shown to have poor response rates and toxicity. Numerous clinical trials investigating a wide range of treatment strategies for advanced RCC failed. Various chemotherapies, hormonal therapies, and immunotherapies had been unsuccessful. The prior art explained that "[a]dvanced RCC is characterized by a high level of resistance to all treatment modalities that have been studied." J.A. 2058. Cancer drugs in general had high failure rates for treatment of advanced RCC in clinical trials, with more than 70% of cancer drugs failing during phase II, and a majority of cancer drugs failing during phase III.

The '131 patent covers methods of administering the compound everolimus to inhibit the growth of advanced RCC tumors. Claims 1–3 are at issue here. Everolimus is recited in claim 1 as formula I:

> 1. A method for inhibiting growth of solid excretory system tumors in a subject, said method consisting of administering to said subject a therapeutically effective amount of a compound of formula I



wherein
R_1 is CH_3,
R_2 is —CH_2—CH_2—OH, and
X is =O.

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

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

'131 patent col. 17 l. 43–col. 18 l. 29 (as amended by Certificate of Correction).

II. mTOR Inhibitors

Everolimus belongs to a class of compounds called mTOR inhibitors. These compounds bind intracellularly to and form a complex with the FK506 binding protein ("FKBP-12"). This complex then binds to and inhibits the

activity of the mammalian target of rapamycin (mTOR) enzyme. By February 2001, the prior art disclosed that (1) compounds called mTOR inhibitors produced effects, such as inhibition of hypoxia-inducible factor 1 ("HIF-1"), that were hypothesized to inhibit tumor growth; (2) everolimus was an mTOR inhibitor; and (3) temsirolimus, another mTOR inhibitor, had shown responses in RCC patients in phase I clinical trials. There was no data on the efficacy of everolimus to treat any type of cancer, let alone to treat advanced RCC.

At the time of the priority date of the '131 patent, mTOR inhibitors were known in the art to have a variety of beneficial properties. Rapamycin, the first mTOR inhibitor, was known to have antimicrobial, immunosuppressive, and antitumor activities. Its poor solubility, however, precluded its development as an anti-cancer agent. Temsirolimus, another mTOR inhibitor and a derivative of rapamycin, was also known to exhibit antitumor properties. Temsirolimus showed improved solubility over rapamycin and demonstrated positive responses as an anticancer agent in phase I clinical trials. Everolimus is structurally similar to temsirolimus and is likewise a derivative of rapamycin.

It was also known in the prior art that advanced RCC tumors are highly vascularized and require angiogenesis to grow. Angiogenesis is the process through which new blood vessels are formed. A prior art article written by Semenza[2] explained that primary tumors and metastases will not grow beyond a certain size without establishing an adequate blood supply. *See* J.A. 2113. By February 2001, studies showed that tumor angiogenesis correlates with

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[2] Gregg L. Semenza, *Hypoxia, Clonal Selection, and the Role of HIF-1 in Tumor Progression*, 35 Critical Revs. in Biochemistry & Molecular Biology 71, 71–103 (2000).

increased expression of vascular endothelial growth factor ("VEGF") and that, in turn, elevated VEGF expression correlates with increased expression of HIF-1. *See* J.A. 2114, 2118–19. The prior art Zhong 1999[3] study reported elevated HIF-1 expression in several types of tumor samples, including in two RCC tumor samples. *See* J.A. 2187. By the time of the priority date of the patent-in-suit, however, HIF-1's precise mechanism of action and role in tumor growth were not yet fully understood. Semenza's Figure 4 disclosed that multiple genes (p53, PTEN, VHL), multiple pathways (RTKs, RAS, PI3K-AKT-FRAP, RAF-MEK-ERK), and multiple downstream effects (relating to VEGF, IGF-2, and glucose transporters) are associated with HIF-1 expression. *See* J.A. 2128. While Semenza noted that "[i]t is possible that inhibition of HIF-1 activity may contribute significantly" to the anti-cancer effects of certain HIF-1 inhibitors, including rapamycin, it cautioned that the role of HIF-1 in RCC "requires further analysis." J.A. 2119, 2127.

The prior art also provided some evidence linking HIF-1 inhibition to mTOR activity, though the exact mechanism of action was not established. The prior art Zhong 2000[4] study investigated the effects of modulating or modifying the mTOR pathway (referred to as the FRAP pathway) in human prostate cancer cell lines. The study reported that treating cells with the mTOR inhibitor rapamycin

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[3] Hua Zhong et al., *Overexpression of Hypoxia-inducible Factor 1a in Common Human Cancers and Their Metastases*, 59 Cancer Res. 5830, 5830–35 (1999).

[4] Hua Zhong et al., *Modulation of Hypoxia-inducible Factor 1a Expression by the Epidermal Growth Factor/Phosphatidylinositol 3-Kinase/PTEN/AKT/FRAP Pathway in Human Prostate Cancer Cells: Implications for Tumor Angiogenesis and Therapeutics*, 60 Cancer Res. 1541, 1541–45 (2000).

inhibited the expression of HIF-1α, the regulated subunit of HIF-1. *See* J.A. 2193. Zhong concluded that "HIF-1α-dependent gene transcription . . . and the expression of a HIF-1-regulated gene product . . . are modulated by the activity of the PI3K/AKT/[mTOR] pathway in [prostate cancer] cells." J.A. 2194. Zhong recognized that the effect of the mTOR pathway "may provide a basis for therapeutic efficacy," but noted that additional studies are required to determine the precise mechanism by which mTOR activity modulates the expression of HIF-1α. J.A. 2196; *see also* J.A. 2194.

III. Asserted Prior Art

West-Ward argued before the district court that '131 patent claims 1–3 would have been obvious over a temsirolimus reference (Hidalgo 2000[5] or Hutchinson[6]) and an everolimus patent (U.S. Patent No. 5,665,772 or U.S. Patent No. 6,004,973), in view of the general knowledge in the art. We discuss each reference in turn.

Hidalgo 2000 discusses the development of rapamycin and temsirolimus (referred to as CCI-779) as anti-cancer agents and the mechanisms of action underlying rapamycin's antitumor activity. The reference explains that blocking mTOR interferes with several intracellular pathways (e.g., $p70^{s6k}$, 4E-BP1/PHAS-1) involved in cell cycle progression, which leads to growth arrest in the G1 phase of the cell cycle. *See* J.A. 2030. This interference is reported to contribute to rapamycin's inhibition of cancer cell growth. *See* J.A. 2030. Hidalgo 2000 also includes summaries of the preliminary results of two phase I

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[5] Manuel Hidalgo & Eric K. Rowinsky, *The Rapamycin-sensitive Signal Transduction Pathway as a Target for Cancer Therapy*, 19 Oncogene 6680, 6680–86 (2000).

[6] Ezzie Hutchinson, *CCI-779: A New Targeted Anticancer Agent*, 1 The Lancet 198, 198 (2000).

temsirolimus clinical trials. These phase I studies were designed to determine the maximum tolerated dose of temsirolimus in patients with a variety of solid tumors. The studies show major tumor responses in RCC and cell lung carcinoma patients, and minor tumor responses in patients having other tumor types. *See* J.A. 2031. They do not disclose the number of RCC patients involved in the studies and do not include any data on everolimus. Hidalgo 2000 notes that "[t]he fact that [temsirolimus] consistently induced tumor regressions at relatively nontoxic doses in the phase I studies is particularly noteworthy," and that disease-directed studies of temsirolimus would be initiated following completion of the phase I studies. J.A. 2031. It also recognized that, while the downstream signaling pathways of temsirolimus were "well characterized," "a critical issue is whether these downstream effects correlate with the anti-tumor activity of [temsirolimus], particularly since malignant cells can traverse the cell cycle and proliferate despite" the effects of mTOR inhibition by rapamycin. J.A. 2032. Hidalgo 2000 concludes that temsirolimus "inhibit[s] the proliferation of a broad range of human tumors both *in vitro* and *in vivo*," but notes that predicting "which tumors will be particularly sensitive to [temsirolimus]" remains a developmental challenge. J.A. 2032–33.

Hutchinson discusses the clinical development of temsirolimus and reviews the updated results from the temsirolimus phase I studies disclosed in Hidalgo 2000. It notes that temsirolimus had "shown promise in a series of phase I studies." J.A. 2038. One study observed twenty-one patients with advanced solid tumors that were administered temsirolimus via intravenous infusion. It reported that, out of sixteen observable patients, three with RCC had a partial (one) or a minor response (two) to the treatment. Another study observed 51 patients with advanced solid tumors that were administered temsirolimus. It reported minor responses in three RCC patients. Hutchinson

also discloses that two phase II clinical trials investigating the use of temsirolimus were then underway, one of which was investigating RCC in particular.

The '772 patent discloses several rapamycin derivatives including everolimus, which is referred to as "40-O-(2-Hydroxy)ethyl-rapamycin." '772 patent col. 2 l. 30. The '772 patent teaches that the disclosed compounds "are particularly useful" for treating several conditions, including organ transplant rejection, autoimmune diseases, asthma, and proliferative disorders such as tumors. *Id.* at col. 3 l. 22–col. 4 l. 1. It also teaches that the disclosed compounds bind to macrophilin-12 (another name for FKBP-12), meaning that they inhibit mTOR activity. *Id.* at col. 6 ll. 1–3. It is undisputed that the '772 patent does not disclose any preclinical or clinical data on the antitumor activity of everolimus. It is also undisputed that the '772 patent does not contain an explicit disclosure that everolimus would be effective in treating advanced RCC.

The '973 patent also discloses everolimus, which is referred to as "40-O-(2-Hydroxy)ethyl rapamycin" and "compound X." '973 patent col. 2 ll. 9–11. The '973 patent discloses everolimus oral formulations, dosage ranges, and formulation techniques. *Id.* at col. 2 l. 25–col. 4 l. 59. It is undisputed that the '973 patent does not contain any preclinical or clinical data showing any antitumor activity of everolimus, and does not disclose that everolimus would be effective in treating advanced RCC.

IV. Procedural History

The '131 patent covers Novartis's Afinitor product. West-Ward's predecessor in interest filed ANDA No. 207486, seeking to manufacture and sell generic versions of Afinitor. In response, Novartis filed the current patent infringement suit. The parties stipulated that West-Ward's ANDA infringes claims 1–3 of the '131 patent and a bench trial proceeded on validity.

West-Ward argued that administering a therapeutically effective amount of everolimus to treat advanced RCC would have been obvious to a person of ordinary skill in the art. According to West-Ward, knowledge in the art about the molecular biology of advanced RCC, the antitumor activity of mTOR inhibitors, phase I temsirolimus clinical trial results, and safe dosing ranges for everolimus, would have provided a person of ordinary skill with a reasonable expectation of success of effectively treating advanced RCC with everolimus. Specifically, West-Ward argued that the '131 claims would have been obvious over either Hidalgo 2000 or Hutchinson in view of either the '772 patent or the '973 patent, further in view of the general knowledge in the art.

The district court rejected West-Ward's arguments. It found that West-Ward failed to prove that a person of skill in the art would have been motivated to select everolimus. The district court recognized that there was a need to find an effective treatment for advanced RCC, there was a preference for oral treatments, temsirolimus showed promising phase I clinical data, and everolimus and temsirolimus shared certain properties. *Decision*, 287 F. Supp. 3d at 515–16. In light of these facts, the district court found that a person of ordinary skill "would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors, including advanced RCC." *Id.* at 516. Despite this finding, however, the district court continued its analysis of whether there would have been a motivation to combine. It criticized West-Ward's expert Dr. Cho for limiting his review of the prior art to only mTOR inhibitors and found that "the relevant prior art would have included art relating to treatments beyond mTOR inhibitors." *Id.* at 515. It noted that there were a variety of other treatments in development at the time of the invention and that the knowledge gaps in the molecular biology of advanced RCC would have led a

person of ordinary skill to search for art beyond those involving mTOR modulation. The district court explained that Dr. Cho's narrow review allowed hindsight bias to inform his analysis. Even though the district court found that there would have been a motivation to pursue everolimus, it ultimately determined that West-Ward "failed to prove by clear and convincing evidence that a POSA would have been motivated to select everolimus." *Id.* at 516.

In addition, the district court determined that the asserted prior art would not have provided a person of ordinary skill in the art with a reasonable expectation of success in using everolimus to treat advanced RCC. *Id.* It noted Dr. Cho's admission that a person of skill in the art would *not* have reasonably expected a drug to work based only on phase I clinical trial results, or on the fact that a drug had entered phase II clinical trials. *Id.* The district court explained that the temsirolimus phase I data disclosed in Hutchinson had diminished weight because it resulted from small sample sizes and because phase I clinical trials are designed to determine safety, not efficacy. *Id.* It further noted that everolimus and temsirolimus differed in pharmacological properties relevant to treatment. These differences, along with the high failure rate of cancer drugs in phase II and III clinical trials, and the fact that the molecular pathways of advanced RCC were not fully understood, all diminished the relevance of the temsirolimus data. Based on these facts, the district court found that West-Ward failed to establish by clear and convincing evidence that a person of skill in the art would have reasonably expected everolimus to effectively treat advanced RCC.

The district court ultimately concluded that West-Ward failed to show by clear and convincing evidence that claims 1–3 of the '131 patent are invalid as obvious. West-Ward appeals the decision of the district court. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Standard of Review

"Following a bench trial on the issue of obviousness, we review the court's ultimate legal conclusions de novo and the underlying factual findings for clear error." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 858 (Fed. Cir. 2015) (quoting *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 974 (Fed. Cir. 2014)). "A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made." *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1406 (Fed. Cir. 2014) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)).

II. Obviousness

A patent is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made" to a person of ordinary skill in the art to which said subject matter pertains. 35 U.S.C. § 103(a).[7] Obviousness is a question of law based on underlying factual determinations including: (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of non-obviousness such as "commercial success, long-felt but unsolved needs, failure of others, etc." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)

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[7] Because the '131 patent does not contain any claim with an effective filing date on or after March 16, 2013, the version of 35 U.S.C. § 103 that applies here is the one preceding the changes made by the America Invents Act. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 293, § 3(n) (2011).

(quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

A party seeking to invalidate a patent based on obviousness must prove "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) (quoting *Alza Corp. v. Mylan Labs.*, Inc., 464 F.3d 1286, 1289 (Fed. Cir. 2006)). "The presence or absence of a reasonable expectation of success is also a question of fact." *Id.*

We hold that the district court erred in its analysis of whether there was a motivation to combine. However, we discern no clear error in the district court's finding that a person of ordinary skill would not have reasonably expected success in using everolimus to treat advanced RCC as of February 2001. We thus agree with the district court's ultimate determination that the challenged claims would not have been obvious. We address both prongs of the obviousness inquiry below.

A. Motivation to Combine

After reviewing the prior art, the district court found that a person of ordinary skill "would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors, including advanced RCC." *Decision*, 287 F. Supp. 3d at 516. This finding should have affirmatively answered whether there would have been a motivation to combine. Yet, the district court continued its analysis and found that West-Ward "failed to

prove by clear and convincing evidence that a POSA would have been motivated to select everolimus." *Id.* The district court erred in applying this heightened standard. "[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." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *see also Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013). It is thus improper to require West-Ward to prove that a person of ordinary skill would have selected everolimus over other prior art treatment methods.

Citing *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), Novartis argues that the district court did not err in concluding that the prior art fails to provide motivation to select everolimus. *See* Appellee Br. 58–59. As West-Ward correctly notes, however, *Takeda* is a lead compound case. *See* Appellant Reply Br. 8 n.2. In lead compound cases, the court first determines whether a person of ordinary skill in the art "would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012). This requires the patent challenger to show by clear and convincing evidence that a person of ordinary skill "would have had a reason to *select* a proposed lead compound or compounds over other compounds in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (emphasis added). The court then determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292.

We have applied a similar test in obviousness cases where the prior art discloses a range and a claim limitation falls within that range, focusing on "whether there would

have been a motivation to select the claimed composition from the prior art ranges." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737–38 (Fed. Cir. 2013) ("The relevant dispute in this case is thus not over whether the prior art discloses all of the claim elements or over the motivation to combine the prior art references. Rather, the dispute is whether there was motivation to select the claimed 0.3% adapalene composition in the disclosed range.").

The '131 patent claims methods of using everolimus to inhibit growth of solid tumors, including in patients having advanced RCC. '131 patent col. 17 l. 42–col. 18 l. 29. It does not claim the everolimus compound itself, but rather methods of using the compound. This case therefore does not require lead compound analysis or analysis of whether a particular dose in a range of prior art doses would have been obvious. The district court, however, appeared to apply or conflate the standard for these types of cases by requiring clear and convincing evidence that a person of ordinary skill "would have been motivated to *select* everolimus." *Decision*, 287 F. Supp. 3d at 516 (emphasis added). To the extent the district court required a showing that a person of ordinary skill would have selected everolimus over other prior art compounds, it erred. The proper inquiry is whether a person of ordinary skill would have been motivated to modify the prior art disclosing use of temsirolimus to treat advanced RCC with the prior art disclosing everolimus. 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 for advanced solid tumors, including advanced RCC." *Id.*

B. Reasonable Expectation of Success

West-Ward also challenges the district court's finding that a person of ordinary skill would not have had a

reasonable expectation of success in using everolimus to treat advanced RCC. *See* Appellant Br. 40–41. It argues that the district court erred by imposing "a heightened standard under which it found no reasonable expectation of success simply because there was not yet clinical proof that everolimus would successfully treat advanced RCC." *Id.* at 41. By February 2001, the prior art disclosed that: (1) RCC patients had shown responses to temsirolimus treatment in phase I clinical trials (Hidalgo 2000, Hutchinson), (2) everolimus was an mTOR inhibitor that was available in oral formulations ('772 patent, '973 patent), and (3) inhibiting mTOR in prostate cancer cells inhibits HIF-1, which was hypothesized to inhibit tumor-promoting angiogenesis (Zhong 2000). According to West-Ward, these disclosures would have provided a person of ordinary skill with a reasonable expectation that inhibiting mTOR would inhibit growth of advanced RCC, and the district court clearly erred by finding otherwise. *See id.* at 49–55.

Novartis counters and points out that by February 2001, there were no clinical trial data on everolimus as an anti-cancer agent, and no clinical trials for cancer had been completed for mTOR inhibitors. *See* Appellee Br. 21. It further argues that the district court correctly recognized the limitations of the temsirolimus phase I data. *Id.* at 24. It also notes the high failure rate of cancer drugs in phase II and phase III clinical trials, the numerous failed attempts to treat advanced RCC, and the pharmacological differences between everolimus and temsirolimus. *See id.* at 24–26. Novartis further argues that the district court correctly found that the roles of HIF-1 and mTOR in the molecular biology of advanced RCC were not completely understood. *See id.* at 43–47.

We conclude that the district court did not clearly err in finding that West-Ward's asserted prior art combination—Hidalgo 2000 or Hutchinson in view of the '772 patent or '973 patent in view of the knowledge in the art—

failed to provide clear and convincing evidence of a reasonable expectation of success. In reaching this finding, the district court relied on the prior art and expert testimony to support subsidiary findings that (1) the temsirolimus phase I data had diminished weight, (2) everolimus and temsirolimus had different pharmacological properties, and (3) the molecular biology of advanced RCC was not completely understood. *Decision*, 287 F. Supp. 3d at 515–17.

The district court correctly recognized that the temsirolimus phase I data resulted from small sample sizes and came from studies that were designed to test safety, not efficacy. *Id.* It also noted that the studies disclosed in Hidalgo 2000 and Hutchinson do not reveal the total number of advanced RCC patients enrolled and that phase II data was not yet available. *Id.* Further, it considered the testimony of West-Ward's expert Dr. Cho, who stated that a person of ordinary skill "would not make a determination or reasonable suggestion simply based in isolation upon whether a drug enters phase II," and who did not dispute that more than seventy percent of oncology drugs failed at phase II. *Id.* (citing J.A. 1072 at 202:7–15); J.A. 1072 at 202:7–20.

The district court also considered evidence that everolimus and temsirolimus are pharmacologically different. *Decision*, 287 F. Supp. 3d at 515–17. Novartis's expert, Dr. Burris, testified that the prior art, which disclosed that rapamycin and everolimus had different binding affinities for FKBP-12, would not have led a person of ordinary skill to reasonably expect that rapamycin, temsirolimus, and everolimus would all have the same antitumor efficacy. *See* J.A. 1394–95 at 524:2–525:6. Dr. Burris further testified that everolimus and temsirolimus had different elimination half-lives and that a person of ordinary skill would not have expected compounds with different half-lives to have the same anti-tumor efficacy. *See* J.A. 1397–1400 at

527:4–530:17. The district court did not err in crediting Dr. Burris's testimony.

In addition, the district court considered several prior art references in finding that the roles of HIF-1 and mTOR in the molecular biology of advanced RCC were not fully understood as of February 2001. *See Decision*, 287 F. Supp. 3d at 511–14. The district court cited Semenza, which showed that numerous pathways are implicated in HIF-1 activation in human cancers. *Id.* at 512; *see* J.A. 2128. Semenza states that "the role of HIF-1α expression in [RCC] requires further analysis." J.A. 2119. The district court also cited to Alexandre,[8] which noted that "there is still much to learn on, firstly, the exact mechanisms by which mTOR controls the G1/S transition and, secondly, on any other cellular targets of rapamycin." *Decision*, 287 F. Supp. 3d at 512 (quoting J.A. 1978). It further recognized Zhong 2000, which cautioned that "[a]dditional studies are required to determine whether this process is modulated by PI3K/AKT/[mTOR] activity and, if so, whether such modulation involves direct phosphorylation of HIF-1α." *Id.* at 513; *see also* J.A. 2194. In addition, the district court noted Sekulić,[9] which states "[c]learly, additional experiments are required to establish the relationship between deregulated PI3K-AKT activity and rapamycin sensitivity in human cancer cells." *Decision*, 287 F. Supp. 3d at 513 (quoting J.A. 2105).

The district court's finding is also consistent with record evidence explaining that inhibiting mTOR does not

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[8] Jérôme Alexandre et al., *Rapamycin and CCI-779*, 86 Bull. Cancer 808, 808–11 (1999).

[9] Aleksandar Sekulić et al., *A Direct Linkage Between the Phosphoinositide 3-Kinase-AKT Signaling Pathway and the Mammalian Target of Rapamycin in Mitogen-stimulated and Transformed Cells*, 60 Cancer Res. 3504, 3504–13 (2000).

necessarily result in tumor growth inhibition. Hidalgo 2000 states that "a critical issue is whether these downstream effects [of mTOR inhibition] correlate with the anti-tumor activity of [temsirolimus], particularly since malignant cells can traverse the cell cycle and proliferate despite the [downstream effects of mTOR inhibition] by rapamycin." J.A. 2032. Dr. Burris explained that in this quote, Dr. Hidalgo was "pointing out that even when thinking that we were inhibiting the mTOR pathway, we could still see tumor cells traverse, continue to grow and proliferate." J.A. 1337–38 at 467:19–468:2. In addition, Dr. Cho testified that mTOR inhibition does not necessarily mean that tumor growth will be inhibited. *See* J.A. 1108 at 238:19–24 ("Q: But you agree that a POSA would understand that you can have mTOR inhibition and still see tumor growth; right? A: A POSA would have been aware that that is possible.").

We discern no clear error with the district court's findings. We also disagree with West-Ward's contention that the district court applied an erroneously heightened standard in its analysis. The 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. *Decision*, 287 F. Supp. 3d at 515–17. We hold that the district court did not err in its determination and affirm its conclusion that claims 1–3 of the '131 patent would not have been obvious in view of the asserted prior art.

CONCLUSION

We have considered West-Ward's remaining arguments and find them unpersuasive. While the district court erred in its motivation to combine analysis, this error is harmless as the district court did not clearly err in its finding regarding reasonable expectation of success. For

the reasons above, we affirm the district court's decision that West-Ward failed to prove by clear and convincing evidence that claims 1–3 of the '131 patent are invalid as obvious.

AFFIRMED