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Paper 7
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2016-01771
Patent 7,622,115 B2

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, Administrative *Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Hospira, Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–5 (Paper 1; "Pet.") of US 7,622,115 B2 (Ex. 1001; "the '115 patent"). Genentech, Inc. ("Patent Owner") elected not to file a Patent Owner Preliminary response. Paper 6.

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314 and 37 C.F.R. § 42.4(a). Upon consideration of the Petition, and for the reasons explained below, we determine that Petitioner has shown that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims. We thus institute an *inter partes* review of claims 1–5 of the '115 patent.

A. Related Proceedings

The parties inform us of no related pending litigations. Pet. 3; Paper 4.

B. The '115 patent (Ex. 1001)

The '115 patent claims methods for treating cancer in a patient comprising administering an effective amount of bevacizumab and assessing the patient for gastrointestinal ("GI") perforation during treatment with bevacizumab. Ex. 1001, 25–51. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody. *Id.* at 40:18–21.

The '115 patent discloses that bevacizumab may be administered concomitantly with chemotherapeutic agent, such as fluorouracil and leucovorin. *Id.* at 34:40–36:50. The '115 patent further discloses that GI perforation can occur in patients receiving bevacizumab in combination with chemotherapeutic agents. *Id.* at 46:18–27, 47:6–9.

C. Illustrative Claims

Petitioner challenges claims 1–5 of the '115 patent. Independent claim 1 is illustrative of the challenged claims and is reproduced below:

> 1. A method for treating cancer in a patient comprising administering an effective amount of bevacizumab and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.

Claims 2–5 depend from claim 1, either directly or indirectly.

D. The Asserted Grounds

Petitioner challenges claims 1–5 of the '115 patent on the following grounds. Pet. 25–60.

Ground	Reference[s]	Basis	Challenged Claims
1	Kabbinavar[1]	§ 102	1–5
2	Margolin[2]	§ 102	1–5
3	2000 Press Release[3]	§ 102	1–5

[1] Kabbinavar et al., *Phase II, Randomized Trial Comparing Bevacizumab Plus Fluorouracil (FU)/Leucovorin (LV) With FU/LV Alone in Patients With Metastatic Colorectal Cancers*, 21 J. OF CLIN. ONCOLOGY 60-65 (2003) (Ex. 1005, "Kabbinavar").

[2] Margolin et al., *Phase Ib Trial of Intravenous Recombinant Humanized Monoclonal Antibody to Vascular Endothelial Growth Factor in Combination With Chemotherapy in Patients With Advanced Cancer: Pharmacologic and Long-Term Safety Data*, 19 J. OF CLIN. ONCOLOGY 851-856 (2001) (Ex. 1006, "Margolin").

[3] Genentech Press Release, Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer (May 21, 2000) (Ex. 1004, "2000 Press Release").

Ground	Reference[s]	Basis	Challenged Claims
4	2003 Genentech Press Release[4]	§ 102	1–4
5	Kabbinavar	§ 103	1–5
6	Margolin	§ 103	1–5
7	2000 Press Release	§ 103	1–5
8	2000 Press Release and 1999 NCI CTC[5]	§ 103	1–5
9	2000 Press Release and Kennedy & Spence [6]	§ 103	1–5
10	2000 Press Release and Matsui[7]	§ 103	1–5
11	2003 Press Release and Kabbinavar	§ 103	1–5

Petitioner supports its challenge with the Declaration of Alfred Neugut, M.D (Ex. 1002).

[4] Genentech Press Release, Phase Ill Trial of Avastin Plus Chemotherapy Markedly Extends Survival of Metastatic Colorectal Cancer Patients (May 19, 2003) (Ex. 1003, "2003 Press Release").

[5] National Cancer Institute Common Toxicity Criteria Version 2.0, April 30, 1999 (Ex. 1017, "1999 NCI CTC").

[6] Kennedy & Spence, Chapter 6: *Gastrointestinal Emergencies*. ONCOLOGIC EMERGENCIES, 117-152 (Oxford Univ. Press 2002) (Ex. 1007, "Kennedy & Spence").

[7] Matsui et al., *Efficacy of Vascular Endothelial Growth Factor in the Treatment of Experimental Gastric Injury*, 66 DIGESTION 99-105 (2002) (Ex. 1008, "Matsui").

II. ANALYSIS

A. Claim Interpretation

We interpret claims using 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, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are generally given 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. 2007) (quoting *Phillips v. AWH Corp*, 415 F.3d 1303, 1312 (Fed. Cir. 2005)).

We determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case.

B. Prior Art

Petitioner relies upon the following prior art in its challenges.[8]

1. 2000 Press Release (Ex. 1004)

The 2000 Press Release discloses preliminary results from a Phase II trial evaluating bevacizumab in combination with 5-FU/leucovorin in

[8] Although Matsui, 1999 NCI CTC, and Kennedy & Spence do not form the basis for the specific patentability challenges upon which we institute trial, Petitioner's expert Dr. Neugut relies upon the teachings of these references to support relevant statements made in his declaration. *See* Ex. 1002 ¶¶ 90–92, 95–97, 98–99, 104, 139–141. We, therefore, consider Matsui, 1999 NCI CTC, and Kennedy & Spence as relevant "background" art in our evaluation of Petitioner's patentability challenges. *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.").

patients with metastatic colorectal cancer. Ex. 1004, 1. The results included higher response rates, longer median time to disease progression, and longer median survival in patients receiving bevacizumab. *Id.* at 2. The 2000 Press Release disclosed "[s]ome mild to moderate adverse events that appeared more in the anti-VEGF arms than with chemotherapy alone included fever, chills, headache, hypertension, infection and rash." *Id.*

2. Kabbinavar (Ex. 1005)

Kabbinavar discloses the results of a Phase II trial investigating the use of bevacizumab in combination with fluorouracil and leucovorin to treat patients with metastatic colorectal cancer. Ex. 1005, 2, Abstract. The treatment resulted in higher response rates, longer median time to disease progression, and longer median survival as compared with treatment with fluorouracil and leucovorin. *Id.*

Kabbinavar discloses that "[s]afety evaluations included physical examinations, laboratory tests (hematology, chemistry and electrolytes, and urinalysis), and ECOG performance status," and that patients were questioned regarding adverse events. *Id.* at 3. Kabbinavar discloses that the adverse events included abdominal pain and gastrointestinal hemorrhage. *Id.* at 3, 5 (Table 5).

3. Kennedy & Spence (Ex. 1007)

Kennedy & Spence is a book chapter that discusses gastrointestinal emergencies in cancer patients. Ex. 1007. Kennedy & Spence discloses that that "[g]astrointestinal complications are common in patients with a diagnosis of cancer . . ." and that gastrointestinal preformation is one of the "most common gastrointestinal emergencies in cancer patients." *Id.* at 3. Kennedy & Spence discloses that "[t]ypically the patient with

gastrointestinal perforation complains of a sudden onset of abdominal pain, nausea, vomiting and fever." *Id.* at 9. Kennedy & Spence reports that "40% of cancer patients with gut perforation will die in the peri-operative period, mostly from bacterial peritonitis." *Id.* at 11.

4. Matsui (Ex. 1008)

Matsui "investigated whether VEGF is expressed during the course of experimental gastric injury and whether injury is exacerbated by neutralization with anti-VEGF antibodies." Ex. 1008, 4. Matsui discloses that "VEGF appears to be an important endogenous mediator of the healing process for gastric injury." *Id.* at 9. Matsui also discloses that "[i]n vivo neutralization studies using specific VEGF antibodies demonstrated an increase in gastric damage in animals treated with anti-VEGF, suggesting that VEGF plays an important role in the tissue healing." *Id.* at 8.

5. 1999 NCI CTC (Ex. 1017)[9]

Dr. Neugut testifies that 1999 NCI CTC "is a publication released by the National Cancer Institute that identifies criteria for grading toxicities associated with cancer therapy." Ex. 1002, ¶ 75; Ex. 1016, 7; Ex. 1017. The 1999 NCI CTC identifies various toxicities associated with cancer therapy and provides a grading scale from 0 to 5, where "0 = No adverse event or within normal limits" and "5 = Death related to adverse event." Ex. 1016, at 4. The 1999 NCI CTC discloses that gastrointestinal toxicity is graded a "4" (i.e., "life-threatening or disabling adverse event") where the patient has a gastrointestinal perforation. *Id.*; Ex. 1017, 10–13.

[9] 1999 NCI CTC (Ex. 1017) was accompanied by the 1999 NCI CTC v.2 Manual, Ex. 1016. *See* Ex. 1002, ¶ 75.

C. Ground 1: Anticipation of Claims 1–5 by Kabbinavar

Petitioner asserts that claims 1–5 are anticipated by Kabbinavar. Pet. 26–30. In support of its assertion that Kabbinavar anticipates claims 1–5, Petitioner provides a detailed discussion and claim chart explaining how each claim limitation is disclosed in Kabbinavar. *Id.* In particular, Petitioner asserts that "Kabbinavar discloses that administering bevacizumab in combination with fluorouracil and leucovorin to patients with metastatic colorectal cancer resulted in higher response rates, longer median time to disease progression, and longer median survival." *Id.* at 29 (citing Ex. 1005, 2, Abstract). Petitioner further asserts that "Kabbinavar teaches that the patients underwent 'physical examinations' and 'laboratory tests' and were 'questioned about . . . adverse effects' during treatment with bevacizumab." *Id.* (citing Ex. 1005, 3).

Additionally, relying on its expert, Dr. Neugut, Petitioner asserts that, at the time of the invention, it was the standard of care to assess cancer patients receiving therapy for GI perforation, a known potential adverse event, and Kabbinavar expressly teaches assessing patients for adverse events. *Id.* (citing Ex. 1002, ¶¶ 105–108, 112); Ex. 1002 ¶ 109 ("The step of 'assessing the patient for gastrointestinal perforation during treatment with bevacizumab' is also expressly disclosed because GI perforation is an adverse event and [Kabbinavar] teaches assessing patients for adverse events."). Dr. Neugut additionally relies on the disclosures in Matsui, Kennedy & Spence, and 1999 NCI CTC, summarized in the previous section.

Upon review of Petitioner's analysis and the evidence of record, we determine that Petitioner has demonstrated that there is a reasonable

likelihood that it would prevail in showing that Kabbinavar anticipates claims 1–5 of the '115 patent.

D. Ground 5: Obviousness of Claims 1–5 over Kabbinavar

Petitioner asserts that claims 1–5 are rendered obvious in view of Kabbinavar. Pet. 45–59. Petitioner relies on the same disclosures discussed above to establish that Kabbinavar discloses each claim limitation of challenged claims 1–5. Petitioner contends that "[t]o the extent that Kabbinavar is found to not disclose the step of assessing the patient for GI perforation during treatment with bevacizumab, that limitation would have been obvious in view of the knowledge of the skilled artisan at the time of the alleged invention." *Id.* at 45.

Relying on its expert, Dr. Neugut, Petitioner asserts that, "[a]s a matter of routine medical practice, cancer patients receiving therapy underwent regular evaluations that would have identified any adverse events the patient may have been experiencing, including GI perforation." *Id.* (citing Ex. 1002 ¶¶ 106–107). Petitioner further asserts that

> Each time a cancer patient was observed for the occurrence of adverse events due to therapy, that patient would have been assessed for GI perforation. (Ex. 1002, Neugut Decl., at ¶ 107.) For example, if a physician would have observed that a patient was experiencing severe abdominal pain, hemorrhaging, or nausea among other symptoms that were known to be associated with GI perforation (*id.* at ¶ 92; Ex. 1007, at 9), the physician would have likely concluded that the patient may have had a GI perforation. (Ex. 1002, Neugut Decl., at ¶ 93.) If a physician would have observed that a patient was not experiencing such symptoms, the physician would have likely concluded that the patient did not have GI perforation. (*Id*.) In both scenarios, the

> patient would have been assessed for GI perforation as required by claim 1 of the patent. (*Id*.)

Id. at 46. In this regard, Petitioner asserts that is was known that some of the patients receiving bevacizumab experienced symptoms that were known at the time to be associated with GI perforation. *Id.* at 48–49 (citing Ex. 1005, 5, Table 5; Ex. 1002 ¶ 92).

Upon review of Petitioner's analysis and the evidence of record, we determine that Petitioner has demonstrated that there is a reasonable likelihood that it would prevail in showing that claims 1–5 of the '115 patent would have been obvious over Kabbinavar.

E. Ground 7: Obviousness of Claims 1–5 over 2000 Press Release

Petitioner asserts that claims 1–5 are rendered obvious in view of 2000 Press Release. Pet. 51–52. In support of this assertion, Petitioner provides a detailed discussion and claim chart explaining how each claim limitation is disclosed in 2000 Press Release. *Id.* at 35–39. Petitioner asserts that 2000 Press Release expressly discloses administering an effective amount of bevacizumab to treat cancer patients and that "[i]t would have been obvious to the skilled artisan to assess cancer patients receiving bevacizumab treatment as described in the 2000 Press Release for GI perforation for the same reasons as explained in detail for Kabbinavar in Ground 5." *Id.* at 51.

Moreover, relying on its expert, Dr. Neugut, Petitioner asserts the following:

> First, it was the standard of care at the time to assess all cancer patients for any adverse events of therapy, including GI perforation. ([Ex. 1002] ¶ 138.) Second, the patients in the study were colorectal cancer patients (Ex. 1004, at 1, Title) who were

> known to be at risk of GI perforation. (Ex. 1002, Neugut Decl., at ¶ 139.) Third, the patients received systemic chemotherapy (Ex. 1004, at 2), which was known to be associated with GI perforation. (Ex. 1002, Neugut Decl., at ¶ 140.) And fourth, some of the patients exhibited symptoms that were known to be associated with GI perforation—e.g., fever and chills. (*Id.* at ¶ 92.)

Id. at 52.

Upon review of Petitioner's analysis and the evidence of record, we determine that Petitioner has demonstrated that there is a reasonable likelihood that it would prevail in showing that claims 1–5 of the '115 patent would have been obvious over 2000 Press Release.

F. Petitioner's Remaining Grounds

Petitioner asserts that the subject matter of claims 1–5 would have been anticipated or obvious in view of the references or combination of references set forth in Grounds 2–4, 6, and 8–11. In view of our instituting an *inter partes* review of all of the challenged claims on other grounds, as set forth above, we deny institution on these additional grounds. *See* 37 C.F.R. § 42.108(a)-(b).

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has shown there is a reasonable likelihood that it would prevail in proving the unpatentability of claims 1–5 of the '115 patent.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or the construction of any claim term. Thus, our view with regard to any

conclusion reached in the foregoing could change upon consideration of Patent Owner's merits response and upon completion of the record.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that *inter partes* review is instituted with regard to the following asserted grounds:

1) Claims 1–5 of the '115 patent as anticipated under 35 U.S.C. § 102(b) by Kabbinavar;
2) Claims 1–5 of the '115 patent as unpatentable under 35 U.S.C. § 103(a) in view of Kabbinavar;
3) Claims 1–5 of the '115 patent as unpatentable under 35 U.S.C. § 103(a) in view of 2000 Press Release.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '115 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial is limited to the ground listed in the Order. No other grounds are authorized.

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