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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2018-00373
Patent 9,795,672 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a); 35 U.S.C. § 325(d)

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 9,795,672 B2 (Ex. 1001, "the '672 patent"). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

We have authority under 35 U.S.C. § 314 to determine whether to institute an *inter partes* review. Upon considering the Petition and the Preliminary Response, along with the circumstances involved in this case, we exercise our discretion under 35 U.S.C. § 325(d) to deny instituting an *inter partes* review of the challenged claims based upon certain grounds, and we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of the challenged claims with respect to the remaining grounds. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

A. Related Proceedings

Petitioner identifies the following pending district court proceedings involving the '672 patent: *Amgen Inc. v. Genentech, Inc. and City of Hope,* No. 17-7349 (C.D. Cal.); *Genentech, Inc. and City of Hope v. Amgen, Inc.*, No. 17-1407 (D. Del.); *Genentech, Inc. and City of Hope v. Amgen, Inc.*, No. 17-1471 (D. Del.). Pet. 3. Patent Owner provides notice of pending patent U.S. Application No. 15/705,006, filed Sept. 14, 2017, claiming the benefit of the '672 patent. Paper 3, 1.

B. The '672 Patent

The '672 patent relates to a method of treating cancer in humans with anti-angiogenesis therapy, alone or in combination with other anti-cancer therapies. Ex. 1001, 1:30–32. The Specification describes angiogenesis as "an important cellular event in which vascular endothelial cells proliferate, prune and reorganize to form new vessels from preexisting vascular network." *Id*. at 1:63–65. According to the Specification, it was known if the art that "[a]ngiogenesis is essential for growth of most primary tumors and their subsequent metastasis. Tumors can absorb sufficient nutrients and oxygen by simple diffusion up to a size of 1-2 mm, at which point their further growth requires the elaboration of vascular supply." *Id*. at 2:13–18. Vascular endothelial cell growth factor ("VEGF") regulates normal and abnormal angiogenesis. *Id*. at 2:41–44.

Studies have revealed VEGF plays a central role in promoting tumor growth, and, thus, has been considered an "attractive target for therapeutic intervention." *Id*. at 3:1–3, 17–18. For example, the Specification explains therapeutic strategies aimed at blocking VEGF are being developed for the treatment of neoplastic diseases. *Id*. at 3:19–21. In particular, bevacizumab (also known as "rhuMAb VEGF" or "Avastin™"), a recombinant humanized anti-VEGF antibody, is "being investigated clinically for treating various cancers, and some early stage trials have shown promising results." *Id*. at 3:29–44. The Specification describes methods of using anti-VEGF antibody for treating cancers. *Id*. at 3:51–54.

C. Challenged Claims

Claim 1 of the ’672 patent is reproduced below:

> 1. A method of treating cancer in a patient comprising administering to the patient an effective amount of bevacizumab, wherein the patient has a grade III hypertensive event resulting from the bevacizumab administration, the method further comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event while continuing bevacizumab treatment being carried out without altering the dosage regimen.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–18 of the ’672 patent on the following grounds:[1]

Claim(s)	**Basis**	**References**
1–18	§ 102 or § 103	Kabbinavar[2]
1	§ 102	Chen [3]
2–18	§ 102 or § 103	Chen

[1] Petitioner asserts that the cited references renders the challenged claims anticipated and/or obvious under pre-AIA §§ 102 or 103. Pet. 3.
[2] Kabbinavar et al., *Phase II, Randomized Trial Comparing Bevacizumab Plus Flurouracil (FU)/Leucovorin (LV) with FU/LV Alone in Patients with Metastatic Colorectal Cancer*, 21 J. CLIN. ONCOL. 60–65 (2003) (Ex. 1011).
[3] Chen et al., *Clinical Trials Referral Resource: Current Clinical Trials of the Anti-VEGF Monoclonal Antibody Bevacizumab*, 15 ONCOL. 1017, 1020, 1023–24 (1998) (Ex. 1005).

Claim(s)	Basis	References
1	§ 102	Yang[4]
2–18	§ 102 or § 103	Yang
1	§ 103	PCT'360[5] and Presta,[6] or in further combination with "Prior Art Clinical Practice"
2–18	§ 103	PCT'360, Chen, Presta, and/or "Prior Art Clinical Practice"

Petitioner also relies upon the Declaration of Ronald Bukowski, M.D. (Ex. 1009).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir.

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[4] Yang et al., *A Randomized Trial of Bevacizumab, an Anti-Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer*, 349 N ENGL. J. MED. 427–34 (2003) (Ex. 1016).
[5] Patent Application Publication No. WO 01/74360 A1 by Jon Curwen et al., published Oct. 11, 2001 (Ex. 1006).
[6] Presta et al., *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, 57 CANCER Res. 4593–99 (1997) (Ex. 1033).

2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes that the broadest reasonable interpretation of the claim term "grade III hypertensive event" is "hypertension requiring therapy or more intensive therapy than previously." Pet. 27–28. Petitioner explains that its proposed construction is taken from the National Cancer Institute's Common Toxicity Criteria ("CTC") provided as guidance to medical oncologists observing adverse events during cancer treatment in 2003. *Id*. at 16, 28 (citing Ex. 1009 ¶ 59). Petitioner asserts that the'672 patent describes two clinical trials which define "grade III hypertension" using CTC terminology. *Id*. (citing Ex. 1001, 37:4–8, 43:13–9, 49:31–35).

Patent Owner does not respond to Petitioner's proposed claim construction. Nor does Patent Owner assert a different proposed construction for the claim term.

We agree with Petitioner that the Specification refers to the CTC when describing hypertensive events. In particular, the Specification states,

> Adverse events were categorized according to the Common Toxicity Criteria of the National Cancer Institute, version 2 [("CTC, version 2")], in which a grade of 1 indicates mild adverse events, a grade of 2 moderate adverse events, a grade 3 of serious adverse events, and a grade of 4 life-threatening adverse events.

Ex. 1001, 43:15–19; *see also id*. at 49:32–38. Based on the Specification reference to the CTC, version 2 when describing grades of adverse events, we agree, on the current record, that a "grade III hypertensive event" should be construed according to the CTC, version 2 description for the term, i.e., "hypertension requiring therapy or more intensive therapy than previously."

For, clarity, our construction modifies that description to read, "hypertension requiring therapy or more intensive therapy than previously *administered*."

In view of our analysis, we determine that construction of additional claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (Only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have had "a medical degree, with a specialization in oncology and at least five years of clinical experience in cancer diagnosis and treatment." Pet. 6 (citing Ex. 1009 ¶ 22). Patent Owner does not address Petitioner's position on this matter and does not propose its own description for the level of ordinary skill in the art at the time of the invention.

For purposes of this Decision, we determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. Moreover, we have reviewed the credentials of Dr. Bukowski (Ex. 1009) and, at this stage in the proceeding, consider him to be qualified to provide his opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. We also note that the

applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. The '672 Patent Priority Date

For a patent to be entitled to the effective filing date of its provisional application, it must satisfy the requirements of 35 U.S.C. § 119(e)(1) (2006). *Dynamic Drinkware*, 800 F.3d 1375, 1378. (Fed. Cir. 2015). To do so, the provisional application must "'contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,' 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application." *Id.* at 1378 (quoting *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002) (emphasis in original)). "[T]o satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Rather, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

The '672 patent issued from U.S. Application No. 15/198,769 (the "'769 application") filed June 20, 2016, and claims priority, through a series of continuation applications, to U.S. Provisional Application No. 60/474,480 (the "provisional application") filed May 30, 2003. Ex. 1001.

Petitioner asserts that the '672 patent is entitled to a priority date no earlier than May 28, 2004, the filing date of the non-provisional '249 application. Pet. 30. Petitioner asserts that the '672 patent is not entitled to the provisional application filing date of May 30, 2003, because the challenged claims are not supported by the written description of the provisional application. *Id*. at 30–31. According to Petitioner, although the provisional application described bevacizumab administration resulting in an increase in grade 3 hypertension, wherein "the symptom was easily managed with oral medications," it fails to describe "whether the bevacizumab doses were altered or discontinued because of hypertension [such that] it cannot be assumed or inferred that the bevacizumab dose was maintained after a grade III hypertensive event, as Claim 1 requires." *Id*. at 31–32.

Petitioner asserts further that Applicant Genentech's arguments during prosecution relating to Chen confirm that the provisional application lacks written description support for maintaining the bevacizumab dose after a grade III hypertensive event. Specifically, Petitioner asserts that Genentech asserted that Chen's disclosure that the bevacizumab clinical trials reveals that, in most cases, hypertension attributable to bevacizumab was mild or "controllable with medication" did not teach or suggest maintaining the bevacizumab dose following a hypertensive event. Pet. 33–34 (citing Ex. 1012, 1020; Ex. 1008, 8). Petitioner asserts that Genentech argued that a person of skill in the art would have instead understood from Chen that the dose of bevacizumab would be reduced or discontinued. *Id*. at 34. Petitioner equates Chen's disclosure that a hypertensive event resulting from bevacizumab is "controllable with medication," with the provisional application's disclosure that such an event is "easily managed with oral

medications," such that Genentech's arguments against Chen's disclosure also apply to the provisional application's disclosure. *Id*.

Similarly, Petitioner asserts that Genentech's arguments during prosecution relating to Gotlib[7] confirm that the provisional application lacks written description support for maintaining the bevacizumab dose after a grade III hypertensive event. In particular, Petitioner asserts that Genentech argued that Gotlib and his colleagues elected to reduce, rather than to maintain, the dose of bevacizumab when managing grade III toxicities. Pet. 35 (citing Ex. 1008, 9). Petitioner notes that a co-author and colleague of Gotlib was Dr. William Novotny, a named inventor of the '672 patent. *Id*. (citing Ex. 1008, 4–6). According to Petitioner, based upon that argument by Genentech, the inventors were not in possession of the claimed method involving maintaining the dose of bevacizumab after a hypertensive event. *Id.*

Patent Owner asserts that Petitioner has not identified all of the relevant teachings in the provisional application relating to bevacizumab dosing. Prelim. Resp. 8. Specifically, Patent Owner draws our attention to the disclosure in the provisional application that "[a]ll treatment continued until disease progression or for a maximum of 96 weeks," and for those patients who experienced "unacceptable toxicity due to chemotherapy were eligible to discontinue chemotherapy and continued [bevacizumab] in the first-line setting." *Id*. (quoting Ex. 1003, 68:14–17). According to Patent

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[7] Gotlib et al., *Phase II Study of Bevacizumab (Anti-VEGF Humanized Monoclonal Antibody) in Patients with Myelodysplastic Syndrome (MDS): Preliminary Results*, 102 BLOOD 425a (2003) (Ex. 1046).

Owner, the provisional application supports the claims by describing such continued treatment with bevacizumab, along with the disclosures that patients who experienced hypertension received oral medication for it. *Id*. at 9 (citing Ex. 1003, 82:4–6).

Based upon our review, we agree with Patent Owner that the provisional application provides written description support for claim 1. In particular, the provisional application describes administering an antihypertensive agent to manage a grade III hypertensive event while continuing bevacizumab treatment without altering the dose of bevacizumab. As identified by the Patent Owner, the provisional application describes, among other things, (a) continuing all treatment in patients, except where unacceptable toxicity due to chemotherapy occurs, in which case, chemotherapy may be discontinued, but bevacizumab therapy continued, and (b) treating hypertensive events caused by bevacizumab with oral antihypertensive medication. Ex. 1003, 68:14–17, 82:4–6. Petitioner's argument otherwise is unpersuasive, as Petitioner has not acknowledged or addressed the description identified by Patent Owner. Moreover, Petitioner's assertions relating to Genentech's arguments during prosecution distinguishing Chen are unpersuasive as Petitioner's comparison of Chen and the provisional application fail to consider each of the relevant disclosures in the provisional application relating to bevacizumab therapy. As for Petitioner's arguments regarding what an inventor named in the provisional application described, with colleagues, in a later publication, i.e., Gotlib, those facts are not relevant to the question of what was described in the provisional application, as explained by Patent Owner. *See* Prelim. Resp. 9.

Thus, based on at least the foregoing, we agree with Patent Owner that the provisional application provides written description support for claim 1. Petitioner does not address the additional limitations of the remaining challenged claims with respect to its priority assertions. For purposes of this Decision, we are satisfied that the remaining challenged claims are also adequately described in the provisional application. Accordingly, for purposes of this Decision, we recognize the '672 patent as receiving the benefit of the provisional application filing date of May 30, 2003. As discussed below, this determination impacts at least Petitioner's grounds relying upon Yang.

D. Challenges Based Upon Yang

Petitioner asserts that claim 1 is anticipated by Yang and that claims 2–18 are anticipated by, or would have been obvious over, Yang. Pet. 58–62. Petitioner asserts that Yang is § 102(a) prior art because the reference was published on July 31, 2003, and the '672 patent is entitled to a priority date no earlier than May 28, 2004. *Id*. at 58. According to Petitioner, "Yang is a printed publication accessible to the public more than one year before that date." *Id*. (citing Ex. 1009 ¶ 94; Ex. 1016, 10).

We disagree with Petitioner. Even if the earliest priority date for the '672 patent was May 28, 2004, Petitioner has not shown that Yang was available "more than one year before that date." Regardless, as discussed above in Section II. C., we recognize the filing date of the provisional application as the priority date for the challenged claims of the '672 patent, i.e., May 30, 2003. Because Yang was published after that priority date, Petitioner has not shown that it is available as prior art for those claims. Consequently, Petitioner has not shown a reasonable likelihood of prevailing

in its challenge to claims 1–18 based upon Yang. Accordingly, we decline to institute an *inter partes* review of claim 1 as anticipated by Yang, or claims 2–18 as anticipated by, or obvious over Yang.

E. Discretionary Denial of the Kabbinavar and Chen Grounds under 35 U.S.C. § 325(d)

Petitioner asserts that claims 1–18 are anticipated by, or rendered obvious over, Kabbinavar.[8] Pet. 5. Petitioner asserts also that claims 1–18 are anticipated by Chen, and that claims 2–18 are, alternatively, rendered obvious by Chen.[9] *Id*. Petitioner acknowledges that the Examiner considered Kabbinavar and Chen during prosecution. *Id*. 11–15. However, regarding Kabbinavar, Petitioner asserts that the Examiner's consideration of the references should not be given deference because the Examiner "did not consider the argument that the '672 patent is entitled to a priority date no earlier than May 28, 2004." *Id*. at 50. Further, Petitioner asserts that "Kabbinavar was only avoided by an *In re Katz* declaration insufficient in

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[8] Petitioner sets forth its argument that dependent claims 2–18 are anticipated by or rendered obvious over Kabbinavar within claim charts. Pet. 44–49. In doing so, Petitioner discusses obviousness only with respect to claims 10–14, and relies upon Kabbinavar in combination with Chen for certain recited dependent claim limitations. *See id*. at 46–49.

[9] Petitioner sets forth its argument that dependent claims 2–18 are anticipated by or rendered obvious over Chen within claim charts. Pet. 53–58. In doing so, Petitioner discusses obviousness only with respect to claims 11–14 and 16, relying upon Chen in combination with a number of references not identified in the asserted grounds for certain recited dependent claim limitations. *Compare id. at 5 with id.* at 55–57.

this proceeding." *Id*. Petitioner does not address § 325(d) with respect to Chen.

Patent Owner asserts that we should exercise our discretion to deny the Petition under 35 U.S.C. § 325(d) because Petitioner's asserted ground relies upon the same or substantially the same prior art previously considered by the Office, and the Petition "rehashes the prosecution history without adding material new evidence." Prelim. Resp. 11, *see also id*. at 13–14.

Institution of an *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). When determining whether to institute such a review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

After considering the arguments and evidence, we agree with Patent Owner that each of Petitioner's asserted grounds involving Kabbinavar and Chen raise the same or substantially the same references previously presented and considered by the Office. As Petitioner acknowledges, during prosecution of the challenged claims, the Examiner considered Kabbinavar with respect to anticipation and obviousness, and also considered Chen with respect to obviousness. Pet. 11–12 (citing Exs. 1007, 1020, and 1034). As Patent Owner asserts, the Petition relies upon those same references to support anticipation and obviousness grounds. Prelim. Resp. 11 and 13–14. Those facts alone provide a sufficient basis for us to exercise our discretion under § 325(d) to deny the Kabbinavar and Chen grounds. *See Unified*

Patents, Inc. v. Berman, IPR2016-01571, Paper 10 at 11–12 (Dec. 14, 2016) (informative) (denying institution of grounds under § 325(d) where reference(s) asserted by petitioner had previously been considered and discussed by examiner during prosecution).

Petitioner asserts no reason why we should not exercise such discretion for the Chen grounds. Regarding Kabbinavar, Petitioner suggests that the Examiner improperly recognized a May 30, 2003 priority date for the '642 patent. Pet. 50. We have considered that argument as a precursor to the ground relying upon Yang, discussed above in Sections II. C. and D. As discussed in those sections, we determined, for purposes of this Decision, that the provisional application provides written description support for the challenged claims, such that the '672 patent is entitled to claim priority to the filing date of the provisional application, i.e., May 30, 2003, the same date recognized by the Examiner. Thus, Petitioner has not provided a persuasive reason for us to question the Examiner's recognition of that priority date. Similarly, Petitioner has not articulated any sufficient reasoning for us to question the Examiner's consideration of the attribution declaration submitted by Applicant Genentech with respect to the Kabbinavar reference for the reasons asserted by Patent Owner. Pet. 43–44; Prelim. Resp. 11–12.

Accordingly, because the Office already considered Kabbinavar and Chen during the prosecution of the challenged claims, we exercise our discretion under § 325(d) and decline to consider grounds based upon those references again.

F. Obviousness over PCT'360, Presta, and "Prior Art Clinical Practice"

Petitioner asserts that claim 1 would have been obvious over PCT'360 and Presta. Pet. 63–64. Additionally, Petitioner asserts that "[t]he obviousness of Claim 1 in view of PCT'360 and Presta is reinforced by the standard of care for hypertension and clinical practice involving bevacizumab and hypertension." *Id*. at 65. Although Petitioner asserts those challenges as two grounds, we consolidate them and consider the PCT'360, Presta, and "Prior Art Clinical Practice" together. Referring to the same grounds, Petitioner further combines Chen to address limitations of certain dependent claims. *Id*. at 66–67. To some extent, we consider that combination, as it relates to the dependent claims, as well.

1. PCT'360

PCT'360 is an international patent application published under the Patent Cooperation Treaty directed to therapeutic combinations of antihypertensive and antiangiogenic agents. Ex. 1006. The application discusses how "[r]ecent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis . . . and vascular permeability . . . ." *Id*. at 1 (citations omitted). Additionally, the application explains that "antagonism of the activity of VEGF is expected to be beneficial in a number of disease states, associated with angiogenesis and/or increased vascular permeability, such as cancer . . . ." *Id*.

Based on an understanding that VEGF receptor tyrosine kinase inhibitor leads to a sustained increase in blood pressure in rats, the application provides "a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of an anti-angiogenic agent and an anti-

hypertensive agent to a warm-blooded animal, such as a human being." *Id*. at 4. The application describes anti-angiogenic agents as including, but not being limited to: receptor antagonists, for example an anti-VEGF receptor antibody (Genentech); protein kinase C inhibitors; tyrosine kinase C inhibitors; modulators of the signaling of the receptors Tie-1 and/or Tie 2; and inhibitors of protein expression. *Id*. at 15. Example 1 describes a general study protocol wherein male rats were administered a VEGF receptor tyrosine kinase inhibitor, 4-(4-Bromo-2-fluoroanilino)-6-methoxy-7 -(1-methylpiperidin-4-ylmethoxy) quinazoline, once daily for ten days. *Id*. at 29. For the next four days, the rats were administered a daily dose of captopril, an antihypertensive agent, in addition to the quinazoline compound. *Id*. The difference between the daily calculated pressure and the starting pressure was compared. *Id*. The application explains that the increase in diastolic pressure in rats was reversed by the addition of captopril, based upon data for a control rate and three different rats dosed with the VEGF tyrosine kinase inhibitor. *Id*.

2. Presta

Presta is a journal article describes the humanization of the murine anti-human VEGF monoclonal antibody, muMAb VEGF. Ex. 1033, 4593. Presta explains that "recombinant humanized Mab VEGF is suitable to test the hypothesis that inhibition of VEGF-induced angiogenesis is a valid strategy for the treatment of solid tumors and other disorders in humans." *Id*.

3. Analysis

"[O]bviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some

underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Petitioner asserts that PCT'360 teaches a method of treating cancer with anti-VEGF therapy, and identifies "A.4.6.1" as an anti-VEGF therapy. Pet. 63; Ex. 1009 ¶¶ 113–114. Petitioner asserts that Presta describes the humanization "A.4.6.1" into bevacizumab and concludes that it is "suitable for clinical trials to test the hypothesis that inhibition of VEGF action is an effective strategy for the treatment of cancer and other disorders in humans." Pet. 64 (quoting Ex. 1033, 4593). Petitioner asserts that PCT'360 teaches that anti-VEGF therapy causes hypertension in rats. *Id*. According to Petitioner, a person of skill in the art would have understood that such hypertension includes grade III hypertension because PCT'360 teaches administering an antihypertensive medication to treat the hypertension. *Id*. In support of that assertion, Petitioner refers to Example 1 in PCT'360, wherein an increase in blood pressure in rats from an anti-VEGF agent was reversed by adding an antihypertensive agent. *Id*. at 65 (citing Ex. 1006, 30:20–21, Figure 1).

Additionally, Petitioner asserts that PCT'360 "teaches combining anti-VEGF agents, like bevacizumab, and antihypertensive agents, where the anti-VEGF dosage regimen is continued and not altered." *Id*. In support of that assertion, Petitioner refers to the description in Example 1 in PCT'360 of administering an anti-VEFG dose to rats for ten days, and then, for the next four days, administering an antihypertensive medication daily, in addition to the anti-VEGF dose. *Id*. (citing Ex. 1006, 30:12–15).

According to Petitioner, a person of ordinary skill in the art would have had a reasonable expectation of success based on PCT'360 alone, however, clinical practice at the time of the invention would have bolstered such expectation of success. *Id*. at 66 (citing Ex. 1009 ¶ 121). In particular, Petitioner asserts also that at the time of the invention, the standard clinical practice was to treat hypertension on an individual patient basis. *Id*. (citing Harrison, 1425, Fig. 246-1).[10] Petitioner states that "[b]ecause even mild hypertension may be considered a 'grade III hypertensive event' at the POSA's discretion, a POSA would reasonably expect that administering an anti-VEGF therapy with an antihypertensive treatment would succeed in line with the normal rates of success associated with each treatment." *Id*. (citing Ex. 1009 ¶ 102). For dependent claims 2–18, Petitioner further asserts that the additional limitations of those claims are taught by Chen. *Id*. at 67–68.

Patent Owner asserts that Petitioner's reliance on PCT'360 demonstrates impermissible hindsight and not obviousness because Petitioner does not explain why a person of ordinary skill in the art would have selected the murine anti-VEGF receptor antibody from the "14-page laundry list of billions or more potential anti-angiogenic agents" disclosed in PCT'360. Prelim. Resp. 17–18 (citing *Apotex Inc. v. Merck Sharp & Dohme Corp*., IPR2015-00419, Paper 14, 11 (P.T.A.B. June 25, 2015) (denying institution because petitioner arbitrarily selected active ingredient from 'laundry list' of 600 compounds) (citing *Otsuka Pharm. Co. v. Sandoz, Inc*.,

[10] Williams et al., *Chapter 246: Hypertensive Vascular Disease in Harrison's Principles of Internal Medicine* (Eugene Braunwald et al. eds., 15th ed. 2001) (Ex. 1025).

678 F.3d 1280, 1295 (Fed. Cir. 2012)). Patent Owner notes further that the experimental data relied upon by Petitioner in Example 1 involved administering a different compound, i.e., 4-(4-Bromo-2-fluoroanilino)-6-methoxy-7 -(1-methylpiperidin-4-ylmethoxy) quinazoline. *Id*. at 17.

Further, Patent Owner asserts that Petitioner has failed to provide a sufficient reason "why a person of ordinary skill in the art would have had a reasonable expectation of success extrapolating the effects of a small molecule in a rat to a humanized antibody in a human." *Id*. at 18. According to Patent Owner, Petitioner's position that modifying PCT'360 for use with bevacizumab confirms a result in humans predicted from animal testing is not supported by the evidence, as "PCT'360 does not report any animal testing of the murine antibody, let alone bevacizumab." *Id*. Patent Owner additionally notes that Petitioner provides no evidence of the murine antibody having been tested with an antihypertensive, or that any increase in blood pressure in rats may predict an increase in human blood pressure. *Id*. at 19.

Having considered the arguments and evidence, we consider Patent Owner's arguments to have merit. In particular, we agree with Patent Owner that Petitioner has not adequately demonstrated that a person of ordinary skill in the art would have reasonably expected the PCT'360 teachings and experimental results relating to rats dosed with a VEGF receptor tyrosine kinase inhibitor (4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy) quinazoline) to apply to a receptor antagonist, e.g., a murine anti-VEGF receptor antibody, and more significantly to the humanized anti-VEGF antibody (bevacizumab) disclosed in Presta. Petitioner has not identified any disclosure in PCT'360 describing

a hypertensive event caused by an anti-VEGF antibody. Rather, the disclosure, while identifying numerous anti-angiogenesis agents, provides teachings relating to one such agent. Ex. 1006, 15. PCT'360 explains that "[t]here are many different categories of anti-angiogenic agents," including, agents which inhibit the action of growth factors. *Id*. PCT'360 discloses some of those categories, including, but not limited to receptor antagonists, e.g., an anti-VEGF receptor antibody, and tyrosine kinase inhibitors. *Id*.

It is the teachings relating to the latter category, tyrosine kinase inhibitors, upon Petitioner relies to support its assertions regarding the former category, a receptor antagonist such as an anti-VEGF murine antibody. For example, Petitioner and its declarant, Dr. Bukowski, assert that "PCT'360 states that anti-VEGF therapy causes hypertension." Pet. 64 (citing Ex. 1006, 4:3–5); Ex. 1009 ¶ 115. However, the referenced portion of PCT'360 states, more particularly, that "a VEGF receptor *tyrosine kinase inhibitor* leads to a sustained increase in blood pressure in rats when administered more than once, particularly when administered chronically." Ex. 1006, 4 (emphasis added).

Similarly, Petitioner and Dr. Bukowski assert that "PCT'360 teaches administering an antihypertensive to manage the grade III hypertension." Pet. 64; Ex. 1009 ¶ 116. In support of that assertion Petitioner and Dr. Bukowski refer to Example 1 of PCT'360, asserting that the example shows that "the increase in blood pressure from the anti-VEGF agent was reversed by adding the antihypertensive agent captopril." Pet. 65. However, PCT'360 Example 1 again involves administration of a VEGF receptor *tyrosine kinase inhibitor*. Petitioner and Dr. Bukowski have not identified, nor do we see, a disclosure in PCT'360 describing such hypertension

resulting from administering an anti-VEGF receptor antibody, or treatment of such hypertension while maintaining the dose of the antibody. Thus, Petitioner's reliance on PCT'360 is unsupported. Petitioner does not rely on the other cited references in the combination to meet this limitation.

To the extent that Petitioner and Dr. Bukowski refer to Genentech's Canadian Patent Application No. 2213833 (Ex. 1005) we remain unpersuaded. Petitioner and Dr. Bukowski explain that reference discloses "various tests with the anti-human VEGF antibody A.4.6.1, including its inhibitory effect on human VEGF and the growth of human cancer cells in mice." Pet. 20–21 (citing Ex. 1005, Examples 1–6, Figs. 1–10); Ex. 1009 ¶ 109. However, Petitioner has not provided evidence that a person of skill in the art would have expected that antibody to be associated with a grade III hypertensive event, or would have had a reasonable expectation of successfully controlling such an event by administering an antihypertensive while maintaining the dose of the antibody.

For at least those reasons, based on the information presented, we determine that Petitioner has not shown a reasonable likelihood of prevailing in showing the unpatentability of claim 1 over the PCT'360, Presta, and "Prior Art Clinical Practice." As Petitioner does not rely upon Chen in a manner that cures the deficiencies in the combination of PCT'360, Presta, and "Prior Art Clinical Practice," we determine also that Petitioner has not shown a reasonable likelihood of prevailing in showing the unpatentability of dependent claims 2–18 over the asserted combination. Accordingly, we deny the Petition and decline to institute an *inter partes* review of the grounds based upon PCT'360.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1–18 of the ’672 patent are unpatentable based upon the Yang or PCT’360 grounds. Further, we exercise our discretion under § 325(d) to deny institution of the grounds based upon Kabbinavar and Chen.

ORDER

Accordingly, it is hereby:

ORDERED that Petitioner’s request for an *inter partes* review of claims 1–18 of the ’672 patent is *denied*.

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