UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Patent No. 7,622,115 B2
Issue Date: November 24, 2009
Title: TREATMENT WITH ANTI-VEGF ANTIBODIES

Inter Partes Review No. 2016-01771

PATENT OWNER GENENTECH, INC.'S NOTICE OF APPEAL

Notice is hereby given, pursuant to 37 C.F.R. § 90.2(a), that Patent Owner Genentech, Inc. ("Genentech") hereby appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision entered March 9, 2018 (Paper 34) as it relates to claims of U.S. Patent No. 7,622,115 ("the '115 patent"), and any finding or determination supporting or relating to that decision, including the Decision on Institution of Inter Partes Review entered March 16, 2017 (Paper 7). A copy of the Final Written Decision is attached hereto as Exhibit A.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Patent Owner indicates that the issues on appeal include, but are not limited to, the Patent Trial and Appeal Board's determinations that Petitioner demonstrated by a preponderance of the evidence that claims 1–5 of the '115 patent are unpatentable as obvious over 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. CLIN. ONCOLOGY 60-65 (2003) ("Kabbinavar") and Genentech Press Release, Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer (May 21, 2000) ("2000 Press Release"). Patent Owner further appeals the Board's claim construction determination of "assessing the patient for gastrointestinal perforation." Patent Owner also appeals the constitutionality of the retroactive

application of inter partes review to this patent, granted before the enactment of the America Invents Act. Patent Owner appeals any finding or determination supporting or relating to those issues, as well as all other issues decided adversely to Patent Owner in any orders, decisions, rulings, and opinions.

Pursuant to 37 C.F.R. § 90.2(a), with this submission: (1) a copy of this Notice of Appeal is being filed electronically with the Patent Trial and Appeal Board in accordance with 37 C.F.R. § 42.6(b); (2) a paper copy of this Notice of Appeal, an electronic copy of this Notice of Appeal on the CM/ECF Document Filing System, and the docketing fee of $500 are being simultaneously filed with the Clerk's Office for the United States Court of Appeals for the Federal Circuit; (3) the original of this Notice of Appeal is being filed by hand with the United States Patent and Trademark Office as provided in 37 C.F.R. § 104.2; and (4) a copy of this Notice of Appeal is being served on Petitioner Hospira, Inc.

Dated: May 10, 2018

Respectfully submitted,

/Thomas S. Fletcher/

Thomas S. Fletcher
Reg. No. 72,383
Lead Counsel for
Patent Owner

Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005

202-434-5497 (Telephone)
202-434-5029 (Facsimile)
tfletcher@wc.com

CERTIFICATE OF FILING

The undersigned hereby certifies that, in addition to being electronically filed through PTAB E2E, the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal* is being filed by hand with the Director May 10, 2018, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, 10B20
600 Dulany Street
Alexandria, VA 22314

The undersigned also hereby certifies that a true and correct paper copy of the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal*, a true and correct electronic copy of the above-captioned *Patent Owner Genentech, Inc.'s Notice of Appeal*, and the docketing fee of $500 are being filed by hand, CM/ECF, and Pay.gov, respectively, with the Clerk's Office of the United States Court of Appeals for the Federal Circuit on May 10, 2018.

Dated: May 10, 2018

Respectfully submitted,

/Thomas S. Fletcher/

Thomas S. Fletcher
Reg. No. 72,383
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005
202-434-5497 (Telephone)
202-434-5029 (Facsimile)
tfletcher@wc.com

CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned *Patent Owner Genentech Inc.'s Notice of Appeal* was served on May 10, 2018 by delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

Thomas J. Meloro
Reg. No. 33,538
tmeloro@willkie.com

Willkie Farr & Gallagher LLP
787 Seventh Avenue
New York, NY 10019-6099
Telephone: (212) 728-8428
Facsimile: (212) 728-8111

Michael W. Johnson
Reg. No. 63,731
mjohnson1@willkie.com

Willkie Farr & Gallagher LLP
787 Seventh Avenue
New York, NY 10019-6099
Telephone: (212) 728-8137
Facsimile: (212) 728-8111

/Thomas S. Fletcher/
Thomas S. Fletcher
Reg. No. 72,383
Lead Counsel for Patent Owner

Date: May 10, 2018

Trials@uspto.gov
Tel: 571-272-7822

Paper 34
Entered: March 9, 2018

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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

EXHIBIT A

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–5 of US 7,622,115 B2 (Ex. 1001; "the '115 patent"). We have jurisdiction under 35 U.S.C. § 6. We conclude for the reasons that follow that Petitioner has shown by a preponderance of the evidence that claims 1–5 of the '115 patent are unpatentable.

A. Procedural History

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. Based on the information set forth in the Petition, we instituted trial on the following grounds of unpatentability asserted by Petitioner:

Ground	Reference[s]	Basis	Challenged Claims
1	Kabbinavar[1]	§ 102	1–5
2	Kabbinavar	§ 103	1–5
3	2000 Press Release[2]	§ 103	1–5

Decision to Institute (Paper 7, "DI").

[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. CLIN. ONCOLOGY 60-65 (2003) (Ex. 1005, "Kabbinavar").

[2] 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").

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 18, "PO Resp."), to which Petitioner filed a Reply (Paper 22, "Reply").

Petitioner relies on the Declarations of Alfred Neugut, M.D (Ex. 1002; Ex. 1025) in support of the proposed grounds of unpatentability.

Patent Owner relies on the Declarations of Michael A. Morse, MD, FACP, MHS (Ex. 2011) and Angela D. Levy, MD (Ex. 2012).

Oral argument was conducted on January 18, 2018. A transcript is entered as Paper 33 ("Tr.").

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 agents, 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.

II. DISCUSSION

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 note that only those claim terms that are in controversy need to be construed, and "only to the extent necessary to resolve the controversy." *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (*citing Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

For purposes of this Decision, we find it necessary to construe only the phrase "assessing the patient for gastrointestinal perforation."

1. "assessing the patient for gastrointestinal perforation"

Petitioner argues that the phrase "assessing the patient for gastrointestinal perforation" should be interpreted to mean, "evaluating the patient in any way that may provide information about whether the patient may be experiencing a GI perforation." To support its construction, Petitioner argues that, while the specification does not define the term assessing,

> the term "assessing" or another form of the verb "assess" is used to describe the evaluation of a particular thing—e.g., "the

> duration of survival" or "quality of life" or "safety"—for the purpose of obtaining information about that thing. Thus, it is clear from the specification that "assessing" means "evaluating."

Pet. 14–16 (citing Ex. 1001, 10:44-47, 41:40-46, 48:33-38; Ex. 1002 ¶¶ 91–92). Petitioner further argues that

> The specification also does not explain or provide any examples of how one practices the specific step of "assessing . . . for gastrointestinal perforation." Moreover, it does not teach any particular signs or symptoms of GI perforation. Rather, it merely teaches that the patients that had GI perforation "had variable clinical presentations." (Ex. 1001, at 47:8-9.) Indeed, the lack of disclosure of any signs or symptoms of GI perforation was the basis for the Examiner's § 112 rejection of the precursor claims that recited "monitoring the patient for signs or symptoms of gastrointestinal perforation." (Ex. 1020, at 96-97.) The applicants did not challenge the basis of that rejection, but amended the claims to remove "monitoring" and "signs or symptoms of." (*Id.* at 107.) Therefore, the meaning of the claim language at issue should not be limited to performing any particular method of evaluation or evaluating *for any particular symptom or sign*.

Id. at 16–17 (emphasis added).

As explained by Petitioner, under its construction,

> the meaning of the claim language at issue should not be limited to performing any particular method of evaluation or evaluating *for any particular symptom or sign*. As Dr. Neugut explains, in actual practice, a physician can evaluate a patient for GI perforation according to the claims by, *for example, visual inspection, physical examination, or questioning the patient about his general health, among other methods*. (Ex. 1002, Neugut Decl., at ¶ 92.)

Id. at 17 (emphasis added).

Patent Owner argues that Petitioner's construction is broad enough to cover visual inspections from a physician observing a patient with, for

example, abdominal pain, a sign of GI perforation, and, as such, "effectively removes all meaning from the concept of 'assessing' someone 'for' GI perforation in particular." PO Resp. 15 (citing Ex. 1002 ¶¶ 91–92; Ex. 2013, 42–43, 50–51, 190–93). We agree. We, however, do not adopt Patent Owner's proposed construction for the phrase at issue, which is proposed to mean "taking diagnostic steps to determine whether a GI perforation exists." *Id.* at 14; *see also id.* (arguing "an assessment 'for' a particular medical condition requires a targeted evaluation capable of revealing whether the condition in question did or did not exist, and is performed for that purpose"). As discussed below, we determine the prosecution history does not support a broadest reasonable construction of this phrase that is co-extensive with generally assessing a patient for signs and symptoms that may, or may not, be indicative of gastrointestinal perforation.

We agree with Patent Owner that the prosecution history established a clear distinction between assessing for GI perforation itself and merely looking for symptoms that could be consistent with GI perforation. PO Resp. 16–19. Here, we note that the application originally claimed a method of treatment with bevacizumab comprising "monitoring the patient for signs or symptoms of gastrointestinal perforation." Ex. 1020 at 90. The Examiner rejected this claim as anticipated by a reference, Gordon (Ex. 1015), reporting on the results of a Phase I bevacizumab clinical study. *Id.* at 94–97, 100–01. The Examiner concluded that Gordon taught "a method for treating cancer in a patient comprising administering rhuMAb VEGF (bevacizumab) and monitoring patients for adverse events during treatment including nausea." *Id.* at 101. The Examiner reasoned, "nausea is a sign or symptom of gastrointestinal perforation, hence the nausea monitored in the

method taught by Gordon et al is a sign or symptom of gastrointestinal perforation." *Id*.

Applicant responded with an amendment substituting the current "assessing the patient for gastrointestinal perforation" language for the rejected "monitoring the patient for signs or symptoms of gastrointestinal perforation" language. *Id*. at 107. Applicant further explained as follows:

> [T]he Examiner contends that the nausea monitored in Gordon's method is a sign or symptom of gastrointestinal perforation. Applicants traverse in view of the claim amendments. . . . *Gordon does not teach assessing patients being treated with bevacizumab for gastrointestinal perforation. In fact, gastrointestinal perforation was a newly observed potential adverse event associated with bevacizumab in the clinical trials described in the instant application*. [] Moreover, the occurrence of gastrointestinal perforation in these patients was unexpected based on the adverse events observed in previous clinical trials using bevacizumab.

Id. at 114-115 (emphasis added).

We agree with Patent Owner that

> This amendment leaves little question that [Patent Owner] and the Examiner drew a distinction between assessing for GI perforation itself and merely looking for symptoms that could be consistent with this condition. And, critically, this amendment makes clear that the amended claims do not cover routine examinations of patients, in clinical trials or otherwise, as that is all that Gordon disclosed (and is all that the prior art in the Grounds instituted upon discloses). Ex. 2011 ¶¶ 52–55, 57; Ex. 1005; Ex. 1006.

PO Resp. 17–18.

Accordingly, we construe the phrase "assessing the patient for gastrointestinal perforation" as indicating a targeted investigation, directed specifically to confirming the presence or absence of GI perforation. This

determination is further supported by Dr. Morse's testimony that oncologists would have understood "assessing the patient for gastrointestinal perforation" to mean an evaluation of a patient to determine if the patient has gastrointestinal preformation. Ex. 2011 ¶¶ 44–47; *see also* PO Resp. 19–21.

B. Prior Art

Petitioner relies upon the following prior art in support of its challenges.[3]

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 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

---

[3] 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. 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 perforation is one of the "most common gastrointestinal emergencies in cancer patients." *Id.* at 3.

Kennedy & Spence discloses that

> Gastrointestinal perforation, in the cancer patient, is most often due to weakening of the gut wall at the site of a tumor. Another important cause is tumor necrosis during radiotherapy or cytotoxic chemotherapy.

Id. at 9. Kennedy & Spence also instructs to "ask if the patient has recently received chemotherapy as this may cause perforation by weakening the bowel wall at a site of tumor." *Id.* Kennedy & Spence discloses that "[t]ypically the patient with gastrointestinal perforation complains of a sudden onset of abdominal pain, nausea, vomiting and fever." *Id.* 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 "[b]locking endogenous VEGF effects with anti-VEGF antibodies exacerbated mucosal injury." *Id.* at 3.

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)[4]

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.

[4] 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

1. Summary of Petitioner's Contentions

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, "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, "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.

2. Summary of Patent Owner's Contentions

Patent Owner contends that Kabbinavar does not disclose "assessing the patient for gastrointestinal perforation." PO Resp. 22. Patent Owner notes that while Kabbinavar provides a list of adverse events experienced by patients enrolled in the study, nowhere does Kabbinavar disclose that any evaluation was performed to determine whether GI perforation had occurred, and further provides no indication "that any physician involved in the trial knew that GI perforation was a particular risk when bevacizumab was administered." *Id.* at 23. Patent Owner further argues,

> Petitioner's position is simply that because patients in the trial were evaluated for *other* adverse events, they necessarily were examined in a way that *might* have provided some information about whether they were experiencing a GI perforation. *See, e.g.*, Pet. 27, 29; Ex. 2013 at 93. This is not "assessing . . . for GI perforation."

Id. at 23-24.

Relying on the testimony of Dr. Morse, Patent Owner contends that adverse events such as abdominal pain, nausea, and vomiting are all symptoms that a physician might notice that are consistent with the presence of a GI perforation, but are not determinative for a diagnosis of GI perforation, at least because such symptoms are "also consistent with a variety of other conditions, many of which are far more common than GI perforations." *Id.* at 7 (citing 2011 ¶¶ 31–34, 45–47, 80–81).

3. Anticipation Analysis

The Court of Appeals for the Federal Circuit summarized the analytical framework for determining whether prior art anticipates a claim as follows:

> To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation. *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). But disclosure of each element is not quite enough—this court has long held that "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim*." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (citing *Soundscriber Corp. v. United States*, [] 360 F.2d 954, 960 (1966) (emphasis added)).

Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334–35 (Fed. Cir. 2008).

To establish inherent disclosure, the evidence must show that a feature necessarily is described in the reference, and that it would be recognized by persons of ordinary skill. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Inherency may not be established by probabilities or possibilities. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

Having considered the parties' positions and evidence of record, summarized above, we conclude that Kabbinavar fails to disclose "assessing the patient for gastrointestinal perforation" as required by the challenged claims. In making this determination, we note that Kabbinavar expressly states that the patients enrolled in the disclosed study underwent regular "baseline tumor assessments [that] included a chest x-ray, abdominal and pelvis computed tomography [("CT")] scans." Ex. 1005 at 3–4. We are not, however, persuaded by Petitioner's argument that "Kabbinavar teaches that the subjects receiving bevacizumab underwent regular CT scans that the Skilled Artisan would have understood (1) were performed *to determine*

whether the subjects were experiencing any GI injury including GI perforation and (2) would have detected signs of GI perforation." Reply 12 (citing Ex. 1025 ¶¶ 26–29; Ex. 1026, 39:6–16) (emphasis added). Rather, we find that Kabbinavar expressly discloses that the CT scans were performed for the purposes of tumor assessment, and not for assessing the patient for GI perforation.

While it is undisputed that CT scans of the abdominal and pelvis, such as those performed in Kabbinavar, are capable of detecting GI perforation (Ex. 1025 ¶ 26; Ex. 1026, 39:6–16; Ex. 1022; Ex. 1023; Ex. 1027, 55:1–57:4), the evidence of record supports a finding that a person of ordinary skill in the art looking for a GI perforation would have performed different steps that are not necessarily taken in cases where GI perforation is not suspected, such as in the case of performing baseline tumor assessments (or tumor staging). Here, we credit the testimony of Dr. Levy, Professor of Radiology at Georgetown University Medical Center, who testified that, where a patient is suspected to have GI perforation, a radiologist would use particular contrast agents and would use a setting known as a "lung window," a setting that is better suited to detect the presence of free air and to more easily identify the location of the perforation. Ex. 2012 ¶¶ 24–35. In contrast, the record fails to establish that the same or equivalent steps would necessarily be used where a radiologist was performing baseline tumor assessments. *See* Reply 14–17; Ex. 1026, 53:8–60:17.

Accordingly, based on the evidence of record, we conclude that the use of a CT scan in the manner disclosed in Kabbinavar would not have necessarily confirmed the presence or absence of GI perforation. That is, while a CT scan is capable of assessing a patient for GI perforation,

Petitioner failed to show that the patients discussed in Kabbinavar necessarily underwent an evaluation to determine if those patients had GI perforation. As such, we find that Kabbinavar fails to explicitly or inherently disclose the requirement for "assessing the patient for gastrointestinal perforation."

In view of the above, we conclude that Petitioner has failed to establish by a preponderance of the evidence that Kabbinavar anticipates claims 1–5 of the '115 patent.

D. Grounds 2 and 3: Obviousness of Claims 1–5 over Kabbinavar and over 2000 Press Release

1. Summary of Petitioner's Contentions with Regard to 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 further contends, "[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. In particular, Petitioner provides the following obviousness rationale:

> [I]t would have been obvious to the skilled artisan to assess cancer patients receiving bevacizumab treatment as described in Kabbinavar for GI perforation at the time of the invention because (1) it was the standard of care at the time to assess all cancer patients for any adverse events of therapy, including GI perforation, (2) the patients in the study were colorectal cancer patients who were known to be at risk of GI perforation, (3) the patients received systemic chemotherapy,

> which was known to be associated with GI perforation, and (4) some of the patients exhibited symptoms that were known to be associated with GI perforation.

Id. at 49.

Petitioner supports its obviousness rationale with the following. To start, Petitioner contends that physicians would have assessed "any cancer patient receiving chemotherapy for GI perforation because it was also well-known that GI perforation was associated with systemic chemotherapy due to the weakening of the GI wall." Pet. 48 (citing Ex. 1002 ¶¶ 79, 139–40). Petitioner further contends that it was known that GI perforation was associated with a high rate of death and that physicians would have been particularly concerned with life-threatening complications such as GI perforation. *Id.* at 47 (citing Ex. 1002 ¶ 90; Ex. 1012, 2; Ex. 1017, 11). Specific to colorectal cancer patients, Petitioner contends that it was known that colorectal cancer patients undergoing systemic chemotherapy were at an increased risk of GI perforation. *Id.* at 48 (citing Ex. 1002 ¶¶ 96–99; Ex. 1007, 9; Ex. 1014, 3.)

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.* at 45 (citing Ex. 1002 ¶¶ 106–107). Petitioner further asserts,

> 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.

Petitioner further 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).

2. Summary of Petitioner's Contentions with Regard to 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 bevacizumab in combination with fluorouracil and leucovorin to patients with metastatic colorectal cancer and that the results showed higher response rates, longer median time to disease progression, and longer median survival. *Id.* at 38, 51.

As for its obviousness rationale, Petitioner contends 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." *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.

3. Summary of Patent Owner's Contentions

Patent Owner contends that both Kabbinavar and the 2000 Press Release fail to teach or suggest the limitation of "assessing the patient for gastrointestinal perforation" as required by the claims. PO Resp. 25–41. Patent Owner does not dispute that a physician would have evaluated a cancer patient during treatment for possible adverse events. PO Resp. 27. Rather, Patent Owner argues that neither Kabbinavar nor the 2000 Press Release disclose or suggest any potential association between bevacizumab and GI perforations that might lead the POSA to assess a patient specifically for GI perforation. *Id.* (citing Ex. 1005, 2 ("bevacizumab was generally well tolerated and did not demonstrate dose-limiting toxicity or interactions with commonly used chemotherapy regimens"). As such, according to Patent Owner, neither reference would have encouraged physicians prescribing bevacizumab to take any steps toward diagnosing GI perforation. *Id.*

Patent Owner further argues that a cancer patient could experience any one of more than 200 separate adverse events, and that the standard of care for evaluating a patient would not have involved ordering "diagnostic steps to confirm the presence of hundreds of medical problems in each

cancer patient," and in particular, GI perforation. *Id.* at 28 (citing Ex. 1016, 8; Ex. 1017; Ex. 2011 ¶¶ 61–62; Ex. 2021, 2; Ex. 2013, 17, 75–79).

Patent Owner acknowledges that Kennedy & Spence discloses that GI perforation is among the "most common [GI] emergencies in cancer patients" (Ex. 1007, 3), but argues that

> [t]he rate of GI cancer patients suffering perforations is just not high enough to warrant these costs of continuous GI perforation assessments over the lifetime of the cancer. *See, e.g.*, *id.* ¶ 64 (citing Ex. 2017 at 3–19 (omitting GI perforations from discussion of the "more important syndromes and problems of [cancer] management" afflicting the alimentary system); Ex. 2009 at 1 ("The incidence [of free perforation of gastric carcinoma] is less than 1% . . . and only two publications have appeared in the English literature over last 20 yr.")).

PO Resp. 33–34. Patent Owner contends that such infrequent occurrences of GI perforations in GI cancer patients would not have driven the person of ordinary skill in the art to assess such patients for GI perforations. *Id.* at 31–32 (citing Ex. 1007, 3; Ex. 2013, 229; Ex. 2011 ¶¶ 63–69).

4. Obviousness Analysis

The parties do not dispute, and we find, that both Kabbinavar and the 2000 Press Release disclose a method of treating cancer in a patient comprising administering an effective amount of bevacizumab, the method recited in claim 1. The parties also do not dispute, and we find, that the references disclose each of the limitations set forth in dependent claims 2–5. *See* Pet. 37–43; *see also*, Ex. 1002 ¶¶ 113–15, 126–28. The question before us is whether a person of ordinary skill in the art would have modified the disclosures of Kabbinavar or the 2000 Press Release to include "assessing the patient for gastrointestinal perforation." Having considered the parties positions and evidence of record, summarized above, we conclude that a

person of ordinary skill in the art would have had adequate reason to assess patients with colorectal cancer receiving bevacizumab in combination with chemotherapeutic agents, such as the patients disclosed in Kabbinavar and the 2000 Press Release, for GI perforation.

In reaching this conclusion, we credit the testimony of Dr. Neugut that the standard of care and the knowledge of a person of ordinary skill in the art would have guided a physician to assess patients receiving bevacizumab for GI perforation. Ex. 1002 ¶¶ 92–108; Ex. 1025 ¶¶ 35–40. We are persuaded that such an assessment necessarily begins with evaluating patients for symptoms of GI perforation, such as nausea and abdominal pain, and in the event of a showing of such signs, a physician would have assessed the patient for GI perforation. *Id.* at ¶¶ 92–94. Guiding that physician would have been the knowledge that GI cancers and systemic chemotherapy each were known to be causally related to GI perforation. Pet. 48; Ex. 1002 ¶¶ 91, 96-99; Ex. 1025 ¶ 39; Ex. 1027, 64:1–24; Ex. 1026, 95:18–96:17; Ex. 1007, 9 ("ask if the patient has recently received chemotherapy as this may cause perforation by weakening the bowel wall at a site of tumor."). The physician would have known that GI perforation was associated with a high rate of death, and thus the physician would have been particularly concerned with a life-threatening complication such as GI perforation. Pet. 47; Ex. 1002 ¶ 90; Ex. 1007, 11. The physician would have also known that chemotherapy promotes GI injury by killing tumor cells and effectively eroding away the tumor as well as by killing epithelial cells that line the gut wall. Pet. 48; Reply 23; Ex. 1002 ¶¶ 98–101; Ex. 1025 ¶ 39; Ex. 1009, 5; Ex. 1010, 3; Ex. 1013, 2. Finally, the physician would have known that the protein VEGF promotes GI injury repair and that a VEGF-neutralizing

antibody, such as bevacizumab, could impair the ability of VEGF to promote GI injury repair and thus potentially exacerbate GI tissue injury caused by chemotherapy. Reply 23; Ex. 1002 ¶ 82; Ex. 1025 ¶ 39; Ex. 1008, 3, 8–9.

We further note that secondary consideration have not been asserted in this case.

Accordingly, in view of the above, we determine that Petitioner has demonstrated, by a preponderance of the evidence, that the subject matter of claims 1–5 of the ’115 patent would have been obvious over Kabbinavar and over the 2000 Press Release.

III. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–5 of the ’115 Patent are held unpatentable; and

FURTHER ORDERED that this is a Final Written Decision; therefore, 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.

PETITIONER:

Thomas Meloro
tmeloro@willlkie.com

Michael Johnson
mjohnson1@willkie.com

PATENT OWNER:

Thomas Fletcher
tfletcher@wc.com

Christopher Suarez
csuarez@wc.com