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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC., APOTEX CORP., APOTEX PHARMACEUTICALS HOLDINGS INC., AND APOTEX HOLDINGS, INC.,
Petitioner,

v.

OSI PHARMACEUTICALS LLC,
Patent Owner.

Case IPR2016-01284
Patent 6,900,221 B1

Before LORA M. GREEN, RAMA G. ELLURU, and ZHENYU YANG, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining That Claims 44–46 and 53 Are Shown to Be Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc., ("Apotex" or "Petitioner") filed a Petition requesting an *inter partes* review of claims 44–47 and 53 of U.S. Patent No. 6,900,221 B1 (Ex. 1001, "the '221 patent"). Paper 3 ("Pet."). OSI Pharmaceuticals LLC[1] ("OSI" or "Patent Owner") filed a Preliminary Response to the Petition.[2] Paper 7 ("Prelim. Resp."). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 44–47 and 53 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, we instituted trial on January 9, 2017, as to all of the challenged claims of the '221 patent. Paper 8 ("Institution Decision" or "Dec. Inst.").

On February 8, 2017, the parties filed a Joint Motion to Limit Petition Under 37 C.F.R. § 42.71, seeking to remove claim 47 from trial. Paper 12. We *granted* that Motion. Paper 19. Thus, trial is limited to claims 44–46 and 53.

Patent Owner filed a Response (Paper 20, "PO Resp.") and Petitioner filed a Reply (Paper 33, "Reply"). Patent Owner also filed a Motion to Exclude Evidence (Paper 37, "Mot. Exclude"), to which Petitioner filed an Opposition (Paper 40, "Opp. Mot. Exclude"), and Patent Owner filed a

[1] Patent Owner underwent a name change from OSI Pharmaceuticals Inc. to OSI Pharmaceuticals LLC, which change was recorded at the United States Patent and Trademark Office. Reply 1 n.2.

[2] OSI further identifies Astellas US LLC, Astellas US Holding, Inc., Astellas Pharma Inc., and Genentech, Inc., as real parties-in-interest. Paper 5, 1.

Reply (Paper 43). Oral hearing was held on October 3, 2017, and a transcript of that hearing has been entered into the record. Paper 48 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and the burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 44–46 and 53 of the '221 patent are unpatentable. We also *deny* Patent Owner's Motion to Exclude in part, and *dismiss* it in part.

A. Related Proceedings

According to Patent Owner, the '221 Patent is presently at issue "in *OSI Pharms. LLC. et al. v. Apotex Inc. et al.*, Case No. 1:15-cv-00772-SLR (D. Del. Sept. 2, 2015) and *OSI Pharms. LLC. et al. v. Breckenridge Pharms. Inc. et al.*, Case No. 1:15-cv-01063-SLR (D. Del. Nov. 17, 2015), which are consolidated in lead Case No. 1:15-00772-SLR." Paper 5, 3–4. Patent Owner further identifies a number of closed matters involving the '221 patent, including *OSI Pharms, Inc. v. Mylan Pharms Inc.*, Case No. 1:09-cv-00185-SLR (D. Del. Mar. 19, 2009). *Id*.

B. The '221 Patent (Ex. 1001)

The '221 patent is generally directed to the B polymorph of N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride. Ex. 1001, Abstract. The '221 patent further discloses that

"N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine, in either its hydrochloride or mesylate forms, or in an anhydrous and hydrous form, is useful in the treatment of hyperproliferative disorders, such as cancers, in mammals." *Id.* at 1:21–25. The '221 patent references U.S. Patent No. 5,747,498 (Ex. 1009, "Schnur"), and incorporates it by reference in its entirety. *Id.* at 1:27–29. In addition, the '221 patent notes that Example 20 of Schnur refers

> to [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride [i.e., the hydrochloride salt of erlotinib], which, the patent discloses, is an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders, such as cancers, in humans.

Id. at 1:28–35.

According to the '221 patent, the method of treating cancer using the disclosed compound

> may be for the treatment of a cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.
>
> The method may also be for the treatment of a cancer selected from non-small cell lung cancer (NSCLC), refractory ovarian cancer, head and neck cancer, colorectal cancer and renal cancer.

Id. at 4:23–30.

C. Illustrative Claim

As discussed above, the claims challenged in this proceeding are 44–46 and 53 of the '221 patent. Claim 44, representative of the challenged subject matter, is the only independent challenged claim and is reproduced below:

> 44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HFV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.

Ex. 1001, 35:26–36. Challenged claim 53 limits the cancer to be treated to non-small cell lung cancer. *Id.* at 35:64–65.

D. Instituted Challenge

We instituted trial on the challenged claims based on the following ground of unpatentability (Dec. Inst. 29):

References	**Basis**	**Claims Challenged**
Schnur[3] and OSI's 10K[4] or Gibbs[5]	§ 103	44–46 and 53

Petitioner relies also on the Declaration of Giuseppe Giaccone, M.D., Ph.D. (Ex. 1002), the Declaration of Laurence S. Lese, Esq. (Ex. 1012), as well as the Reply Declaration of Dr. Giaccone (Ex. 1053) and Kristopher A. Boushie (Ex. 1054).

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[3] Schnur et al., U.S. Patent No. 5,747,498, issued May 5, 1998 (Ex. 1009) ("Schnur").

[4] Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the Fiscal Year Ended September 30, 1998, Commission File Number 0-15190, OSI Pharmaceuticals, Inc. (Ex. 1011) ("OSI's 10K").

[5] J.B. Gibbs, "*Anticancer Drug Targets: Growth Factors and Growth Factor Signaling*," 105 J. CLIN. INV. 9–13 (2000) (Ex. 1010) ("Gibbs").

Patent Owner relies on the Declarations of Paul Bunn, M.D. (Ex. 2021), and Mark L. Reisenauer (Ex. 2023).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–45 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Institution Decision, we determined that none of the terms in the challenged claims required express construction at that time. Dec. Inst. 6 (citing *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'")). In its Response, Patent Owner agrees that the claims terms should be construed according to their ordinary and customary meaning (PO Resp. 28 (citing Pet. 13)), and Petitioner does not dispute that

in its Reply. We note, however, that for purposes of our final written decision there is now a need to clarify the construction of "treatment" and "therapeutically effective amount" based on the specific definition of "treatment" in the '221 patent.

i. "treatment" and "therapeutically effective amount"

Independent claim 44 is drawn to treatment of non-small cell lung cancer, pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus, Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of erlotinib or a pharmaceutically acceptable salt thereof to a mammal. As discussed above, the parties agree that the terms of the claim should be given their ordinary and customary meaning.

According to the '221 patent:

> The term "treating" as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

Ex. 1001, 14:9–15. Both parties agree this construction of "treating" provided in the specification is the proper construction of that term. *See, e.g.,* Tr. 30 (Counsel for Patent Owner stating "[t]he term 'treatment' both sides agree is defined in the patent."). We further conclude that this construction is consistent with its ordinary and customary meaning and how the ordinary artisan would understand the term "treat," "treating," or "treatment." In view of this construction of "treatment," we conclude that the ordinary artisan would understand the ordinary and customary meaning

of "a therapeutically effective amount" of erlotinib for the treatment of the conditions listed by the preamble to claim 44 to be an amount sufficient to treat the mammal as defined above. The challenged claims, therefore, do not require administration of a clinically effective amount of erlotinib to a human. *Cf.* Tr. 50:16–17 (counsel for Patent Owner noting that a "major clinical response" is "a higher standard than treatment as defined in the claims").

B. Level of Ordinary Skill in the Art

Petitioner contends, relying on its expert, Dr. Giaccone:

> A person of ordinary skill in the art relevant to the challenged claims of the '221 patent would have a medical degree and at least some specialized training in oncology, and more particularly, specialized training in thoracic oncology. (*See* **Ex. 1002** at ¶ 52.) A person of ordinary skill in the art would also have several years of clinical experience, and a substantive understanding and experience using the medications and therapies effective for treating various lung cancers at the relevant time. (*See* **1002** at ¶ 52.) A person of ordinary skill in the art may have collaborated with others having expertise in pharmaceutical formulation development and pharmaceutical drug development. (**Ex. 1002** at ¶ 51.)

Pet. 13.

Patent Owner responds, relying on its expert, Dr. Bunn, that the ordinary artisan "would be a medical oncologist who would hold an M.D. degree and would have completed several years of practice in the field of oncology." PO Resp. 26 (citing Ex. 2021 ¶¶ 22–23).

Patent Owner disagrees with Petitioner's expert, Dr. Giaccone, that the ordinary artisan would have specialized training in thoracic oncology and a substantive understanding using medications and therapies for treating various lung cancers. *Id.* at 26–27 (citing Ex. 1002 ¶ 52). Petitioner

responds that under its definition, the ordinary artisan "would have the ability to infer facts from disclosures in the prior art directed to the development of drugs to treat lung cancer, and specifically NSCLC, and would not require every fact to be explicitly laid out in the prior art." Reply 2.

Given that claim 44 encompasses cancers in addition to non-small cell lung cancer, we adopt Patent Owner's statement of the level of ordinary skill in the art. Because the claim's requirement to treat cancers in addition to non-small cell lung cancer, we find that the ordinary artisan would be a medical oncologist who would hold an M.D. degree and would have completed several years of practice in the field of oncology. Moreover, we note that the level of ordinary skill in the art in this proceeding is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). In addition, during oral hearing, counsel for both parties opined that the outcome of the obviousness analysis would be the same under either parties' definition of the ordinary artisan. Tr. 22:3–8, 37:9–11. Thus, our analysis would be the same under either Petitioner's or Patent Owner's definition of the ordinary artisan.

C. Obviousness over Schnur and OSI's 10-K or Gibbs

Petitioner asserts that claims 44–46 and 53 are rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs. Pet. 23–35. Petitioner presents a claim chart demonstrating where the limitations of the challenged claims may be found in the relied upon references. Pet., Appendix A. Patent Owner disagrees with Petitioner's contentions, asserting that the

Petition fails to demonstrate the obviousness of the challenged claims by a preponderance of the evidence. PO Resp. 29–66.

i. Overview of the Prior Art Relied Upon

We find the following as to the teachings of the relevant prior art.

a. Schnur (Ex. 1009)

Schnur "relates to 4-(substituted phenylamino) quinazoline derivatives which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals." Ex. 1009, 1:9–11. Schnur recognizes that there is a continuing need for anti-cancer pharmaceuticals. *Id.* at 1:64–67. Schnur notes that it is known that a cell may become cancerous through transformation of a portion of its DNA into an oncogene, many of which "encode proteins which are aberrant tyrosine kinases capable of causing cell transformation." *Id.* at 1:20–25. According to Schnur:

> Receptor tyrosine kinases are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR) which possesses tyrosine kinase activity is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Id. at 1:30–44. Thus, Schnur teaches that is known that inhibitors of receptor tyrosine kinases "are useful as [ ] selective inhibitors of the growth of mammalian cancer cells." *Id.* at 1:45–47.

Of the 4-(substituted phenylamino) quinazoline derivatives taught by Schnur, Schnur teaches that [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine (i.e., erlotinib) is preferred (*id.* at 3:47–48; 4:8–9), and specifically discloses its synthesis (*id.* at 22:30–49 (Example 20)).

Schnur teaches:

> The active compounds of this invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. In particular. the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, *lung*, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors), and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., BPH). It is, in addition, expected that a quinazoline of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

Id. at 14:1–16 (emphasis added).

Schnur teaches that the "amount of active compound administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician." *Id.* at 15:55–58. Schnur teaches, however, that "an effective dosage is in the range of approximately 0.001–100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses," which, "[f]or an average 70 kg human, this would amount to 0.05 to 7 g/day, preferably 0.2

to 2.5 g/day." *Id.* at 15:58–62. Schnur also discusses pharmaceutical composition comprising the active compound. *Id.* at 15:63–16:45.

In addition, Schnur discloses both *in vitro* and *in vivo* methods for testing the activity of the compounds. *Id.* at 14:31–15:47. Schnur explicitly claims erlotinib (i.e., [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine. *Id.* at 39:33, 40:1–2, claim 8. Schnur also claims pharmaceutical compositions comprising a pharmaceutically effective amount of the disclosed compounds (*see, e.g.*, *id.* at 39:15–18, claim 3; 41:51–54, claim 11), as well as methods of treatment of hyperproliferative disorders, such as lung cancer (*see, e.g.*, *id.* at 41:55, claim 12; *id.* at 41:61–62, claim 14).

b. OSI's 10K (Ex. 1011)

OSI's 10K is a filing with the Securities and Exchange Commission ("SEC") by OSI Pharmaceuticals, Inc. Ex. 1011, 1.

OSI's 10 K discloses

> With its collaborative partner Pfizer, OSI has focused since 1986 on the discovery and development of novel classes of orally active, molecularly targeted, small molecule anticancer drugs based on oncogenes and tumor suppressor genes and the fundamental mechanisms underlying tumor growth. *The first of these programs to yield a clinical candidate, CP-358,774, which targets a variety of cancers including* ovarian, pancreatic, *non-small cell lung* and head and neck, achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients. *CP-358,774 is a potent, selective and orally active inhibitor of the epidermal growth factor receptor, a key oncogene in these cancers*. In addition, two other compounds, CP-564,959 and CP-609,754, have been identified and are in advanced stages of pre-clinical development. Nine other targets are in active R&D at OSI. CP-564,959 is being developed as an

> orally available, potent and selective inhibitor of a key protein tyrosine kinase receptor involved in blood vessel growth or angiogenesis. Angiogenesis is induced by solid tumors which require nutrients that will enable growth. The Company believes that the ability to safely and effectively inhibit this process represents one of the most exciting areas of cancer drug development. CP-609,754 is an orally active inhibitor of the ras oncogene, which is another important target involved in many major tumors including colon and bladder. The types of novel anticancer drugs being developed in the OSI/Pfizer collaboration are expected to be safer and more effective than standard chemotherapeutic agents.

Ex. 1011, 5–6 (emphasis added).

c. Gibbs (Ex. 1010)

Gibbs provides "a broad overview of a growth factor signal transduction system, with a focus on those points that have been translated to drugs or clinical candidates." Ex. 1010, 9. Gibbs notes, however, that "[d]ue to editorial restrictions limiting the number of reference citations, much of the clinical data gleaned from abstracts is not listed in the references," and points the reader to additional references. *Id.*

Gibbs teaches:

> The EGF receptor is also the target for the development of inhibitors of the intracellular tyrosine kinase domain. *ZD-1839 and CP-358,774*, competitive inhibitors of ATP binding to the receptor's active site*, are currently in clinical trials* (12, 13). Their mechanism of action has led to some concern about safety, given the variety and physiological significance of protein kinases and other enzymes that bind ATP. However, *these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer*.

Id. at 10 (emphasis added).

Gibbs provides Table 1, which sets forth examples of inhibitors of growth factor signaling, and their development status, which is reproduced below:

Table 1
Examples of inhibitors of growth factor signaling for cancer treatment

Target	Compound	Mechanism of action	Development status
HER2/c-neu	Trastuzumab	mAb	Launched as Herceptin™
EGF receptor	C225	mAb	Phase III
	E7.6.3	mAb	Preclinical
	ZD-1839	Kinase inhibitor	Phase II
	CP-358,774	Kinase inhibitor	Phase II
	PD-168,393	Kinase inhibitor	Preclinical
PDGF receptor	SU-101	Kinase inhibitor	Phase III
IGFR	AS ODN	Antisense	Preclinical
Ras	ISIS-2503	Antisense	Phase II
	R115777	FTI	Phase II
	SCH 66336	FTI	Phase II
	L-778,123	FTI	Phase I
	BMS-214662	FTI	Phase I
Raf	ISIS-5132	Antisense	Phase II
	ZM 336372	Kinase inhibitor	Preclinical
	L-779,450	Kinase inhibitor	Preclinical
MEK	PD-184352	Kinase inhibitor	Preclinical
	U0126	Kinase inhibitor	Preclinical
PKC	ISIS-3521	Antisense	Phase II
	CGP 41251	Kinase inhibitor	Phase II
	UCN-01	Kinase inhibitor	Phase I
PI 3'-kinase	LY 294002	Kinase inhibitor	Preclinical

Id.

ii. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *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 skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

Secondary considerations may include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406; *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358–59 (Fed. Cir. 2013). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness" and "enable[ ] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd.*, 726 F.3d at 1358 (first alteration in original) (internal quotation marks and citations omitted). "This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citations omitted).

The obviousness analysis requires that "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success," even "[i]f all elements of the claims are found in a combination of prior art references." *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

iii. Analysis

Petitioner relies on Schnur for teaching a genus of compounds that includes erlotinib, asserting that Schnur discloses that erlotinib is a preferred compound. Pet. 24 (citing Ex. 1009, 3:47–48, 4:8–9, 38:13–39:12, 39:33–40:65; Ex. 1002 ¶ 93). In particular, Petitioner asserts that Schnur's claim 8 includes erlotinib as one of 49 preferred compounds. *Id.* (citing Ex. 1009, 3:47–48; 4:8–9; 39:33–40:65; Ex. 1002 ¶ 93). According to Petitioner, Schnur "discloses that the compounds can be administered to a mammal for the treatment of a hyperproliferative disorder." *Id.* (citing Ex. 1009, 5:49–52).

Petitioner further relies on Schnur for teaching a "therapeutically effective amount" of erlotinib. *Id.* at 25. Specifically, Petitioner asserts that Schnur teaches that the "therapeutically effective amount can depend on the subject being treated, on the severity of the affliction, on the manner of administration, and on the judgment of a prescribing physician." *Id.* (citing Ex. 1009, 15:55–58). According to Petitioner, Schnur teaches that a generally therapeutically effective dose is in the range of 0.001–100 mg/kg, preferably from 1 to 35 mg/kg, making the dose for an average 70 kg person from 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. *Id.* (citing Ex. 1009, 15:58–62). Petitioner contends that "*Schnur*'s disclosure of the therapeutically effective dose is identical to that disclosed by the '221 patent." *Id.* (emphasis removed) (citing Ex. 1009, 15:55–62; Ex. 1001, 24:19–27, 24:33–43, 30:29–35).

The only difference between Schnur and the method of challenged claims 44 and 53, Petitioner asserts, is that Schnur "does not expressly identify 'NSCLC' as a hyperproliferative disorder." *Id.* at 26 (citing

Ex. 1005, 23; Ex. 1006, 2). Petitioner notes, however, that Schnur "discloses that erlotinib is useful to treat, *inter alia*, 'lung cancer.'" *Id.* (citing Ex. 1009, 14:1–6). Petitioner notes further that the Examiner "reached the same conclusion during prosecution of the '221 patent, and allowed claim 44 to issue because it was 'drawn to treatment of specific cancers by any polymorph of the claimed compounds. These specific cancers are not found in *Schnur* ('498).'" *Id.* (quoting Ex. 1006, 2).

Petitioner relies on Gibbs for teaching that CP-358,774, which Petitioner contends is anhydrous erlotinib hydrochloride, is "a kinase inhibitor 'with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer,' and had entered Phase-II clinical trials." *Id.* at 27 (citing Ex. 1010, 9–10, Table 1).

Petitioner relies on OSI's 10K for similarly teaching that CP-358,774 is "a clinical candidate that had 'achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients.'" *Id.* at 28 (quoting Ex. 1011, 6). Petitioner relies on OSI's 10K also for its disclosure "that CP-358,774 is a potent, selective and orally active inhibitor of the EGFR and being used to target ovarian, pancreatic, non-small cell lung, and head and neck cancers." *Id.* (citing Ex. 1011, 6).

Petitioner asserts, therefore, that Gibbs or OSI's 10K would have pointed an ordinary artisan towards erlotinib from the compounds of Schnur (*id.* at 28 (citing Ex. 1002 ¶¶ 102–105)), and would have also taught its use to treat non-small cell lung cancer (*id.* (citing Ex. 1010, 10, Ex. 1011, 6, Ex. 1002 ¶ 106)). That is, Petitioner asserts, "the preferred use of erlotinib to treat NSCLC is made explicit when *Schnur* is viewed through the lens of

Gibbs or *OSI's 10-K*." *Id.* at 29 (citing Ex. 1002 ¶ 107); *see also id.* at 33–35 (discussing the reason to combine Schnur with Gibbs or OSI 10-K). Moreover, Petitioner asserts, the teachings of Schnur as combined with Gibbs or OSI's 10K would have provided a reasonable expectation of success of achieving the method of challenged claim 44. *Id.* at 29 (citing Ex. 1002 ¶¶ 105, 109).

Patent Owner responds initially that the Petition does not "establish a link between the compounds discussed in OSI 10-K and Gibbs [i.e., CP-358,774] and any compound disclosed in Schnur—let alone erlotinib, specifically." PO Resp. 30; *see id.* at 30–32. We note that Patent Owner is not arguing that CP-358,774 is not erlotinib. Rather, as counsel for Patent Owner, Ms. Wigmore, stated during oral argument, Patent Owner is arguing that there is "a procedural deficiency in the[ ] petition." Tr. 35:6.

As noted in our Decision on Institution (Dec. Inst. 15–16), Petitioner pointed us to paragraph 28 of the Declaration of Dr. Giaccone in discussing the structure of erlotinib (*see* Pet. 24 n. 3). We noted (Dec. Inst. 15–16) that the next paragraph of the Declaration specifically stated:

> During joint clinical development of erlotinib between OSI and Pfizer, and then subsequently, only OSI, the hydrochloride salt of erlotinib was commonly referred by the identifier CP-358,774, which was prepared as set forth in PCT Pub. No. WO 96/30347. (*See* Ex. **1016**[6] at 4839, col. 1; *See also* V.A. Pollack *et al.*, "Inhibition of Epidermal Growth Factor Receptor-Associated Tyrosine Phosphorylation in Human Carcinomas with CP-358,774: Dynamics of Receptor Inhibition In Situ and Antitumor Effects in Athymic Mice," *J. Pharmacol.*

[6] Moyer et al., *Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase*. 57 CANCER RESEARCH 4838–4848 (1997) ("Moyer").

> *Exp. Ther.* 291(2):739–748 (Nov. 1999) ("*Pollack*," Ex. 1015) at 740 ("CP-358,774 . . . a colorless, crystalline, anhydrous compound, was synthesized in our laboratories (Arnold and Schnur, 1998)).)

Ex. 1002 ¶ 29. We noted further that statement is supported by Moyer, which defines "CP-358,774" as "[6,7-Bis(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynylphenyl) amine." Dec. Inst. 16 (quoting Ex. 1016, 4839); *see Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F. 3d 1359, 1365 (Fed. Cir. 2015) ("Art can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.").

Thus, the Decision on Institution clearly put Patent Owner on notice as to the evidence we were relying on in establishing that the ordinary artisan would have understood at the time of invention that CP-358,774 is the hydrochloride salt of erlotinib. In that regard, we agree with Petitioner that Moyer is indicative of the state of the art, and as Patent Owner's expert, Dr. Bunn admitted, "at least by 1997, Moyer (Ex. 1016) defined CP-358,774 with the chemical name for erlotinib, and also admitted that Moyer defines CP-358,774 with a chemical structure, which has remained the same." Reply 13 (citing Ex. 1048, 90:7–92:20; Ex. 1016 at 4839). Thus, we determine that the Petition sufficiently established that the ordinary artisan would understand that CP-358,774 is the hydrochloride salt of erlotinib.

As to OSI's 10-K, Patent Owner argues that the Petition, as well as the Declaration of Mr. Lese (Ex. 1012), does not explain why the ordinary artisan would have relied on that reference as providing a reason for pursuing treatment of non-small cell lung cancer, as that reference is a financial document filed with the United States Securities Exchange

Commission. PO Resp. 32.[7] Patent Owner avers that Petitioner's expert, Dr. Giaccone, admitted that before this proceeding, he had never relied on or heard of a 10-K, testifying that it is not a scientific publication, and that it does not contain scientific data. *Id.* at 33 (citing Ex. 2020, 77:21–78:8, 81:17–20, 75:15–17, 86:11–14, 81:17–20). Patent Owner notes further that its expert, Dr. Bunn, testifies also that the ordinary artisan would not rely on a 10-K "in determining potential cancer treatments to pursue." *Id.* at 33–34 (citing Ex. 2021 ¶¶ 66–67). According to Patent Owner, as an ordinary artisan would not have relied on a securities filing in determining how to treat non-small cell lung cancer, Petitioner is engaging in impermissible hindsight in it obviousness analysis of the challenged claims. *Id.* at 34–35.

Petitioner responds that Patent Owner's expert, Dr. Bunn, testified that many companies were vying to develop tyrosine kinase inhibitors around the time of invention, and that such companies would have employed oncologists who would qualify as ordinary artisans. Reply 10 (citing Ex. 2021 ¶ 96; Ex. 1048, 95:12–97:19). In addition, Petitioner notes that Patent Owner's "fact witness, Dr. Gibbs, admitted that a director at a pharmaceutical company (such as himself) would routinely request and review competitors' product development information as a part of his job responsibilities." *Id.* (citing Ex. 1049, 20:13–21:1). Moreover, Petitioner asserts, "Dr. Giaccone testified that his peers working at pharmaceutical companies routinely reviewed documents similar to OSI's 10-K to learn of the development status of potentially competing products, and Dr. Giaccone

[7] Counsel for Patent Owner did note during oral argument that Patent Owner is not arguing that OSI's 10-K does not constitute prior art to the challenged patent. Tr. 35:23–24.

even gave an example of [an ordinary artisan], who at the relevant time would likely have reviewed OSI's 10-K." *Id.* (citing Ex. 2020, 75:18–76:16, 78:9–80:5).

We find that an ordinary artisan would have looked to OSI's 10-K to determine what drugs and treatments pharmaceutical companies were working on at the time of invention. We acknowledge that Patent Owner's expert, Dr. Bunn, opined that "[m]edical oncologists would not turn to securities filings because those publications are not focused on reporting reliable efficacy data from clinical trials." Ex. 2021 ¶ 67. We find, however, that researchers interested in the subject matter of the challenged claims, which only require treatment of mammals and are, thus, not limited to clinical treatment of humans, would have been interested in research involving potential cancer treatments and their indications. That is corroborated by the testimony of Dr. Gibbs, who at the time of the Gibbs reference relied upon by Petitioner, worked as a senior director of cancer research at Merck Research Laboratories. Ex. 1049, 19:3–12. Dr. Gibbs noted that "competitor data could be made available," and that is something he would review as "it related to [his] project." *Id.* at 20:19–21:1. Thus, we find that competitor pharmaceutical companies working in the same area as Patent Owner at the time of invention, which would have employed medical oncologists who met the requirements of an ordinary artisan, would have been aware of company filings such as OSI's 10-K.

Patent Owner contends further that the ordinary artisan would not have combined Gibbs or OSI's 10-K with Schnur "because none of these references discusses using erlotinib to treat NSCLC or contains any data relating thereto." PO Resp. 35. Patent Owner asserts that Schnur only

contains in vitro data, and does not mention non-small cell lung cancer, and that neither Gibbs nor OSI's 10-K "disclose or cite any evidence showing the use of erlotinib in NSCLC." *Id.* Moreover, Patent Owner argues, Petitioner's expert, Dr. Giaccone, admitted that "he is 'not aware of any efficacy data with respect to non-small cell lung cancer specifically that was available before March 30th, 2000 for erlotinib.'" *Id.* (quoting Ex. 2020, 126:6–12). Thus, Patent Owner contends that the ordinary artisan would not have had a reason to treat non-small cell lung cancer using erlotinib as encompassed by challenged claim 44 and as required by challenged claim 53 "[g]iven the undisputed lack of data concerning the use of erlotinib in NSCLC as of the time of the claimed invention." *Id.*

Patent Owner argues further that the ordinary artisan would not have had a reasonable expectation of success in achieving the invention of the challenged claims. PO Resp. 35. According to Patent Owner, the Decision on Institution overlooked the requirement of the challenged claims "of ***treating*** NSCLC with a ***therapeutically effective*** amount of erlotinib." *Id.* at 36–37 (citing Ex. 2020, 52:2–6). That is, Patent Owner asserts, the claims require a "therapeutic benefit." *Id.* (emphasis removed) (citing Ex. 2020, 49:4–50:3).

Patent Owner contends that the facts of this proceeding are distinguishable from those that contain *in vitro* data or testing in animal models, as none of the prior art on which the challenges rely "include ***any*** evidence of using erlotinib against NSCLC—whether *in vitro*, animal model, or human." *Id.* at 37. The lack of data, Patent Owner asserts, is especially relevant "in the highly unpredictable field of NSCLC drug development." *Id.* at 37–38 (citing *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353,

1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on … 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

Thus, Patent Owner contends, without "any evidence to suggest efficacy in NSCLC," the ordinary artisan at the time of invention would not have had a reasonable expectation of success of using erlotinib to treat non-small cell lung cancer. *Id.* at 38. According to Patent Owner, the majority of cancer drugs, and especially drugs targeting non-small cell lung cancer that make it to Phase II or Phase III studies fail during clinical development. *Id.* (citing Ex. 2021, ¶¶ 34–41, 79, 82, 90–101, 108). Patent Owner also cites the deposition of Dr. Giaccone, who stated that "the odds of finding a successful treatment for non-small cell lung cancer, at least as of the 2000 time period, were not good." *Id.* (emphasis removed) (quoting Ex. 2020, 139:14–18).

Petitioner responds that "therapeutically effective treatment" is not required by any of the challenged claims. Reply 2, 6 (citing Ex. 2021 ¶ 43). In addition, Petitioner asserts, Patent Owner's expert, Dr. Bunn, testifies that a reasonable expectation of success in treating non-small cell lung cancer with erlotinib would require "a specific disclosure of such treatment supported by 'vetted scientific data.'" *Id.* at 7 (citing Ex. 2021 ¶¶ 68, 78; Ex. 1048, 93:20–94:8). That is, Petitioner asserts, accepting Patent Owner's definition of a reasonable expectation of success "would only be satisfied by actual success: a successfully completed Phase II clinical study." *Id*. (citing Ex. 2021 ¶ 79; Ex. 1048, 64:17–67:13). Dr. Bunn, however, Petitioner contends, acknowledged "the specification of the '221 patent itself does not

satisfy" that standard. *Id.* (citing Ex. 1048, 60:7–63:12, 64:17–67:13). Petitioner responds further that because "Schnur is presumed to be enabled to treat lung cancer, all that is required is a reasonable expectation that erlotinib would similarly treat NSCLC with the same efficacy disclosed in Schnur." *Id.* at 8 (citing *Amgen Inc. v. Hoeschst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003) (noting that under an obviousness analysis, a prior art reference is presumed enabling "for whatever is disclosed therein.").

Petitioner contends also that OSI's 10-K and Gibbs each confirms actual treatment of non-small cell lung cancer in mammals with erlotinib "by disclosing that erlotinib completed Phase I clinical studies and had entered Phase II clinical studies." Reply 14 (citing Ex. 1010, 2; Ex. 1011, 6). According to Petitioner, the ordinary artisan at the time of invention would have understood that completion of Phase I trial, and entry into Phase II, "meant that preclinical development was successful in showing that erlotinib treated NSCLC in mammals." *Id.* Petitioner relies on the cross-examination of Patent Owner's expert, Dr. Bunn, who testified that "before Phase I studies can be initiated, animal studies and *in-vitro* studies proving biological activity for intended therapeutic targets are required" by the Food and Drug Administration ("FDA"). *Id.* (citing Ex. 1048, 28:1–33:5, 38:12–39:12). Moreover, Petitioner asserts, Gibbs "expressly states that erlotinib treated NSCLC in humans." *Id.* (citing Ex. 1010, 2). According to Petitioner, that "statement in the Gibbs reference is corroborated by a publication reporting on data presented at the American Society of Clinical Oncology meeting May 15–18, 1999 (Ex. 2024) that showed NSCLC tumors in a patient were stabilized during Phase I studies." *Id.* at 14–15 (citing Ex.

1048, 71:22–76:16, 78:18–79:3; 83:19–22; Ex. 1031, 3267, 3274; Ex. 2024, 5, Abstract 1498). Finally, Petitioner asserts that "Dr. Bunn admitted that NSCLC patients were included in the Phase I clinical studies for erlotinib that were performed before March 30, 2000." *Id.* at 15 (citing Ex. 1048, 69:19–70:1, 86:12–87:1; Ex. 1010, 2; Ex. 1011, 6; Ex. 2024, 5, Abstract 1498).

Patent Owner's arguments are unavailing. That is, we find that the ordinary artisan would have combined Gibbs or OSI 10-K with Schnur and had a reasonable expectation of success of achieving the invention of challenged claims 44 and 53. In that regard, we agree with Petitioner (Pet. 26) that Schnur discloses all of the elements of claims 44 and 53, except for specifically teaching the treatment of non-small cell lung cancer. Specifically, Schnur teaches a genus of compounds that encompasses erlotinib (Ex. 1009, 1:9–11) in which the synthesis of erlotinib is specifically disclosed (*id.* at 22:30–49 (Example 20)), and erlotinib is specifically claimed (*id.* at 39:33 (claim 8)). In addition, Schnur discloses the treatment of hyperproliferative disorders such as cancer (*id.* at 1:9–11), and specifically claims treating lung cancer with the genus of compounds (*id.* at 14:1–13). Thus, as Schnur specifically discloses and claims erlotinib, and specifically discloses and claims treatment of lung cancer, we conclude that Schnur suggests the treatment of lung cancer with erlotinib. As acknowledged by Petitioner, however, Schnur does not specifically teach treatment of non-small cell lung cancer. Pet. 26.

As to the combination of Schnur and OSI 10-K, Petitioner notes that OSI 10-K specifically teaches that erlotinib (i.e., CP-358,774) may be used

in the treatment of non-small cell lung cancer. Pet. 28. Namely, OSI's 10-K teaches:

> *The first of these programs* [performed in collaboration with Pfizer] *to yield a clinical candidate, CP-358,774, which targets a variety of cancers including* ovarian, pancreatic, *non-small cell lung* and head and neck, achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients. *CP-358,774 is a potent, selective and orally active inhibitor of the epidermal growth factor receptor, a key oncogene in these cancers*.

Ex. 1011, 5–6 (emphasis added). Thus, given Schnur's suggestion of treating lung cancer with erlotinib and related compounds, OSI's 10-K would have provided the ordinary artisan a reason to use erlotinib to treat non-small cell lung cancer.

Similarly, as to the combination of Schnur and Gibbs, Petitioner notes that Gibbs specifically teaches that erlotinib (i.e., CP-358,774) may be used in the treatment of non-small cell lung cancer. Pet. 27. To be exact, Gibbs teaches:

> The EGF receptor is also the target for the development of inhibitors of the intracellular tyrosine kinase domain. ZD-1839 and CP-358,774, competitive inhibitors of ATP binding to the receptor's active site, are currently in clinical trials (12, 13). Their mechanism of action has led to some concern about safety, given the variety and physiological significance of protein kinases and other enzymes that bind ATP. However, these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer.

Ex. 1010, 10. Again, given Schnur's suggestion of treating lung cancer with erlotinib and related compounds, Gibbs would have provided the ordinary artisan a reason to use erlotinib to treat non-small cell lung cancer.

Patent Owner's arguments against the combinations are, in essence, that the ordinary artisan would not have had a reasonable expectation of success in achieving the claimed invention as none of the references relied upon by Petitioner contain any data. *See*, *e.g.*, PO Resp. 35. However, all that is required is a reasonable expectation of success, not absolute predictability of success. *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988). Indeed, "the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, "[c]onclusive proof of efficacy is not necessary to show obviousness." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

As discussed above, Schnur suggests the treatment of lung cancer with erlotinib and related compounds. As a U.S. patent, Schnur is presumed to be enabled. *Regeneron Pharms., Inc. v. Merus N.V.*, 864 F.3d 1343, 1368 (Fed. Cir. 2017). Moreover, Patent Owner has not argued or demonstrated that the disclosure in Schnur is not enabled. OSI's 10-K and Gibbs take the teaching of Schnur one step further, and suggest the treatment of non-small cell lung cancer using erlotinib.

We do not find the lack of data in OSI's 10-K and Gibbs to be determinative of the obviousness analysis in this proceeding. As noted above, proof of efficacy is not required to demonstrate obviousness. In addition, the claims are not limited to treatment of human patients with non-small cell lung cancer, but are drawn to the treatment of any mammal, and, given the definition of treatment in '221 patent, only require some level of therapeutic benefit, such as alleviating the progress of the disease. *See* Ex. 1001, 14:9–15. Thus, given the teaching of Schnur that compounds such

as erlotinib are known to treat lung cancer, the ordinary artisan would have a reasonable expectation of using erlotinib to treat a specific type of lung cancer, that is, non-small cell lung cancer.

Moreover, OSI's 10-K notes that Phase I trials have been completed, and teaches also the initiation of Phase II trials. Ex. 1011, 5–6. Gibbs goes one step further, not only teaching the completion of Phase I trials and initiation of Phase II trials, but teaches that erlotinib, along with another compound, "appear[s] to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer." Ex. 1010, 10.

As to what is required for filing an investigational new drug application with the FDA, Patent Owner's expert, Dr. Bunn testified:

> Q. Now, once you've completed a study of a certain drug on a human tumor in a mouse, is that when -- and let's say you were successful in that study, is that when you would file an investigational new drug application ["IND"] with the FDA?
>
> A. Right. To get an IND you have to have toxicology, and so you have to know what the lethal dose in an animal was. You would have to have a lot of pharmacokinetic information about the drug. You would have to know a lot about drug interactions with other known enzymes involved in drug metabolism. So, yeah, there are a number of things in addition to what you mentioned that are required for an IND.
>
> Q. (BY MR. COBLENTZ) So when you submit an IND to the FDA, you also submit what's called an investigator's brochure; is that correct?
>
> A. That's correct.
>
> Q. (BY MR. COBLENTZ) Do you know what goes into an investigator's brochure?
>
> A. I've submitted INDs and investigative brochures before, yes.

> Q. (BY MR. COBLENTZ) Do you know what sorts of information that go into the investigator's brochure when you submit the IND?
>
> A. Yes, I do.
>
> Q. (BY MR. COBLENTZ) Can you -- . . . .
>
> A. So you have to have toxicology studies so you know what a lethal dose is, you have to have pharmacokinetic data so you know how the drug behaves in an animal, and you have to have a clinical trial, proposed clinical trial. The clinical trial has to be approved by an IRB [Institutional Review Board] before an IND would be activated. *And you have to have all the preclinical efficacy data*, as well as the animal safety data.

Ex. 1048, 30:4–33:3 (objections omitted) (emphasis added).

Thus, Dr. Bunn's testimony is evidence that the ordinary artisan would understand that the filing of an IND and investigative brochures with the FDA, which need to be submitted to the FDA before starting Phase I trials, require preclinical animal efficacy data. That is also consistent with the testimony of Dr. Giaccone, Petitioner's expert. Dr. Giaccone testified:

> Q. So the term "treating," according to column 14, means "reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition," correct?
>
> A. Yes.
>
> Q. And it's your opinion that that includes some effect in a preclinical model?
>
> A. Yes.
>
> Q. What effect?
>
> A. It would be an effect on a tumor that is implanted in mice, for instance, the most common preclinical in vivo model that is used. So it would mean having an effect on the tumor growth implanted in the animal.

> Q. Now, turning back to claim 44, we talked about the term "therapeutically effective amount."
>
> A. Right. . . .
>
> Q. With respect to "therapeutically effective," do you agree it requires a therapeutic benefit?
>
> A. Yes, but this would be for the mice as well.
>
> Q. What do you mean by that?
>
> A. I mean it could be therapeutically effective in preventing, reducing the tumor growth in the mice implanted with the tumor.
>
> Q. So "therapeutically effective" would require some therapeutic benefit, but that benefit could be in an animal; is that right?
>
> A. Yes. Exactly.

Ex. 2020, 48:11–49:21.

Besides the lack of any data in OSI's 10-K or Gibbs, Patent Owner appears to be arguing that clinical results demonstrating efficacy of treating non-small cell lung cancer with erlotinib in human patients is required before the ordinary artisan would have a reasonable expectation of success of achieving the claimed invention. *See, e.g.,* PO Resp. 38. For example, Patent Owner relies on the Declaration of Dr. Bunn. Dr. Bunn averred:

> Petitioners contend that a skilled artisan would have a reasonable expectation of success in part because CP-358,774 entered Phase II clinical trials. I disagree with this contention. Even oncology drugs that enter Phase II cancer clinical trials are exceedingly unlikely to be established as therapeutically effective treatments for any given cancer type. For example, one 2007 study reported that only seven of 1,631 new drugs tested in Phase II clinical trials for NSCLC obtained FDA approval. *See* Ramaswamy Govindan, *Phase III failure rates in oncology drugs unacceptable*, 16 Oncology News Int'l at 1 (Aug. 1, 2007) (Ex. 2008). A skilled artisan would not have derived any expectation

> of success from the mere fact that a compound had completed a Phase I safety trial and entered Phase II clinical trials. Some evidence suggesting a successful treatment of NSCLC with a therapeutically effective amount of erlotinib is needed; otherwise, the extremely high failure rate for cancer compounds generally would foreclose any reasonable expectation of success.

Ex. 2021 ¶ 79. Dr. Bunn testified also that "[g]oing from a patent filing to a drug approval, most claims never lead to a drug approval. But in this case this claim did and it did with an effective drug." Ex. 1048, 66:3–6. Completion of Phase II trials and FDA approval, however, are not the appropriate standard to measure obviousness in this proceeding, as the claims do not require treatment of humans, nor, as discussed above in the section addressing claim construction, do they require clinical efficacy. As Dr. Bunn also testified:

> Q. So other promising activities would be if they passed those specific tests that you just were talking about in preclinical models; is that correct?
>
> A. Many drugs would pass those and still fail, correct.
>
> Q. (BY MR. COBLENTZ) And that would be failures in Phase I, Phase II, or Phase III?
>
> A. Correct.
>
> Q. But they would pass the preclinical models?
>
> A. Correct. We're on the same page.

Ex. 1048, 39:1–12 (objection omitted).

Patent Owner argues also that the ordinary artisan would not have a reasonable expectation of success of combining OSI's 10-K with Schnur. PO Resp. 39. In particular, Patent Owner argues that Petitioner is relying on the reference to Phase I and Phase II trials to "demonstrate treatment of NSCLC with erlotinib." *Id.* (citing Pet. 19). Patent Owner asserts that is in

error, however, as the "mere completion of 'Phase I ***safety*** trials' in an unspecified population of cancer patients does not suggest that any patients had been successfully ***treated for NSCLC*** with erlotinib, as required by the instituted claims." *Id.* All it means, Patent Owner asserts, is that the compound had an acceptable pharmacokinetic and safety profile such that the compound can now proceed to Phase II trials. *Id.* (citing Ex. 2021 ¶¶ 36, 75–77). Patent Owner also cites testimony of Petitioner's expert, Dr. Giaccone, to support its assertion that Phase I trials are not geared towards assessing efficacy. *Id.* at 40 (citing Ex. 1002 ¶ 67; Ex. 2020, 16:13–20:14, 94:15–96:12, 57:21–59:10, 86:8–9). Patent Owner asserts that OSI's 10-K does not provide any data to suggest that erlotinib would have efficacy in treating non-small cell lung cancer. *Id.* at 40–41 (citing Ex. 2021 ¶ 76, 83).

Moreover, Patent Owner asserts, the fact that Phase II trials may have been initiated would not provide a reasonable expectation of success, as the ordinary artisan would understand that does not mean that any non-small cell lung cancer patients had been dosed with erlotinib, much less treated. *Id.* at 41 (citing Ex. 2020, 84:18–85:6). Thus, Patent Owner contends, "[w]ithout any evidence suggesting efficacy in NSCLC, [an ordinary artisan] would not have expected that erlotinib's likelihood of success was any greater than the abysmal failure rate of other cancer compounds that had made it to Phase II or even Phase III." *Id.* at 41–42 (footnote omitted) (citing Ex. 2021 ¶¶ 34, 37, 73–90, 93; *Eisai*, 533 F.3d at 1359).

Patent Owner also contends that the statement in OSI's 10-K that erlotinib (i.e., CP-358,774) targets a variety of cancers does not provide a reasonable expectation of success of treating non-small cell lung cancer as the ordinary artisan would understand that statement to mean that erlotinib

targets an oncogene in those cancers. *Id.* at 43 (citing Ex. 2021 ¶¶ 52, 78). But the ordinary artisan, Patent Owner asserts, would not understand that statement to be based "on any actual data suggesting the successful treatment of NSCLC with a therapeutically effective amount of erlotinib." *Id.* (citing Ex. 2021 ¶ 48; Ex. 2020, 126:6–12). Patent Owner argues, therefore, the "mere suggestion" that erlotinib may have efficacy against cancers correlated with the overexpression of the epidermal growth factor receptor ("EGFR") does not provide a reasonable expectation of success of using erlotinib to treat non-small cell lung cancer. *Id.* (citing Ex. 2021 ¶¶ 31–37). That is, Patent Owner asserts, the ordinary artisan at the time of invention did not know if overexpression EGFR caused non-small cell lung cancer, or was only correlated with non-small cell lung cancer. *Id.* at 43–44 (citing Ex. 1028, 45); *see also id.* at 10 (noting that "EGFR expression is one step in a complex signaling pathway that leads to cell proliferation.").

Petitioner responds that "Schnur discloses that erlotinib blocks EGF receptors and can be administered in the same therapeutically effective amount to treat lung cancer as is disclosed and claimed by the '221 patent, but for the specific disclosure of NSCLC." Reply 11 (citing Ex. 1005, 23; Ex. 1006, 2). Thus, Petitioner contends, OSI's 10-K was only required to lead the ordinary artisan to the treatment of non-small cell lung cancer. *Id.* (citing Ex. 1002 ¶¶ 101–109, 129).

We have reviewed Patent Owner's arguments and evidence and find that Petitioner has shown, by a preponderance of the evidence, that the ordinary artisan would have had a reasonable expectation of success in combining Schnur and OSI 10-K to arrive at the invention of the challenged claims, and Patent Owner's arguments and evidence do not convince us

otherwise. That is, proof of efficacy, such as demonstration of clinical efficacy in human non-small cell lung cancer patients, is not required to demonstrate obviousness of the challenged claims.

We acknowledge Patent Owner's argument, relying on *Eisai*, that the lack of data is especially relevant in the highly unpredictable field such as non-small cell lung cancer drug development. PO Resp. 37–38 (citing *Eisai,* 533 F.3d at 1359). *Eisai*, however, involved a lead compound analysis to arrive at a claimed chemical compound. *Eisai,* 533 F.3d at 1359. As we have noted above, Schnur suggests treatment of lung cancer with erlotinib, and OSI's 10-K and Gibbs both explicitly suggest treatment of non-small cell lung cancer with erlotinib. Thus, the combination of Schnur and OSI's 10-K suggests the method of challenged claims 44 and 53, and, as discussed above, the ordinary artisan would have had a reasonable expectation of success of achieving the claimed invention.

Patent Owner also contends that the ordinary artisan would not have had a reasonable expectation of success of combining Gibbs with Schnur. PO Resp. 44. In particular, Patent Owner asserts that the Petition mischaracterizers Gibbs in asserting that Gibbs discloses treatment of non-small lung cancer with erlotinib. *Id.* (citing Ex. 1002 ¶¶ 109, 119; Pet. 10, 11, 29).

Patent Owner notes that the Petition states that "Gibbs discloses … that erlotinib had entered Phase II clinical trials … [and] that erlotinib was shown to have good anti-cancer activity 'with an acceptable therapeutic index, particularly in patients with NSCLC.'" *Id.* at 45 (alterations original) (quoting Pet. 18). Patent Owner contends, however, that Gibbs' statement that erlotinib had entered Phase II clinical trials "does not suggest successful

'treatment' of NSCLC, as required by the instituted claims." *Id.* at 46. That is, Patent Owner asserts, as argued with OSI's 10-K, the "mere completion of Phase I trials against unspecified cancers does not suggest that any patients had been successfully ***treated for NSCLC*** with erlotinib." *Id.* And also similarly to the argument with respect to OSI's 10-K, Patent Owner asserts that Gibbs does not present any data "from which a skilled artisan could divine successful treatment of NSCLC with erlotinib." *Id.* In addition, Patent Owner notes that "the author of Gibbs, Dr. Jackson Gibbs, has testified that 'my research at the time of my article did not identify any information suggesting that CP-358,774 exhibited anti-tumor activity in NSCLC,' and that 'I was (and still am) not aware of any published abstracts or articles describing the clinical or preclinical response of a NSCLC tumor to CP-358,774 that were available as of the time my article was published.'" *Id.* (citing Ex. 2022 ¶¶ 10–14).

Moreover, Patent Owner asserts, in referencing the Phase II trial of erlotinib, Gibbs does not state that patients had actually been treated with the drug. *Id.* Patent Owner avers that "[w]ithout any evidence to suggest efficacy in NSCLC, [the ordinary artisan] would not have had any reason to believe that erlotinib's likelihood of success was any greater than the high failure rate of other cancer compounds—including compounds that had made it to Phase II and even Phase III." *Id.* at 47 (citing Ex. 2021 ¶¶ 34–40, 75–79, 82–101; Ex. 2020, 131:11–17, 132:11–17).

According to Patent Owner, the ordinary artisan would not view the statement in Gibb that ZD-1839 and CP-358,774 "appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer," as suggesting

successfully treating non-small cell lung cancer with erlotinib. PO Resp. 48 (quoting 1010, 10; citing Ex. 2021 ¶ 83, Ex. 2020, 116:9–117:2). Patent Owner avers that statement in Gibbs is only supported by two references, Woodburn[8] and Moyer,[9] neither of which teaches or suggests treatment of non-small cell lung cancer with erlotinib. *Id.*; *see also id.* at 49–50 (discussing the teachings of Woodburn and Moyer).

Patent Owner notes (PO Resp. 50–51) that we relied on the statement in Gibbs "that a number of citations directed to clinical data were left out, pointing the reader to another reference." Dec. Inst. 20 (citing Ex. 1010, 9). Patent Owner contends that it was improper for us "to find obviousness based on references merely cited or alluded to in an instituted reference but not included in the Petition," as it is Petitioner's burden to establish obviousness. PO Resp. 51.

Patent Owner argues that it reviewed the 1999 ASCO Abstracts and the 1999 AACR Abstracts cited by Gibbs in stating that "[d]ue to editorial restrictions limiting the number of reference citations, much of the clinical data gleaned from abstracts is not listed in the references" (Ex. 1010, 9), asserting that only two of the abstracts discuss erlotinib. PO Resp. 51–52 (citing Ex. 2024, Abstract 1498, Abstract 1499; Ex. 2021 ¶¶ 60–61, 62–64; Ex. 2020, 15:20–18:3, 112:9–113:18, 115:3–15, 94:19–95:1, 95:9–12, 114:16–22). And neither of those Abstracts, Patent Owner contends, discuss

[8] J.R. Woodburn et al., *ZD1839, an epidermal growth factor tyrosine kinase inhibitor selected for clinical development*, 38 AACR PROGRAM/PROCEEDINGS 633 (1997) ("Woodburn") (Ex. 2006).

[9] James D. Moyer et al., *Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase*, 57 CANCER RES. 4838 (1997) ("Moyer") (Ex. 1016).

non-small cell lung cancer. *Id.* at 51–52; *see also id.* at 51–56 (discussing the content of the abstract volumes).

Thus, Patent Owner asserts, the only anti-cancer activity for erlotinib contained in any of the references cited by Gibbs was for head, neck, and colon tumors, not non-small cell lung cancer. PO Resp. 53 (citing Ex. 2021 ¶¶ 62–64). The ordinary artisan, Patent Owner asserts, would understand that when Gibbs was referring to "acceptable therapeutic index," the reference was referring to ZD-1839, and not erlotinib. *Id.* (citing Ex. 2021 ¶¶ 54–64, 83–89; Ex. 2020, 130:8–131:5).

Petitioner responds that the ordinary artisan, reading the statement in Gibbs, "could have only understood it to mean that ZD-1839 (getfinib) and CP-358,774 (erlotinib) both had good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer," and would have "instructed [the ordinary artisan] that erlotinib treated NSCLC in humans." Reply 16 (citing Ex. 1010, 2). In addition, Petitioner asserts, Dr. Gibbs admitted "that the paragraph on page two of Exhibit 1010 involving ZD-1839 (getfinib) and CP-358,774 (erlotinib) concerned only two compounds and makes particular reference to NSCLC," and that he had "never attempted to correct the publication, and that one of his areas of expertise is his journal editorial experience with over 128 publications." *Id.* (citing Ex. 1049, 24:15–25:4, 28:19–29:1, 29:18–30:16[10]).

[10] Petitioner's citation in the Reply Brief here is to Ex. 1049, "39:18–30:16." We assume that Petitioner meant to cite "29:18–30:16," and determine this to be a clerical error. In any event, it does not change our analysis.

Petitioner argues further that its expert, Dr. Giaccone, testified that the statement in Gibbs "is a pretty strong and precise statement saying, there is activity in non-small cell lung cancer patients." *Id.* (quoting Ex. 2020, 115:12–20). In addition, Petitioner asserts, Dr. Giaccone testified further that statement by Dr. Gibbs would have been based on the information Dr. Gibbs had at the time, and that as Dr. Gibbs was a reputable pharmacologist, and as the statement was made in "a peer-reviewed journal of high impact," he would have trusted that Dr. Gibbs "was saying something very important." *Id.* at 16–17 (quoting Ex. 2020, 115:12–20).

Again, for the reasons set forth above, we find that Petitioner has shown, by a preponderance of the evidence, that the ordinary artisan would have had a reasonable expectation of success in combining Schnur and Gibbs to arrive at the invention of the challenged claims, and Patent Owner's arguments and evidence do not persuade us otherwise That is, as discussed above, proof of clinical efficacy, such as demonstration of clinical efficacy in human non-small cell lung cancer patients, is not required to demonstrate obviousness of the challenged claims.

Patent Owner also appears to be arguing that the ordinary artisan would not read Gibbs as suggesting the treatment of non-small cell lung cancer with erlotinib. In that regard, we recognize that Dr. Gibbs, the author of the Gibbs reference relied upon by Petitioner in challenging the claims, states:

> Based on references 12 and 13, the abstracts from the 1999 ASCO and AACR Conferences, and my own personal recollection, my research at the time of my article did not identify any information suggesting that CP-358,774 exhibited anti-tumor activity in NSCLC. I was (and still am) not aware of any published abstracts or articles describing the clinical or

> preclinical response of a NSCLC tumor to CP-358,774 that were available as of the time my article was published, and I reviewed no such abstracts or articles in drafting my article.

Ex. 2022 ¶ 14.

Gibbs, however, explicitly teaches:

> The EGF receptor is also the target for the development of inhibitors of the intracellular tyrosine kinase domain. ZD-1839 and *CP-358,774*, competitive inhibitors of ATP binding to the receptor's active site, *are currently in clinical trials* (12, 13). Their mechanism of action has led to some concern about safety, given the variety and physiological significance of protein kinases and other enzymes that bind ATP. *However, these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer*.

Ex. 1010, 10 (emphasis added). As erlotinib (i.e., CP-358,774) is one of only two compounds mentioned, and as Gibbs clearly states "these compounds," the clear inference is that erlotinib has anti-cancer activity against non-small cell lung cancer. We credit the testimony of Dr. Giaccone, who testified that the statement in Gibbs "is a pretty strong and precise statement saying, there is activity in non-small cell lung cancer patients." Ex. 2020, 115:12–20. In addition, Dr. Giaccone testified further that statement by Dr. Gibbs would have been based on the information he had at the time, and that as Dr. Gibbs was a reputable pharmacologist, and as the statement was made in "a peer-reviewed journal of high impact," he would have trusted that Dr. Gibbs "was saying something very important." Ex. 2020, 115:12–20.

Moreover, Dr. Gibbs testified:

> Q Dr. Gibbs, let's go back to Exhibit 1010. So you never attempted to offer any sort of correction for this publication. Isn't that correct?

A That is correct.

Q And you state in your declaration that you have written over 128 articles. Isn't that correct?

A That is correct.

Q And so you have -- you would agree with me that you have experience in writing articles such as this Gibbs reference. Isn't that correct?

A That is correct.

Q And of the 128 articles, have you ever asked that an article be retracted?

A I have not.

Q And according to your C.V., one of your areas of expertise is that you have extensive journal editorial experience. Isn't that correct?

A Yes.

Ex. 1049, 29:18–30:16 (objections omitted). Given the testimony that Dr. Gibbs was an experienced editor, and never attempted to correct or retract the Gibbs reference, we decline to afford his Declaration (Ex. 2022) much weight in this regard.

Patent Owner argues also that to single out erlotinib from the compounds disclosed by Gibbs, as well as the 105 exemplary compounds of Schnur, is impermissible hindsight. PO Resp. 47; *see also id.* at 17 (discussing the various combinations of compounds and hyperproliferative disorders encompassed by Schnur).

Patent Owner's arguments in this regard are also unavailing. The prior art's disclosure of a multitude of combinations does not render any particular combination less obvious. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). In addition, as discussed above, Schnur specifically discloses and claims erlotinib, and discloses and claims

the treatment of lung cancer. Finally, both OSI's 10-K and Gibbs specifically suggests the treatment of non-small cell lung cancer with erlotinib.

Before we make our final determination of whether the challenged claims are obvious, however, we must consider the objective evidence of non-obviousness proffered by Patent Owner PO Resp. 56–65. That is, in *KSR*, the Supreme Court reaffirmed that, despite the importance of a flexible and common-sense approach when evaluating obviousness, fact finders "should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." 550 U.S. at 421. Accordingly, the Federal Circuit has noted, even after *KSR*, fact finders must "still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how *or why* the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (emphasis added). The totality of the evidence submitted may show that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, skepticism, licensing, and praise. *See Graham*, 383 U.S. at 17.

Patent Owner argues that secondary considerations, including long-felt need, failure of others, unexpected results, and commercial success, support the patentability of the challenged claims. PO Resp. 56–65. Patent Owner asserts that as Petitioner's challenge is focused on the treatment of non-small cell lung cancer with a therapeutically effective amount of

erlotinib, nexus "is presumed, because the approved label for Tarceva, for the entire period since the product's approval in 2004 to the present, has included one or more NSCLC indications, and the challenged claims recite a method for the treatment of NSCLC, among other diseases." *Id.* at 57. That nexus is especially relevant to claim 53, Patent Owner argues, as claim 53 is limited to treatment of non-small cell lung cancer. *Id.*

Patent Owner asserts that long-felt need supports the patentability of the challenged claims. *Id.* at 58–59. According to Patent Owner, "[p]rior to the invention of the '221 patent, there was a long-felt, unmet need for therapeutically effective NSCLC treatments without the efficacy limitations and dose-limiting toxicities of chemotherapy described above." *Id.* at 58. Thus, Patent Owner avers, "Tarceva filled a significant void when it was introduced in 2004 and continues to be an important therapy today." *Id.* (citing Ex. 2021 ¶¶ 106–107). That is, Patent Owner asserts, "Tarceva was a breakthrough therapy offering 'the prospect of greater selectivity, more effective tumor control, and reduced side effects.'" *Id.* at 58–59 (citing Ex. 2019, 449; Ex. 2020, 155:4–155:21, 163:12–164:1).

Petitioner responds that erlotinib did not satisfy a long-felt need as it does not treat nearly 90% of patients with non-small cell lung cancer. Reply 19 (citing Ex. 1053 ¶¶ 8–10; Ex. 1046, 2; Ex. 1051, 3–4; Ex. 1048, 23:9–26:6). Thus, as Dr. Bunn testified, Petitioner asserts that Tarceva's label was required by the FDA to be amended and identify a narrow patient population. *Id.* (citing Ex. 1048, 106:21–107:8).

We find Patent Owner's evidence of non-obviousness to be weak as to long-felt need. All types of objective evidence of nonobviousness must be shown to have a nexus to the claimed invention. *In re GPAC Inc.*, 57 F.3d

1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need). The stronger the showing of nexus, the greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

As we have discussed above, the claims are not limited to the treatment of human patients with non-small cell lung cancer, but are drawn to treatment of mammals. In addition, the claims do not require a clinically significant effect. *See, e.g.* Tr. 50:16–17 (Counsel for Patent Owner stated that the claims do not require a "major clinical response, which is a higher standard than treatment as defined in the claims."). As Patent Owner notes, 1,631 new drugs were tested in Phase II clinical trials for non-small cell lung cancer (PO Resp. 59 (citing Ex. 2008, 1)), and, thus, those compounds made it through preclinical trials. Patent Owner notes further that ZD-1839, which was also disclosed by Gibbs, successfully emerged from the clinic with FDA-approved indications for the treatment of non-small cell lung cancer. PO Resp. 60. Moreover, Patent Owner acknowledges that the FDA required it to change its label as it is only effective in treating approximately 10% of patients with non-small cell lung cancer. *Id.* at 12; Reply 19.

Patent Owner contends further that the failure of others also supports the patentability of the challenged claims. PO Resp. 59–61. Patent Owner argues that both before and after the time of invention of the '221 patent, "many others tried and failed to develop therapeutically effective treatments for NSCLC." *Id.* at 59. According to Patent Owner, "from 1990–2005, only seven of 1,631 new drugs tested in Phase II clinical trials for NSCLC

obtained FDA approval." *Id.* (citing Ex. 2008, 1). Patent Owner asserts that several drug companies attempted to develop drugs that were selective inhibitors of the tyrosine kinase activity of enzymes in signal transduction cascades, but the drugs failed "due to efficacy, toxicity, and pharmacokinetic limitations of the compound." *Id.* at 59–60 (citing Ex. 2021 ¶¶ 33–40, 96–100). In addition, Patent Owner contends, pharmaceutical companies have continued to attempt to design targeted drug therapies, but there are continued failures. *Id.* at 60 (citing Ex. 2021 ¶ 98). And of all the compounds disclosed in Gibbs, Patent Owner asserts that "[o]nly CP-358,774 and ZD-1839 successfully emerged from the clinic with FDA-approved indications for the treatment of NSCLC." *Id.*

Petitioner responds that FDA approval is irrelevant to the challenged claims, as the claims only require treatment of non-small cell lung cancer in any mammal. Reply 20 (citing Ex. 2021 ¶¶ 93–101; Ex. 1053 ¶ 11). Instead, according to Petitioner:

> the correct standard for assessing success is by looking at how many other drugs reached the same level of treatment as provided in the '221 patent. (*See* Ex. 1001 at claim 44–46 and 53; Ex. 1053 at ¶ 11.) Thus, rather than showing a failure of others, the fact 1,631 new drugs reached Phase II human clinical studies for NSCLC, means that a plethora of new drugs showed the same preclinical therapeutic efficacy for NSCLC, as erlotinib. (Ex. 1053 at ¶ 11.) Indeed, Dr. Bunn admits that if 1,631 drugs were tested in Phase II studies, then 1,631 drugs successfully passed preclinical animal studies, and Phase I human studies. (Ex. 1048 at 95:3 – 8; Ex. 1053 at ¶11.)

Id.

Failure of others is closely related to long felt need. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1082–83 (Fed. Cir. 2012). Thus, for the reasons

set forth for long felt need, we also find that Patent Owner's evidence of failure of others is weak. That is, as the claims do not require treatment of humans, much less regulatory approval, Patent Owner has failed to establish that the long felt need for FDA approved drugs to treat non-small cell lung cancer has the required nexus to the challenged claims.

Patent Owner contends further that the challenged claims achieved unexpected results. PO Resp. 61. In particular, Patent Owner asserts:

> Because the vast majority of compounds in preclinical and clinical development ultimately failed to have the necessary properties (including safety, efficacy, and pharmacokinetics) to be successful in the treatment of NSCLC, [the ordinary artisan] could not have predicted in advance whether a compound would be therapeutically effective. *See Eisai*, 533 F.3d at 1359. Accordingly, the survival benefit to NSCLC patients provided by the method of treating NSCLC with a therapeutically effective amount of erlotinib was unexpected at the time of the invention of the '221 patent. (Ex. 2021, Bunn Decl. ¶¶ 108–109.)

Id.

Petitioner responds that "OSI does not argue, nor did Dr. Bunn analyze, whether erlotinib provides any results that are unexpected when compared to the closest prior art." Reply 17 (citing Ex. 1048, 11:9–113:16, 114:17–115:7; Ex. 1053 ¶¶ 5–6). Moreover, according to Petitioner, when viewed in light of Schnur, as Dr. Bunn testified, erlotinib's activity against non-small cell lung cancer was expected because of its activity as a tyrosine kinase inhibitor. *Id.* at 18 (citing Ex. 1048, 113:17–114:9). In addition, Petitioner asserts further that the purported unexpected results are not commensurate in scope with the challenged claims, as the claims are directed to treatment of all non-small cell lung cancer patients, but, as Dr. Bunn admitted, erlotinib only treats about 12% of non-small cell lung cancer

patients. *Id.* at 18–19 (citing Ex. 2021 ¶ 109; Ex. 1048, 23:9–26:6, 115:14–116:7). Thus, Petitioner asserts, the challenged claims do not achieve unexpected results. *Id.* at 18.

We agree with Petitioner that "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter-Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). As Patent Owner does not identify what it views as the closest prior art, or compare its purported unexpected results to that art, we determine that the evidence of record does not support a finding that the challenged claims demonstrate unexpected results.

As to commercial success, Patent Owner contends that "Tarceva is a commercial success and has been throughout the period it has been sold in the United States, and much of that success is tied directly to the method of treatment for NSCLC that is covered by the instituted claims." PO Resp. 62 (citing Ex. 2023 ¶¶ 8–17). According to Patent Owner, the Tarceva label has had FDA approval for one or more indications related to non-small cell lung cancer since the drug was approved in November of 2004. *Id.* (citing Ex. 2023 ¶¶ 6–7; Exs. 2026–2030).

Specifically, Patent Owner argues that "[d]uring the first 12 months of its launch, Tarceva was the most successful oncology drug launch in the United States in terms of number of patients treated and fourth most successful in terms of sales at that time." *Id.* (citing Ex. 2023 ¶ 8; Ex. 2033, 4). Net sales for Tarceva during 2005 were approximately $275 million, and during most of that year, Patent Owner asserts, the only indication on the Tarceva label was for treatment of patients with locally advanced or

metastatic non-small cell lung cancer after failure of at least one chemotherapy regimen. *Id.* (citing Ex. 2023 ¶¶ 6, 11).

Patent Owner asserts that annual revenue for Tarceva in the United States continued to be significant. *Id.* at 63 (citing Ex. 2023 ¶¶ 9–17; Ex. 2034; Ex. 2035). According to Patent Owner, "[n]otwithstanding the introduction of other competing drugs indicated for the treatment of NSCLC, including Merck's Keytruda and Bristol-Myers Squibb's Opdivo in 2015, substantial use of Tarceva in connection with NSCLC treatment has persisted." *Id.* (citing Ex. 2023 ¶¶ 13, 17; Ex. 2035; Ex. 2041).

Petitioner responds that Patent Owner has only provided sales figures for Tarceva, which is not sufficient for a finding of commercial success. Reply 21. In addition, Petitioner asserts, Schnur claims the compound used in the method treating non-small cell lung cancer claimed by the '221 patent, thus, giving Patent Owner the ability to exclude others from using erlotinib. *Id.* at 23 (citing *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005)). In fact, Petitioner asserts, Patent Owner submitted expert testimony in district court asserting that the commercial success of Tarceva "is attributable to the compound erlotinib claimed in a subsequent reissue of Schnur, not the method of treatment of NSCLC in a mammal recited in the challenged claims of the '221 patent." *Id.* at 22 (citing Ex. 1028, 34). Patent Owner, Petitioner argues, "never asserted that the commercial success of Tarceva® could be attributed to the '221 patent." *Id.* (citing Ex. 1028, 45).

Petitioner asserts further that the sales of Tarceva "were not driven by its actual treatment of cancer, but instead an overly broad approval by FDA that was subsequently revoked." *Id.* That is, Petitioner argues, "on October

18, 2016[,] FDA eliminated the original label and limited the patient population to those who tested positive for epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations, which only accounts for about 10% of the NSCLC patient population. " *Id.* at 23 (citing Ex. 1048, 23:9–26:6, 99:22–101:13; Ex. 1053 ¶ 10; Ex. 1051, 3–4).

Patent Owner asserts:

> To the extent that Petitioners attempt to argue a lack of commercial success under the holding in *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005)—i.e., because the patent that covers the erlotinib compound (Schnur) blocked market entry—such reliance is misplaced. The Federal Circuit in *Merck* did not broadly hold that commercial success has no probative value where there is another patent blocking market entry. Rather, in *Merck*, the claimed invention was a modification of an already-marketed dosage. *Id*. Here, by contrast, there was no prior approved method of using erlotinib to treat NSCLC, there was fierce competition among drug companies to identify better treatment methods for NSCLC than existed in the late 1990s, and Tarceva was immediately successful upon launch with its sole NSCLC treatment indication. In any event, there is no requirement that the claimed invention must be the only basis for commercial success. *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

PO Resp. 65.

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). That presumption of nexus, however, is rebuttable, as "a patent challenger may respond by

presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329 (quoting *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988)).

We do not disagree that Tarceva is commercially successful in terms of dollar figures. *See* PO Resp. 62. However, as discussed herein, erlotinib was previously known and patented. *See* Ex. 1009 (Schnur). "Where 'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the claims], from evidence of commercial success, is weak.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (bracketed materials original, quoting *Merck & Co.* 395 F.3d at 1377). Thus, although the revenues generated by Tarceva may be substantial, its commercial success is mitigated by the existence of a blocking patent. We are persuaded, rather, by Petitioner's argument that the blocking patent would have deterred others from exploring the commercial potential of Tarceva, and thus, that blocking patent to Tarceva limits the applicability of other evidence of commercial success. That is, "[f]inancial success is not significantly probative of that question in this case because others were legally barred from commercially testing . . . [the] ideas" in OSI's 10-K and Gibbs. *Merck*, 395 F.3d at 1377. In addition, we do not read *Merck* to be limited to those cases in which there is a modification of an existing dosage, as argued by Patent Owner (PO Resp. 65).

iii. Conclusion as to Obviousness

We determine, therefore, that Petitioner has demonstrated that the preponderance of the evidence of record supports that it would have been obvious to the ordinary artisan at the time of invention to combine Schnur

with either OSI's 10-K or Gibbs, with a reasonable expectation of success of achieving the method of challenged claims 44 and 53. Moreover, we conclude that when that strong evidence regarding the first three *Graham* factors is weighed with the weak evidence of objective indicia in this proceeding, we conclude that Petitioner has met its burden of demonstrating by a preponderance of the evidence that challenged claims 44 and 53 are rendered obvious by the combination of Schnur and OSI's 10-K, as well as the combination of Schnur and Gibbs.

Patent Owner does not separately argue challenged dependent claims 45 and 46. After considering Petitioner's argument and evidence as to those claims (Pet. 30–35), we conclude that Petitioner has also established the unpatentability of those claims by a preponderance of the evidence.

D. Patent Owner's Motion to Exclude

Patent Owner seeks to exclude Petitioner's Exhibits 1031, 1039, 1040, 1044, 1045, 1047, 1050, 1052, and 1055–1065 in their entirety, and also seeks to exclude portions of Exhibits 1048 and 1049. Mot. Exclude 1.

Exhibit 1031, the Hidalgo reference, Patent Owner asserts, was not cited in the Petition, and, thus, was not part of the instituted grounds. *Id.* at 1–2. Patent Owner also seeks to exclude portions of Dr. Bunn's testimony (Ex. 1048) and Dr. Gibbs testimony (Ex. 1049) that relate to the Hidalgo reference. *Id.* at 2. According to Patent Owner, "Exhibit 1031 is irrelevant as it is not prior art and not part of the instituted grounds, and Petitioner's characterization and use of the exhibit is misleading, confusing, and unfairly prejudicial." *Id.* at 2, *see id.* at 2–7.

Petitioner responds that Exhibit 1031 was introduced to refute Patent Owner's attempts to discredit Gibbs (Ex. 1010) and OSI's 10-K (Ex. 1011).

Opp. Mot. Exclude 4. We agree with Petitioner that Hidalgo was proper reply evidence. *See Ariosa Diagnostics*, 805 F.3d at 1368 (Fed. Cir. 2015) ("The Board must make judgments about whether a Petition identified the specific evidence relied on in a Reply and when a Reply contention crosses the line from the responsive to the new."). In addition, the fact that Hidalgo is not prior art to the challenged claims goes to the weight to be accorded the reference, rather that its admissibility. Thus, we *deny* Patent Owner's motion to exclude as to Exhibit 1031,[11] as well as to portions of Exhibits 1048 and 1049 that relate to that Exhibit.

Patent Owner argues further that the transcript of Mark Reisenauer, Exhibit 1050, should be excluded as it was not cited in any paper, and was impermissibly incorporated by reference. Mot. Exclude 8.

It is unclear to us how Exhibit 1050 was improperly incorporated by reference, as it was not cited in any paper. In addition, as we did not rely on that Exhibit, we *dismiss* the Motion to Exclude as to this Exhibit as moot.

Patent Owner also seeks to exclude the Declaration of Kristopher A Boushie (Exhibit 1054), as well as the Exhibits relied upon by Mr. Boushie in forming his opinions, that is, Exhibits 1039, 1040, 1044, 1045, 1047, 1052, and 1055–1065. Mot. Exclude 8.

As we did not rely on the Declaration of Dr. Boushie, we *dismiss* this part of the Motion to Exclude as moot.[12]

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[11] Patent Owner also objected to Petitioner's slides 19 and 63–74 as they related to the Hidalgo reference. Paper 47, 1. As we deny Patent Owner's Motion to Exclude as to Hidalgo, we also overrule its objections as to those slides.

[12] Patent Owner also objected to Petitioner's slide 105 as it was an excerpt of the Boushie Declaration. Paper 47, 2. As we did not rely on that

III. CONCLUSION

After considering Petitioner's and Patent Owner's positions and evidence, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 44–46 and 53 of the '221 patent are unpatentable.

Patent Owner's Motion to Exclude is denied in part as to Exhibit 1031, as well as to portions of Exhibits 1048 and 1049 that relate to that Exhibit, and dismissed as moot in part as to Exhibits 1050, as well as to Exhibit 1054 and the Exhibits relied upon by Mr. Boushie in forming his opinions, that is, Exhibits 1039, 1040, 1044, 1045, 1047, 1052, and 1055–1065.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has demonstrated by a preponderance of the evidence that claims 44–46 and 53 of the '221 patent are unpatentable under 35 U.S.C. § 103(a);

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied in part* and *dismissed as moot* in part; and

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

Declaration, we overrule the objection as moot. In addition, as to Patent Owner's objections to slides 47 and 111 as misleading (Paper 47, 1–2), we overrule those objections as we can place the objections to statements in context with the record as a whole. Moreover, as we stated in our Oral Hearing Order (Paper 44, 3), the slides are merely an aid to argument, and are not evidence of record.

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