UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.
Petitioner

v.

GENENTECH, INC.
Patent Owner

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

Inter Partes Review No. Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,622,115 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42 *ET SEQ.*

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(Filed Pursuant to 37 C.F.R. § 42.6)

Hospira Exhibit Number	Description
1001	U.S. Patent No. 7,622,115 to Fyfe et al.
1002	Declaration of Alfred Neugut, M.D., with Exhibits
1003	Genentech Press Release, *Phase Ill Trial of Avastin Plus Chemotherapy Markedly Extends Survival of Metastatic Colorectal Cancer Patients* (May 19, 2003), http://www.gene.com/media/press-releases/6147/2003-05-19/phase-iii-trial-of-avastin-plus-chemothe
1004	Genentech Press Release, *Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer* (May 21, 2000), http://www.gene.com/media/press-releases/4617/2000-05-21/anti-vegf-monoclonal-antibody-with-chemo
1005	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)
1006	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)
1007	Kennedy & Spence, Chapter 6: *Gastrointestinal Emergencies*. ONCOLOGIC EMERGENCIES, 117-152 (Oxford Univ. Press 2002)
1008	Matsui et al., *Efficacy of Vascular Endothelial Growth Factor in the Treatment of Experimental Gastric Injury*, 66 DIGESTION 99-105 (2002)
1009	Hata et al., *Intestinal Perforation Due to Metastasis of Breast Carcinoma, with Special Reference to Chemotherapy: a Case Report*,

	31 JPN. J. CLIN. ONCOL. 162-164 (2001)
1010	Wada et al., *Spontaneous gastrointestinal perforation in patients with lymphoma receiving chemotherapy and steroids*, 66 J. NIPPON MED. SCH. 37-40 (1999)
1011	Reese et al., *A Phase II Trial of Humanized Anti-Vascular Endothelial Growth Factor Antibody for the Treatment of Androgen-Independent Prostate Cancer*, 3 THE PROSTATE JOURNAL, 65-70 (2001)
1012	Mandava et al., *Perforated Colorectal Carcinomas*, 172 THE AMERICAN JOURNAL OF SURGERY 236-238 (1996)
1013	Liaw et al., *Spontaneous Gastrointestinal Perforation in Patients with Cancer Receiving Chemotherapy and Steroids*, 72 CANCER 1382-1385 (1993)
1014	Fata et al., *5-Fluorouracil-Induced Small Bowel Toxicity in Patients with Colorectal Carcinoma*, 86 CANCER 1129-1134 (1999)
1015	Gordon et al., *Phase I Safety and Pharmacokinetic Study of Recombinant Human Anti-Vascular Endothelial Growth Factor in Patients With Advanced Cancer*. 19 JOURNAL OF CLINICAL ONCOLOGY 843-850 (2001)
1016	National Cancer Institute Common Toxicity Criteria Manual Version 2.0, June 1, 1999, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf (last visited August 27, 2016) ("1999 NCI CTC v.2 Manual")
1017	National Cancer Institute Common Toxicity Criteria Version 2.0, April 30, 1999, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf (last visited August 27, 2016) ("1999 NCI CTC v.2")
1018	U.S. Provisional Application No. 60/474,480 filed May 30, 2003 ("'480 Provisional Application")
1019	Excerpts from Certified Prosecution File History of U.S. Application No. 10/857,249 filed May 28, 2004 ("'249 Application Prosecution History Excerpts")

1020	Excerpts from Certified Prosecution File History of U.S. Patent No. 7,622,115 filed June 14, 2007 ("'115 Patent Prosecution History Excerpts")
1021	Jones et al. *Gene Therapy for Gastric Ulcers With Single Local Injection of Naked DNA Encoding VEGF and Angiopoietin-1*. 121 GASTROENTEROLOGY 140-1047 (2001)

Hospira, Inc. requests *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 *et seq.* of claims 1 to 5 of U.S. Patent No. 7,622,115 (the "'115 Patent") to Fyfe et al., titled "TREATMENT WITH ANTI-VEGFANTIBODIES." (Ex. 1001.)

Pursuant to 37 C.F.R. § 42.15, the Petition Fee of $23,000 is being paid concurrently with the filing of this Petition. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to deposit account 232405.

I. OVERVIEW

The challenged claims of the '115 Patent are unpatentable over the prior art cited in this Petition and should not have been issued. Because Petitioner is, at a minimum, reasonably likely to prevail in demonstrating unpatentability, this Petition should be granted and trial instituted on all of the challenged claims.

The claims of the '115 Patent are generally directed to methods for treating cancer with the anti-VEGF antibody, bevacizumab. The claimed methods require: (1) administering an effective amount of bevacizumab to a patient and (2) assessing the patient for gastrointestinal ("GI") perforation during treatment with bevacizumab.

Under Grounds 1 to 11, Petitioner challenges claims 1 to 5 of the '115 Patent. This Petition and the Declaration of Alfred Neugut, M.D. (Ex. 1002.)

explain that every element of claims 1 to 5 of the '115 Patent was disclosed or suggested in the prior art and known to those of ordinary skill in the art. First, the step of administering bevacizumab to a patient to treat cancer was known in the prior art. As explained in further detail below, the use of an effective amount of bevacizumab for cancer treatment had been disclosed in multiple published clinical studies and Genentech, Inc. press releases. Second, the prior art discloses expressly or inherently the step of assessing the patient for GI perforation during bevacizumab treatment. Moreover, that step simply recites the standard of medical care in the art at the time of the invention.

Because claims 1 to 5 of the '115 Patent recite the known step of administering an effective amount of bevacizumab for cancer treatment in combination with the known step of assessing for GI perforation, which simply recites the standard of care in the art at the time, the claims are invalid under 35 U.S.C. §§ 102 and 103 as set forth in detail below, and should be cancelled.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Hospira, Inc. ("Hospira" or "Petitioner") is the real parties-in-interest for Petitioner. Out of an abundance of caution, Petitioner also identifies Pfizer, Inc. as a real party-in-interest who, going forward, may have control or an interest in the outcome of this proceeding. No other parties exercised or could have exercised

control over this petition; no other parties funded or directed this petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759-60.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

The following patents and patent applications claim the benefit of the priority of the filing date of the '115 Patent: U.S. Application Nos. 11/935,897 (abandoned), 12/415,599 (abandoned), 12/576,085 (abandoned), 13/019,414 (abandoned), 13/355,205 (abandoned), 13/602,619 (abandoned), 14/134,121 (abandoned), 14/597,754 (abandoned), 15/080,897 (pending).

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Pursuant to 37 C.F.R. §§ 42.8(b)(3) and 42.10(a), Petitioner designates the following counsel:

Lead Counsel	Back-Up Counsel
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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to lead counsel at the contact information above. Hospira consents to service by electronic mail at tmeloro@willkie.com and mjohnson1@willkie.com. A Power of Attorney is being filed concurrently herewith under 37 C.F.R. § 41.10(b).

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the '115 Patent is available for IPR, and that Petitioner is not barred or estopped from requesting IPR of any claim of the '115 Patent on the grounds set forth herein.

IV. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22)

Petitioner requests *inter partes* review and cancellation of claims 1 to 5 of the '115 Patent under 35 U.S.C. §§ 102 and 103, as set forth herein. Petitioner's detailed statement of the reasons for the relief requested is set forth in Section VII below.

V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least [one] of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets that threshold. As explained below, for each of the grounds of unpatentability presented below,

there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VI. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Inter partes review of claims 1 to 5 of the '115 Patent is requested. Per 37 C.F.R. § 42.6(c), copies of the references are filed herewith. In support of the proposed grounds for unpatentability, this Petition is accompanied by the Declaration of Alfred Neugut, M.D. (Ex. 1002), which explains the '115 Patent, its prosecution history and the teachings of the cited prior art and which are also summarized herein.

A. The Challenged Claims and Grounds (37 C.F.R. §§ 42.104(b)(1) and (2))

Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), the following grounds are offered as reasons for canceling the challenged claims of the '454 Patent:

Ground	Reference(s)	Statutory Basis	Challenged Claims
1	2000 Press Release (Ex. 1004)	§ 102(b)	1 to 5
2	Kabbinavar (Ex. 1005)	§ 102(a)	1 to 5
3	Margolin (Ex. 1006)	§ 102(b)	1 to 5
4	2003 Genentech Press Release (Ex. 1003)	§ 102(a)	1 to 4
5	2000 Press Release (Ex. 1004)	§ 103(a)	1 to 5

Ground	Reference(s)	Statutory Basis	Challenged Claims
6	Kabbinavar (Ex. 1005)	§ 103(a)	1 to 5
7	Margolin (Ex. 1006)	§ 103(a)	1 to 5
8	2000 Press Release (Ex. 1004) and 1999 NCI CTC v.2 (Ex. 1017)	§ 103(a)	1 to 5
9	2000 Press Release (Ex. 1004) and Kennedy & Spence (Ex. 1007)	§ 103(a)	1 to 5
10	2000 Press Release (Ex. 1004) and Matsui (Ex. 1008)	§ 103(a)	1 to 5
11	2003 Press Release (Ex. 1003) and Kabbinavar (Ex. 1005)	§ 103(a)	1 to 5

B. The ’115 Patent and its Prosecution History

The ’115 Patent is titled “TREATMENT WITH ANTI-VEGF ANTIBODIES.” The ’115 Patent issued from U.S. Application No. 11/763,263 (the “’263 Application”) which was filed on June 14, 2007. The ’263 Application is a continuation of Application No. 10/857,249 (the “’249 Application”) filed May 28, 2004, and claims priority to Provisional Application No. 60/474,480 (the “’480 Provisional Application”) filed May 30, 2003.

1. The ’115 Patent

The ’115 Patent states that “the invention concerns the treatment of human patients susceptible to or diagnosed with cancer using an anti-VEGF antibody,

preferably in combination with one or more additional anti-tumor therapeutic agents." (Ex. 1001, Abstract.) The '115 Patent also states that "the invention provides an effective approach for treating cancers, partially based on the unexpected results that adding anti-VEGF antibody to a standard chemotherapy results in statistically significant and clinically meaningful improvements among cancer patients." (*Id*. at 3:37-41.) The '115 Patent describes two bevacizumab clinical trials. Example 1 describes a stage III clinical trial in which patients were given either irinotecan/fluorouracil/leucovorin ("IFL") plus bevacizumab or IFL plus placebo. Example 1 teaches the following about how safety was assessed:

> Safety was assessed on the basis of reports of adverse events, laboratory-test results, and vital sign measurements. Adverse events were categorized according to the Common Toxicity Criteria of the National Cancer Institute, version 2, in which a grade of 1 indicates mild adverse events, a grade of 2 moderate adverse events, a grade of 3 serious adverse events, and a grade of 4 life-threatening adverse events. Prespecified safety measures included the incidence of all adverse events, all serious adverse events, and adverse events that have been associated with bevacizumab—hypertension, thrombosis, bleeding of grade 3 or 4, and proteinuria—as well as diarrhea of grade 3 or 4, and changes from baseline in various laboratory values and vital signs.

(*Id*. at 42:24-36.) With respect to gastrointestinal perforation ("GI perforation"), Example 1 discloses:

> Gastrointestinal perforation occurred in six patients (1.5 percent) receiving IFL plus bevacizumab. One patient died as a direct result of this event, whereas the other five

> recovered (three of them were able to restart treatment without subsequent complications). . . . Factors other than the study treatment that may have been associated with gastrointestinal perforation were colon surgery within the previous two months in two patients and peptic-ulcer disease in one patient.

(*Id*. at 46:18-27.) Example 1 teaches that six patients—about 1.5% of the patients—in the bevacizumab arm experienced GI perforations compared to zero patients in the placebo arm, and that one patient died as a result. (*Id*. at 46:18-22.) Example 1 does not indicate that the higher incidence of GI perforation observed in the bevacizumab arm compared to the placebo is statistically significant. (*Id*. at 45:63-64.) It also teaches that the patients in the bevacizumab arm received treatment on average for 40.4 weeks compared to only 27.6 weeks for those in the placebo arm. (*Id*. at 45:59-62.)

Example 1 also discloses that "[o]ne new potential adverse effect that occurred was gastrointestinal perforation" and that GI perforation "was uncommon and had variable clinical presentation." (*Id*. at 47:6-9.)

Example 2 describes a stage II clinical trial in which patients were given either fluorouracil with leucovorin plus bevacizumab or fluorouracil with leucovorin plus placebo. (*Id*. at 47:35-38.)

Example 2 discloses the following about how safety was assessed:

> Safety was assessed from reports of adverse events, laboratory test results, and vital sign measurements. Adverse events and abnormal laboratory results were

> categorized using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), Version 2. Prespecified safety measures included four adverse events of special interest (hypertension, proteinuria, thrombosis, and bleeding) based on findings of previous clinical trials of bevacizumab.

(*Id*. at 48:39-47.) Regarding GI perforation, Example 2 teaches that two patients—about 2% of the patients—in the bevacizumab arm experienced GI perforations at days 110 and 338 of treatment compared to zero patients in the placebo arm, and that one patient died as a result. (*Id*. at 50:49-54.) Both cases were associated with a colonic diverticulum. (*Id.*) Example 2 provides no statistical analysis regarding the difference in the incidence of GI perforation in the bevacizumab arm compared to the placebo arm.

The '115 Patent claims methods of treating cancer patients comprising administering an effective amount of bevacizumab and assessing the patients for GI perforation. Claim 1, which is the only independent claim, recites:

> 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.

(*Id*. at 52:26-29.) Claim 2 is dependent from claim 1 and limits the types of cancer to those explicitly recited. (*Id*. at 52:30-36.) Claim 3 is dependent from claim 1 and requires the additional step of "administering a chemotherapeutic agent." (*Id*. at 52:37-38.) Claim 4 is dependent from claim 3 and limits the type of

chemotherapeutic agent to those explicitly recited. (*Id*. at 52:39-48.) Claim 5 is dependent from claim 1 and requires a specific bevacizumab dosing schedule—"about 5-15 mg/kg every 2-3 weeks." (*Id*. at 52:49-51.)

2. The '115 Patent Prosecution History

The '480 Provisional Application, from which the '115 Patent claims priority, was filed with 44 claims directed to methods of treating cancer using VEGF antibodies alone or in combination with chemotherapeutic agents and articles of manufacture and kits related thereto. (Ex. 1018, '480 Provisional Application, at 86-90.) None of the claims were related to GI perforation or any other adverse event. (*Id*.)

Additionally, the specification of the '480 Provisional Application included no data regarding the incidence of GI perforation in patients receiving bevacizumab. (*See id*.) The specification of the '480 Provisional Application only mentioned GI perforation once—"In addition, bowel perforation, although rare, may be increased in the IFL/rhuMab VEGF arm (Arm2)." (*Id*. at 85.)

The '249 Application, which claims priority from the '480 Provisional Application, was filed with 46 claims directed to methods of treating cancer using VEGF antibodies alone or in combination with chemotherapeutic agents and articles of manufacture and kits related thereto. (Ex. 1019, '249 Application Prosecution History Excerpts, at 79-83.) However, none of the claims in the '249

Application were related to GI perforation or any other adverse event. (*Id*. at 79-83.)

The examiner mailed a Non-Final Office Action on December 14, 2006 (*id*. at 92-110) rejecting all the claims, in part, as anticipated and/or rendered obvious by various prior art references, including Margolin and Kabbinavar. (*Id*. at 95-109.) The application became abandoned on August 23, 2007, for failure to timely file a proper reply to the December 14, 2006 Non-Final Office Action. (*Id*. at 111.)

The '263 Application, which is a continuation of the '249 Application, was filed with 46 claims directed to methods of treating cancer using VEGF antibodies alone or in combination with chemotherapeutic agents and articles of manufacture and kits related thereto. (Ex. 1020, '115 Patent Prosecution History Excerpts, at 76-80.) None of the claims in the '263 Application as originally filed were related to GI perforation or any other adverse event. (*Id*. at 76-80.)

On November 2, 2007, Applicants filed a Preliminary Amendment cancelling claims 1 to 46 and adding new claims 47 to 50. (*Id*. at 89-91.) Claim 47 recited:

> 47. (New) A method for treating cancer in a patient comprising administering an effective amount of anti-VEGF antibody and monitoring the patient for signs or symptoms of gastrointestinal perforation during treatment with the anti-VEGF antibody.

(*Id*. at 90.) The examiner rejected claims 47, 49, and 50 in a Non-Final Office Action mailed December 23, 2008. (*Id*. at 92-102.) The examiner rejected claim 47 under 35 U.S.C. § 112 because the limitation "monitoring the patient for signs or symptoms of gastrointestinal perforation during treatment with the anti-VEGF antibody" constituted new matter without proper written description in the specification. (*Id*. at 94-95.) The examiner argued that the cited support for the new claims "does not disclose any signs or symptoms of gastrointestinal perforation, or methods comprising monitoring patients for signs or symptoms of gastrointestinal perforation." (*Id*. at 96-97.) The examiner also noted that "[t]he specification only discloses that gastrointestinal perforation occurred in 6 patients, of which one died, and that it was an uncommon event, had variable clinical presentations, and may be explained by prior colon surgery or peptic ulcer." (*Id*. at 97.)

The examiner also rejected claim 47 under 35 U.S.C. § 102(b) as being anticipated by Gordon et al. in view of US News & World Report.com, December 10, 2008. (*Id*. at 100.) The examiner noted that "Gordon et al. teach a method for treating cancer in a patient comprising administering rhuMAb VEGF (bevacizumab) and monitoring patients for adverse events during treatment including nausea" and that "[a]s evidenced by US News & World Report.com, nausea is a sign or symptom of gastrointestinal perforation (p. 2, first paragraph),

hence the nausea monitored in the method taught by Gordon et al. is a sign or symptom of gastrointestinal perforation." (*Id*. at 101.)

A personal interview was held on June 1, 2009, during which the "[a]pplicants and Examiner discussed proposed claim amendments to overcome the rejections of new matter . . ., particularly with regards to deleting the terms 'signs or symptoms' and finding an alternative term for 'monitoring'" according to the Examiner's Interview Summary. (*Id*. at 104.)

Applicants amended claim 47 to recite:

> 47. (Currently Amended) A method for treating cancer in a patient comprising administering an effective amount of ~~an anti-VEGF antibody~~ bevacizumab and ~~monitoring~~ assessing the patient for ~~signs or symptoms of~~ gastrointestinal perforation during treatment with ~~the anti-VEGF antibody~~ bevacizumab.

(*Id*. at 107.) Applicants also cancelled claims 48-50 and added new claims 51 to 54. (*Id*.) Applicants noted that claim 47 was amended "to incorporate the subject matter of cancelled claim 50 and to more particularly point out the claimed subject matter applicants intend to pursue in this application." (*Id*. at 109.)

Regarding the Examiner's new matter written description rejection, the applicants explained that "[t]he instant application describes generally how safety was assessed in patients being treated with bevacizumab in the clinical trial described in Examples 1 and 2." (*Id*. at 111-112.) The Applicants further explained:

> As described at page 68, line 1-2, gastrointestinal perforation was a new potential adverse event that occurred in a few patients treated with bevacizumab. . . . Based on these results first disclosed in the instant application, one of ordinary skill in the art would include gastrointestinal perforation as a potential adverse event associated with bevacizumab and, thus, assess patients treated with bevacizumab for gastrointestinal perforation. Accordingly, applicants believe this rejection may properly be withdrawn.

(*Id*. at 113 (emphasis in original).)

Regarding the Examiner's U.S.C. § 102(b) rejection of claim 47, Applicants argued that the rejection should be withdrawn in view of the amended claim because "Gordon does not teach assessing patients being treated with Bevacizumab for gastrointestinal perforation." (*Id*. at 114.) The applicants argued that "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.)

The examiner mailed a Notice of Allowance on August 20, 2009, in which claims 47 to 51 were allowed. (*Id*. at 121.) The examiner provided no substantive explanation for why the claims were allowed. (*Id*. at 121-122.)

C. Claim Construction (37 C.F.R. § 42.104(b)(3))

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable construction in light of the specification of the '115 Patent. The terms in the challenged claims are presumed to take on their ordinary and customary meaning based on the broadest reasonable construction of the claim language in view of the specification.

Claim 1 is reproduced in its entirety above and in the claim charts in Section VII below. Petitioner submits that the step of "assessing the patient for gastrointestinal perforation" in claim 1 should be construed to have its plain and ordinary meaning: "evaluating the patient in any way that may provide information about whether the patient may be experiencing a GI perforation." Petitioner's proposed construction is supported by the specification and the prosecution history, and reflects the practice of qualified physicians who are persons of ordinary skill in the relevant art as explained by Dr. Neugut. (Ex. 1002, Neugut Decl., at ¶¶ 91-94.)

Petitioner's proposed construction is consistent with the intrinsic evidence. The specification does not define "assessing," but the term is used on several occasions consistently with Petitioner's proposed construction:

> For cancer therapy, efficacy in vivo can, for example, be measured by assessing the duration of survival, time to disease progression (TTP), the response rates (RR), duration of response, and/or quality of life.
>
> An interim analysis was scheduled to be performed after 300 patients underwent randomization, at which time an

> unblinded, independent data-monitoring committee was to assess the safety of IFL plus bevacizumab . . . .
>
> In addition, patients completed the Functional Assessment of Cancer Therapy—Colorectal (FACT-C), Version 4, a validated instrument for assessing quality of life (QOL) in colorectal cancer patients, at baseline and prior to each treatment cycle until disease progression.

(Ex. 1001, at 10:44-47); (*Id*. at 41:40-46); (*Id*. at 48:33-38). In each of these instances, 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." Moreover, Dr. Neugut explains that in actual practice the way one assesses for GI perforation is by evaluating the patient. (Ex. 1002, Neugut Decl., at ¶¶ 91-92; Ex. 1007, at 9.)

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. 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.) Petitioner's proposed construction reflects this aspect by simply requiring "evaluating the patient."

Moreover, it is logical that when a medical professional assesses a patient for an adverse event, the medical professional performs an evaluation that may provide him with information about whether the patient may be experiencing that adverse event. (*Id*. at ¶ 91.) That is supported by the specification's description of how "safety," for example, was "assessed"—"from reports of adverse events, laboratory test results, and vital sign measurements." (Ex. 1001, at 48:40-41.) Reports of adverse events, laboratory test results, and vital signs were part of the evaluation because each may provide information that allows the evaluation of safety. Petitioner's proposed construction reflects this aspect of the claim language at issue by reciting "in a way that may provide information about whether the patient may be experiencing GI perforation."

Lastly, assessing a patient for an adverse event does not require any particular result or a confirmed diagnosis. As Dr. Neugut explains, a medical professional who evaluates a patient for an adverse event, performs the step of "assessing the patient" irrespective of the outcome of the assessment or whether a definitive diagnosis is reached. (Ex. 1002, Neugut Decl., at ¶ 93.) That is consistent with Petitioner's proposed construction which merely requires that the patient is evaluated without requiring a particular diagnosis or outcome or particular steps to be undertaken for the evaluation.

Thus, Petitioner's proposed construction is supported by the intrinsic evidence and is consistent with the actual practice in the relevant art at the time of the alleged invention. For these reasons, we respectfully request that the panel adopt Petitioner's construction.

VII. STATEMENT OF THE REASONS FOR THE RELIEF REQUESTED (37 C.F.R. §§ 42.104(b)(4) and (5))

A. Level of Ordinary Skill in the Art

A person of ordinary skill in the art is presumed to be aware of all pertinent art, think along the line of conventional wisdom, and possess ordinary creativity in the pertinent field. A person of ordinary skill in the art is possessed of "common sense" and is "not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). The education level of a person of ordinary skill in the art to the '115 Patent would include a medical degree and specialization in oncology.

Moreover the person would have at least five years of experience in the diagnosis and treatment of cancer. (Ex. 1002, Neugut Decl. at ¶ 38.)

B. The Prior Art

Genentech Press Release dated May 19, 2003 ("2003 Press Release") is titled "Phase III Trial of Avastin Plus Chemotherapy Markedly Extends Survival of Metastatic Colorectal Cancer Patients." (Ex. 1003, at 1.) The 2003 Press Release was published before May 30, 2003, the earliest possible effective filing date of the '115 Patent. It is prior art under 35 U.S.C. § 102(a) in view of the earliest filing date recited on the face of the '115 Patent. The 2003 Press Release was not disclosed to the U.S. Patent and Trademark office ("PTO") and was not considered by the examiner during examination of the '115 Patent. To Petitioner's knowledge, the 2003 Press Release teaches that using bevacizumab plus chemotherapy is efficacious at treating colorectal cancer. (*Id*. at 1.) The 2003 Press Release also explicitly teaches that "[g]astrointestinal perforation, although uncommon, may be increased by the addition of Avastin to chemotherapy."[1] (*Id*. at 2.)

Genentech Press Release dated May 21, 2000 ("2000 Press Release") is titled "Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer." (Ex. 1004, at 1.) The

[1] Avastin is the brand name for bevacizumab.

2000 Press Release was published more than one year before May 30, 2003, the earliest possible effective filing date of the '115 Patent and is prior art under 35 U.S.C. § 102(b). To Petitioner's knowledge, the 2000 Press Release was not disclosed to the PTO and was not considered by the examiner during examination of the '115 Patent.

The 2000 Press Release teaches that bevacizumab at 5 mg/kg and 10 mg/kg every two weeks plus chemotherapy is efficacious at treating colorectal cancer. (*Id*. at 1.) The 2000 Press Release also teaches that "adverse events were primarily those expected with 5-FU/leucovorin chemotherapy." (*Id*. at 2.) Fever, chills, headache, hypertension, infection, rash, nosebleeds, and thrombosis were observed at a higher incidence in the bevacizumab arms. (*Id*.)

Kabbinavar is titled "Phase II, Randomized Trial Comparing Bevacizumab Plus Fluorouracil (FU)/Leucovorin (LV) with FU/LV Alone in Patients with Metastatic Colorectal Cancer" and published on January 1, 2003. (Ex. 1005, at 2.) Kabbinavar was published before May 30, 2003, the earliest possible effective filing date of the '115 Patent. It is prior art under 35 U.S.C. § 102(a) in view of the earliest filing date recited on the face of the patent. Kabbinavar was considered by the examiner during examination of the '249 application.

Kabbinavar teaches that using bevacizumab plus chemotherapy (FU/LV) is efficacious at treating colorectal cancer. (*Id*. at 2 and 6.) Kabbinavar teaches

administering bevacizumab at 5 to 10 mg/kg every two weeks. (*Id*. at 2, Abstract.) Kabbinavar also teaches that patients receiving bevacizumab plus chemotherapy experience various adverse events described in Table 5, including grade 3/4 GI hemorrhaging, abdominal pain, and diarrhea. (*Id*. at 5, Table 5.) Specifically, Table 5 shows that 6% and 16% of patients in the 5mg/kg and 10mg/kg study groups, respectively, experienced GI hemorrhage compared to 0% for the placebo group. (*Id*.) Three of the patients in the 10mg/kg study group experienced grade 3/4 GI hemorrhaging. (*Id*.) Additionally, although a similar percentage of patients experience abdominal pain in the study and placebo groups, a higher number of patients experienced grade 3/4 abdominal pain in the bevacizumab groups compared to placebo. (*Id*.) Accordingly, Kabbinavar teaches that "[b]leeding, hypertension, and thrombosis have been observed in other clinical trials of bevacizumab and occurred at an increased incidence in the bevacizumab arms in this trial." (*Id*. at 5.)

Margolin is titled "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" and was published on February 1, 2001. (Ex. 1006, at 2.) Margolin was published more than one year before May 30, 2003, the earliest possible effective filing date of the '115 Patent and is prior art under 35 U.S.C. § 102(b).

Margolin was considered by the examiner during examination of the '249 Application.

Margolin describes a Phase I clinical study that investigated "the safety and pharmacokinetics of weekly intravenous (IV) rhuMAbVEGF with one of three standard chemotherapy regimens" in cancer patients, including doxorubicin, carboplatin plus paclitaxel, and fluorouracil plus leucovorin.[2] (*Id*. at 2, Abstract.) Margolin also teaches administering bevacizumab weekly at 3 mg/kg and every two weeks at 6 mg/kg. (*Id*. at 2, Abstract and 5, left-hand column.) Margolin teaches that "[t]hree patients (one on each chemotherapy regimen) experienced antitumor responses and continued to be treated beyond the 8 weeks of treatment specified in the protocol." (*Id*. at 5.)

The **1999 NCI CTC v.2** provides criteria for grading adverse events associated with cancer therapy. (Ex. 1017.) The 1999 NCI CTC v.2 was accompanied by the 1999 NCI CTC v.2 Manual which helps explain the adverse event grading system. (Ex. 1016, at 7.) The 1999 NCI CTC v.2 and the 1999 NCI CTC v.2 Manual were published more than one year before May 30, 2003, the earliest possible effective filing date of the '115 Patent and are prior art under 35 U.S.C. § 102(b). The 1999 NCI CTC v.2 is referenced in the '115 Patent (Ex.

[2] rhuMAbVEGF is bevacizumab.

1001, at 42:24-30), but to Petitioner's knowledge was not considered by the examiner during examination of the '115 Patent.

The 1999 NCI CTC v.2 Manual explains:

> The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) were developed in 1982 for use in adverse drug experience reporting, study adverse event summaries, Investigational New Drug (IND) reports to the Food and Drug Administration (FDA), and publications. The CTC have been used widely for collecting treatment-related adverse event data to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures.

(Ex. 1016, at 7.) The 1999 NCI CTC v.2 Manual identifies 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." (*Id*. at 4.) The 1999 NCI CTC v.2 Manual instructs that a grade of "4" corresponds to a "[l]ife-threatening or disabling adverse event." (*Id*.) The 1999 NCI CTC v.2 instructs that GI toxicities which result in GI perforation are graded a 4 on the scale. (Ex. 1017, at 10-13.)

Kennedy & Spence is titled "Gastrointestinal Emergencies" and was published in 2002 as Chapter 6 in Oncologic Emergencies. (Ex. 1007.) Kennedy & Spence was published before May 30, 2003, the earliest possible effective filing date of the '115 Patent. It is prior art under 35 U.S.C. § 102(a) in view of the earliest filing date recited on the face of the '115 Patent. To Petitioner's

knowledge, Kennedy & Spence was not considered by the examiner during examination of the '115 Patent.

Kennedy & Spence teaches:

> 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. Perforation due to peptic ulceration is also common and is often associated with the use of non-steroidal anti-inflammatory drugs or corticosteroids.

(*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 also teaches that "[t]ypically the patient with gastrointestinal perforation complains of a sudden onset of abdominal pain, nausea, vomiting and fever." (*Id*.)

Matsui is titled "Efficacy of Vascular Endothelial Growth Factor in the Treatment of Experimental Gastric Injury" and was published in Volume 66 of the scientific journal DIGESTION in 2002. (Ex. 1008, at 3.) Matsui was published before May 30, 2003, the earliest possible effective filing date of the '115 Patent. It is prior art under 35 U.S.C. § 102(a) in view of the earliest filing date recited on the face of the '115 Patent. To Petitioner's knowledge, Matsui was not considered by the examiner during examination of the '115 patent.

Matsui "investigated whether VEGF is expressed during the course of experimental gastric injury and whether injury is exacerbated by neutralization with anti-VEGF antibodies." (*Id*. at 4, left-hand column.) Matsui teaches that VEGF, the target protein which is inactivated by bevacizumab, is involved in the repair of GI tissue damage. (*Id*. at 9, left-hand column ("VEGF appears to be an important endogenous mediator of the healing process for gastric injury.").) Matsui also teaches 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, right-hand column.)

C. Anticipation

All the claims of the '115 Patent are anticipated at least by the 2000 Press Release, Kabbinavar, or Margolin because each reference teaches expressly or inherently all the limitations of claims 1 to 5. Additionally, claims 1 to 4 are also anticipated by the 2003 Press Release because it teaches expressly or inherently all the limitations of those claims. Therefore, claims 1 to 5 of the '115 Patent should be cancelled.

1. Legal Standard

Anticipation of a patent requires that a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *In re Cruciferous*

Sprout Litig., 301 F.3d 1343, 1349 (Fed. Cir. 2002). When every material element of claimed subject matter is disclosed by a reference, an additional reference may be relied on to show that the primary reference has an enabling disclosure. *In re Samour*, 571 F.2d 559, 562-653 (C.C.P.A 1978). "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *See In re Preda*, 401 F.2d 825, 826 (C.C.P.A 1968). An inherent disclosure requires that "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharm., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). Newly discovered results or a new benefit of a known process directed to the same purpose are not patentable because such results are inherent. *Id.*; *see also In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007) (citing *Bristol-Myers*, 246 F.3d at 1376).

2. Ground 1: Kabbinavar Anticipates All the Claims of the '115 Patent

Kabbinavar anticipates claims 1 to 5 of the '115 Patent because it expressly or inherently discloses all the limitations of claims 1 to 5 as shown in the following chart and explained below.

Claim Limitations	**Disclosed in Kabbinavar 2003**
1. A method for treating cancer in a	"This phase II trial investigated the

Claim Limitations	Disclosed in Kabbinavar 2003
patient comprising administering an effective amount of bevacizumab	safety and efficacy of two doses of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, plus fluorouracil (FU)/leucovorin (LV) versus FU/LV alone in patients with metastatic colorectal cancer." (Ex. 1005 at 2, Abstract (emphasis added).) "Compared with the FU/LV control arm, treatment with bevacizumab (at both dose levels) plus FU/LV resulted in higher response rates . . ., longer median time to disease progression . . ., and longer median survival . . . ." (*Id.* (emphasis added).) "[P]atients in the two experimental arms received bevacizumab (5 or 10 mg/kg) . . . every 2 weeks until disease progression or for up to 48 weeks . . . ." (*Id*. at 3 (emphasis added).)
and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.	"Safety evaluations included physical examinations, laboratory tests (hematology, chemistry and electrolytes, and urinalysis), and ECOG performance status. Vital signs were monitored before, during, and after bevacizumab infusions (before chemotherapy for patients in the control arm). Patients were questioned regarding concomitant medication use, adverse events, and changes in menstrual cycles (if applicable)." (*Id*. at 3 (emphasis added).) "More patients in the bevacizumab arms experienced at least one National Cancer Institute common toxicity criteria (version 1) grade 3 or 4 adverse

Claim Limitations	Disclosed in Kabbinavar 2003
	event." (*Id*. at 5, left-hand column (emphasis added).) "Bleeding, hypertension, and thrombosis have been observed in other clinical trials of bevacizumab and occurred at an increased incidence in the bevacizumab arms in this trial." (*Id*., left-hand column (emphasis added).) "Three patients in the 10-mg/kg arm had a grade 3 or 4 gastrointestinal hemorrhage." (*Id*., right-hand column (emphasis added).)
2. The method of claim 1, wherein the cancer is colorectal cancer, ...	"This phase II trial investigated the safety and efficacy of two doses of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, plus fluorouracil (FU)/leucovorin (LV) versus FU/LV alone in patients with metastatic colorectal cancer." (*Id*. at 2, Abstract (emphasis added).)
3. The method of claim 1, wherein the method further comprises administering a chemotherapeutic agent.	"The goal of this trial was to investigate the safety, efficacy, and pharmacokinetics of bevacizumab plus fluorouracil (FU)/leucovorin (LV) . . . ." (*Id*. (emphasis added).)
4. The method of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of . . . folio [sic] acid analogs, pyrimidine analogs, ...	"The goal of this trial was to investigate the safety, efficacy, and pharmacokinetics of bevacizumab plus fluorouracil (FU)/leucovorin (LV) . . . ." (*Id*. (emphasis added).)
5. The method of claim 1, wherein the bevacizumab is administered to the patient at about 5-15 mg/kg every 2-3	"[P]atients in the two experimental arms received bevacizumab (5 or 10 mg/kg) . . . every 2 weeks until disease

Claim Limitations	Disclosed in Kabbinavar 2003
weeks.	progression or for up to 48 weeks." (*Id*. at 3 (emphasis added).)

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 2, Abstract.) Thus, Kabbinavar discloses the claim 1 limitations (1) "[a] method for treating cancer in a patient" and (2) "comprising administering an effective amount of bevacizumab."

Additionally, Kabbinavar teaches that the patients underwent "physical examinations" and "laboratory tests" and were "questioned about . . . adverse effects" during treatment with bevacizumab. (*Id*. at 3.) As Dr. Neugut explains, patients undergoing the evaluations described in Kabbinavar as part of cancer therapy are assessed for GI perforation as required by claim 1. (Ex. 1002, Neugut Decl., at ¶ 112.) Moreover, it was the standard of care at the time to assess cancer patients receiving therapy for GI perforation. (*Id*. at ¶¶ 105-108.) Therefore, Kabbinavar explicitly discloses the claim 1 limitation "assessing the patient for gastrointestinal perforation during treatment with bevacizumab." Thus, Kabbinavar anticipates claim 1.

Claim 2 depends from claim 1 and limits the types of cancer to those explicitly recited in the claim, including colorectal cancer. (Ex. 1001, at 52:30-36.)

Kabbinavar also discloses that the patients in the clinical trial were colorectal cancer patients. (Ex. 1005, at 2, Abstract.) Therefore, Kabbinavar discloses the additional limitation of claim 2 and anticipates claim 2.

Claim 3 depends from claim 1 and requires the additional limitation of "administering a chemotherapeutic agent." (Ex.1001, at 52:37-38.) Claim 4 depends from claim 3 and limits the chemotherapeutic agent to the agents explicitly recited in the claim, including "pyrimidine analogs" and "folic acid analogs." (*Id*. at 52:39-48.) Kabbinavar discloses administering bevacizumab in combination with the chemotherapeutic agents fluorouracil and leucovorin. (Ex. 1005 at 60, Abstract.) Fluorouracil is a pyrimidine analog and leucovorin is a folic acid analog. (Ex. 1002, Neugut Decl. at ¶ 114.) Therefore, Kabbinavar discloses the additional limitations of claims 3 and 4 and anticipates those claims.

Claim 5 depends from claim 1 and requires that "the bevacizumab is administered to the patient at about 5-15mg/kg every 2-3 weeks." (Ex.1001, at 52:49-51.) Kabbinavar discloses administering bevacizumab at 5 or 10 mg/kg every two weeks to colorectal cancer patients (Ex. 1005, at 6, left-hand column). Therefore, Kabbinavar discloses the additional limitation of claim 5 and anticipates the claim.

3. Ground 2: Margolin Anticipates All the Claims of the '115 Patent

Margolin anticipates claims 1 to 5 of the '115 Patent because it expressly or inherently discloses all the limitations of claims 1 to 5 as shown in the following chart and explained below.

Claim Limitations	**Disclosed in Margolin**
1. A method for treating cancer in a patient	"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." (Ex. 1006, at 2, Title (emphasis added).) "Three responding patients continued treatment with rhuMAbVEGF and chemotherapy . . . ." (*Id*. at 2, Abstract (emphasis added).) "Three patients (one on each chemotherapy regimen) experienced antitumor responses and continued to be treated beyond the 8 weeks of treatment specified in the protocol." (*Id*. at 5, left-hand column (emphasis added).) "rhuMAbVEGF, 3 mg/kg IV, was administered weekly for 8 weeks." (*Id*. at 2, Abstract (emphasis added).) "Patients who continued rhuMAbVEGF were enrolled onto a separate extension study, in which the antibody was administered at twice the dose every 2
comprising administering an effective amount of bevacizumab	

Claim Limitations	Disclosed in Margolin
	weeks along with chemotherapy on the original schedule." (*Id*. at 5, left-hand column (emphasis added).)
and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.	"[W]eekly during therapy, all patients had clinical laboratory tests . . . . Toxicity evaluation, using the national Cancer Institute common toxicity criteria (original version) was recorded weekly." (*Id*. at 4, left-hand column (emphasis added).) "Table 3 lists the details of toxicities by chemotherapeutic regimen." (*Id*., right-hand column (emphasis added).)
2. The method of claim 1, wherein the cancer is colorectal cancer, . . . breast cancer, . . . renal cancer, . . . soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, . . . mesothelioma, ...	Table 2 reports that some patients were suffering from colon cancer, breast cancer, sarcoma, renal cancer, mesothelioma, and carcinoid carcinoma among other cancer types. (*Id*. at 5, left-hand column (emphasis added).)
3. The method of claim 1, wherein the method further comprises administering a chemotherapeutic agent.	"rhuMAbVEGF, 3 mg/kg IV, was administered weekly for 8 weeks with (1) doxorubicin 50 mg/m^2 every 4 weeks; (2) carboplatin at area under the curve of 6 plus paclitaxel 175 mg/m^2 every 4 weeks; and (3) fluorouracil (5-FU) 500 mg/m^2 with leucovorin 20 mg/m2 weekly, weeks 1 to 6 every 8 weeks." (*Id*. at 2, Abstract (emphasis added).)
4. The method of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of . . . folio [sic] acid analogs, pyrimidine analogs, . . . antibiotics, . . . platinum	"rhuMAbVEGF, 3 mg/kg IV, was administered weekly for 8 weeks with (1) doxorubicin 50 mg/m^2 every 4 weeks; (2) carboplatin at area under the curve of 6 plus paclitaxel 175 mg/m^2

Claim Limitations	Disclosed in Margolin
coordination complexes	every 4 weeks; and (3) fluorouracil (5-FU) 500 mg/m^2 with leucovorin 20 mg/m^2 weekly, weeks 1 to 6 every 8 weeks." (*Id*., Abstract (emphasis added).)
5. The method of claim 1, wherein the bevacizumab is administered to the patient at about 5-15 mg/kg every 2-3 weeks.	"rhuMAbVEGF, 3 mg/kg IV, was administered weekly for 8 weeks." (*Id*., Abstract (emphasis added).) "Patients who continued rhuMAbVEGF were enrolled onto a separate extension study, in which the antibody was administered at twice the dose every 2 weeks along with chemotherapy on the original schedule." (*Id*. at 5, left-hand column (emphasis added).)

Margolin discloses treating patients suffering from various cancer types with bevacizumab. (*Id*. at 3, right-hand column ("Patients were required to have advanced solid tumors for which treatment with one of the three chemotherapy regimens in this study was planned.").) Margolin also discloses that some of the patients receiving bevacizumab, "experienced antitumor responses and continued to be treated beyond the 8 weeks of treatment specified in the protocol." (*Id*. at 5, left-hand column.) Thus, Margolin discloses the claim 1 limitations (1) "[a] method for treating cancer in a patient" and (2) "comprising administering an effective amount of bevacizumab."

Additionally, Margolin teaches that the patients underwent "physical examination" and "laboratory evaluation" and that toxicity was monitored. (*Id*. at

4, left-hand column.) As Dr. Neugut explains, patients undergoing the evaluations described in Margolin as part of cancer therapy are assessed for GI perforation as required by claim 1. (Ex. 1002, Neugut Decl., at ¶ 118.) Moreover, it was the standard of care at the time to assess cancer patients receiving therapy for GI perforation. (Ex. 1002, Neugut Decl., at ¶¶ 105-108.) Therefore, Margolin explicitly discloses the claim 1 limitation "assessing the patient for gastrointestinal perforation during treatment with bevacizumab." Thus, Margolin anticipates claim 1.

Claim 2 depends from claim 1 and limits the types of cancer to those explicitly recited in the claim, including colorectal cancer. (Ex. 1001, at 52:30-36.) Margolin also discloses that the patients in the clinical trial were colorectal cancer patients. (Ex. 1006 at 5, Table 2.) Therefore, Margolin discloses the additional limitation of claim 2 and anticipates the claim.

Claim 3 depends from claim 1 and requires the additional limitation of "administering a chemotherapeutic agent." (Ex. 1001, at 52:37-38.) Claim 4 depends from claim 3 and limits the chemotherapeutic agent to the agents explicitly recited, including "pyrimidine analogs," "folic acid analogs," "antibiotics," and "platinum coordination complexes" (*Id*. at 52:39-48.) Margolin also discloses administering bevacizumab in combination with the chemotherapeutic agents fluorouracil, leucovorin, doxorubicin, carboplatin, and

paclitaxel. (Ex. 1006 at 2, Abstract.) Fluorouracil is a pyrimidine analog and leucovorin is a folic acid analog. (Ex. 1002 at ¶ 120.) Also, doxorubicin is an antibiotic and carboplatin is a platinum coordination complex. (Ex. 1002 at ¶ 120.) Therefore, Margolin discloses the additional limitations of claims 3 and 4 and anticipates those claims.

Claim 5 depends from claim 1 and requires that "the bevacizumab is administered to the patient at about 5-15mg/kg every 2-3 weeks." (Ex. 1001, at 52:49-51.) Margolin also discloses administering bevacizumab at 3 mg/kg every week or 6 mg/kg every two weeks. (Ex. 1006, at 4, left-hand column; 5, left-hand column). Therefore, Margolin discloses the additional limitation of claim 5 and anticipates the claim.

4. Ground 3: The 2000 Press Release Anticipates All the Claims of the '115 Patent

The 2000 Press Release anticipates claims 1 to 5 of the '115 Patent because it expressly or inherently discloses all the limitations of claims 1 to 5 as shown in the following chart and explained below.

Claim Limitations	**Disclosed in 2000 Press Release**
1. A method for treating cancer in a patient	"Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer" (Ex.1004, at 1, Title (emphasis added).) "We are encouraged by these preliminary Phase II results that
comprising administering an effective amount of bevacizumab	

Claim Limitations	Disclosed in 2000 Press Release
	demonstrate that the addition of anti-VEGF to standard chemotherapy appears to be an active therapy in metastatic colorectal cancer . . . ." (*Id*. at 1 (emphasis added).) "The response rates were 40 percent . . . in the low dose and 24 percent . . . in the high dose anti-VEGF combination arms, compared to a response rate of 17 percent . . . in the 5-FU/leucovorin alone arm." (*Id*. at 2 (emphasis added).) "Time to disease progression was 9.0 months in the low dose and 7.2 months in the high dose combination arms, compared to 5.2 months in the 5-FU/leucovorin alone arm." (*Id*. (emphasis added).) "Patients were randomized into one of three treatment arms receiving either anti-VEGF at 5 mg/kg (low dose) or anti-VEGF at 10 mg/kg (high dose), every two weeks . . . ." (*Id*. (emphasis added).)
and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.	"Safety . . . data . . . were presented . . . ." (*Id*. at 1 (emphasis added).) "Anti-VEGF was generally well tolerated and adverse events were primarily those expected with 5-FU/leucovorin chemotherapy. Some mild to moderate adverse events that appeared more in the anti-VEGF arms than with chemotherapy alone included fever, chills, headache, hypertension,

Claim Limitations	Disclosed in 2000 Press Release
	infection, and rash. Nosebleeds occurred in 16 of 35 patients in the low dose arm and 17 of 32 patients in the high dose arm (five of 35 in the 5-FU/leucovorin alone arm). There were 13 reported incidents of thrombosis . . . that may have been attributed to anti-VEGF." (*Id*. at 2-3 (emphasis added).)
2. The method of claim 1, wherein the cancer is colorectal cancer, ...	"Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Patients" (*Id*. at 1, Title (emphasis added).)
3. The method of claim 1, wherein the method further comprises administering a chemotherapeutic agent.	"Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Patients" (*Id*. at 1, Title (emphasis added).)
4. The method of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of . . . folio [sic] acid analogs, pyrimidine analogs, ...	"Patients were randomized into one of three treatment arms receiving either anti-VEGF at 5 mg/kg (low dose) or anti-VEGF at 10 mg/kg (high dose), every two weeks until disease progression, in combination with 5-FU/leucovorin chemotherapy, or 5-FU/leucovorin alone." (*Id*. at 2 (emphasis added).)
5. The method of claim 1, wherein the bevacizumab is administered to the patient at about 5-15 mg/kg every 2-3 weeks	"Patients were randomized into one of three treatment arms receiving either anti-VEGF at 5 mg/kg (low dose) or anti-VEGF at 10 mg/kg (high dose), every two weeks . . . ." (*Id*. (emphasis added).)

The 2000 Press Release 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 2.) Thus, the 2000 Press Release discloses the claim 1 limitations (1) "[a] method for treating cancer in a patient" and (2) "comprising administering an effective amount of bevacizumab."

Additionally, the 2000 Press Release teaches that adverse events were observed during the clinical trial as described in the claim chart above. For example, the 2000 Press Release teaches that "safety" data was collected (*id*. at 1) and reports that fever, chills, headache, hypertension, infection, rash, nose bleeds, and thrombosis were observed. (*Id*. at 2-3.) As Dr. Neugut explains, because safety was investigated, the patients in the study were assessed for any adverse events, including GI perforation. (Ex. 1002, Neugut Decl., at ¶ 125.) Indeed, it was the standard of care at the time to assess cancer patients receiving cancer therapy for GI perforation. (Ex. 1002, Neugut Decl., at ¶¶ 105-108.) Therefore, the 2000 Press Release explicitly discloses the claim 1 limitation "assessing the patient for gastrointestinal perforation during treatment with bevacizumab." Thus, the 2000 Press Release anticipates claim 1.

Claim 2 depends from claim 1 and limits the types of cancer to those explicitly recited in the claim, including colorectal cancer. (Ex. 1001, at 52:30-36.)

The 2000 Press Release also discloses that the patients in the clinical trial were colorectal cancer patients. (Ex. 1004, at 1, Title.) Therefore, the 2000 Press Release discloses the additional limitation of claim 2 and anticipates the claim.

Claim 3 depends from claim 1 and requires the additional limitation of "administering a chemotherapeutic agent." (Ex. 1001, at 52:37-38.) Claim 4 depends from claim 3 and limits the chemotherapeutic agent to the agents explicitly recited, including "pyrimidine analogs" and "folic acid analogs." (*Id*. at 52:39-48.) The 2000 Press Release also discloses administering bevacizumab in combination with the chemotherapeutic agents fluorouracil and leucovorin. (Ex. 1004, at 2.) Fluorouracil is a pyrimidine analog and leucovorin is a folic acid analog. (Ex. 1002, Neugut Decl., at ¶ 127.) Therefore, the 2000 Press Release discloses the additional limitations of claims 3 and 4 and anticipates those claims.

Claim 5 depends from claim 1 and requires that "the bevacizumab is administered to the patient at about 5-15mg/kg every 2-3 weeks." (Ex. 1001, at 52:49-51.) The 2000 Press Release also discloses administering bevacizumab at 5 or 10 mg/kg every two weeks to colorectal cancer patients (Ex. 1004, at 2). Therefore, the 2000 Press Release discloses the additional limitation of claim 5 and anticipates the claim.

5. Ground 4: The 2003 Press Release Anticipates Claims 1 to 4 of the '115 Patent.

The 2003 Press Release anticipates claims 1 to 4 of the '115 Patent because it expressly or inherently discloses all the limitations of claims 1 to 4 as shown in the following chart and explained below.

Claim Limitations	**Disclosed in 2003 Press Release**
1. A method for treating cancer in a patient comprising administering an effective amount of bevacizumab	"Genentech, Inc. . . . today announced that Phase III study of Avastin . . . plus chemotherapy in previously-untreated metastatic colorectal cancer patients met its primary endpoint of improving overall survival. The magnitude of the benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary endpoints of progression-free survival, response rate, and duration of response." (Ex. 1003, at 1 (emphasis added).)
and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.	"While bleeding, thrombosis, asymptomatic proteinuria and hypertension were identified in Phase II studies as possible safety events, only Grade 3 hypertension, easily managed with oral medications, was clearly increased in this Phase II study. Gastrointestinal perforation, although uncommon may be increased by the addition of Avastin to chemotherapy." (*Id*. at 2 (emphasis added).)
2. The method of claim 1, wherein the cancer is colorectal cancer, ...	"Genentech, Inc. . . . today announced that Phase III study of Avastin . . . plus chemotherapy in previously-untreated metastatic colorectal cancer patients

Claim Limitations	**Disclosed in 2003 Press Release**
	met its primary endpoint of improving overall survival." (*Id*. at 1 (emphasis added).)
3. The method of claim 1, wherein the method further comprises administering a chemotherapeutic agent.	"This multi-center study enrolled more than 900 patients, and randomized 800 patients to receive either Avastin plus standard of care chemotherapy (5-FU/leucovorin/CPT-11 called the Saltz regimen) or the Saltz regimen plus an Avastin placebo." (*Id*. at 2 (emphasis added).)
4. The method of claim wherein the chemotherapeutic agent is selected from the group consisting of . . . folio[sic] acid analogs, pyrimidine analogs, . . . topoisomerase inhibitor, ...	"This multi-center study enrolled more than 900 patients, and randomized 800 patients to receive either Avastin plus standard of care chemotherapy (5-FU/leucovorin/CPT-11 called the Saltz regimen) or the Saltz regimen plus an Avastin placebo." (*Id*. at 2 (emphasis added).)

The 2003 Press Release discloses that administering bevacizumab in combination with the standard of care chemotherapy at the time—i.e., 5-FU/leucovorin/CPT-11—improved overall survival, progression-free survival, response rate, and duration of response in patients with colorectal cancer. (*Id*. at 1.) The precise amount of bevacizumab dosed in the clinical trial is not specified, but the skilled artisan would have been enabled to administer an effective amount because effective amounts of bevacizumab had been published by at least Kabbinavar, Margolin, and the 2000 Press Release as described above. When

every material element of claimed subject matter is disclosed by a reference, an additional reference may be relied on to show that the primary reference has an enabling disclosure. *See In re Samour*, 571 F.2d at 562-563. Therefore, the 2003 Press Release discloses the claim 1 limitations (1) "[a] method for treating cancer in a patient" and (2) "comprising administering an effective amount of bevacizumab." Thus, the 2003 Press Release anticipates claim 1.

Additionally, the 2003 Press Release teaches that adverse events were observed during the clinical trial. For example, the 2003 Press Release teaches that "Grade 3 hypertension . . . was clearly increased in this Phase III study" and that "[g]astrointestinal perforation, although uncommon, may be increased by the addition of Avastin to chemotherapy." (*Id*. at 2.) The disclosure that some patients were observed to have GI perforation indicates that the patients in the clinical trial were assessed for GI perforation. Indeed, it was the standard of care at the time to assess cancer patients receiving cancer therapy for GI perforation. (Ex. 1002, Neugut Decl., at ¶¶ 105-108.) Therefore, the 2003 Press Release explicitly discloses the claim 1 limitation "assessing the patient for gastrointestinal perforation during treatment with bevacizumab."

Claim 2 depends from claim 1 and limits the types of cancer to those explicitly recited, including colorectal cancer. (Ex. 1001, at 52:30-36.) Additionally, the 2003 Press Release discloses that the patients in the clinical trial

were colorectal cancer patients. (Ex. 1003, at 1.) Therefore, the 2003 Press Release discloses the additional limitation of claim 2 and anticipates the claim.

Claim 3 depends from claim 1 and requires the additional limitation of "administering a chemotherapeutic agent." (Ex. 1001, at 52:37-38.) Claim 4 depends from claim 3 and limits the chemotherapeutic agent to the agents explicitly recited, including "pyrimidine analogs," "folic acid analogs," and "topoisomerase inhibitors." (*Id*. at 52:39-48.) Additionally, the 2003 Press Release discloses administering bevacizumab in combination with the standard of care chemotherapy at the time—i.e., 5-FU/leucovorin/CPT-11. (Ex. 1003, at 2.) It was known at the time of the alleged invention that 5-FU (fluorouracil) is a pyrimidine analog, leucovorin is a folic acid analog, and CPT-11 (irinotecan) is a topoisomerase inhibitor. (Ex. 1002, Neugut Decl., at ¶ 134.) Therefore, the 2003 Press Release discloses the additional limitations of claims 3 and 4 and anticipates those claims.

D. Obviousness

Claims 1 to 5 of the '115 Patent would have been obvious over any of the 2000 Press Release, Kabbinavar, or Margolin alone and also over various combinations of the prior art, including the 2003 Press Release, the 1999 NCI CTC v.2, Kabbinavar, and Kennedy & Spence, as explained in the following grounds. Therefore, claims 1 to 5 of the '115 Patent should be cancelled.

1. Legal Standard

A patent claim is invalid under 35 U.S.C. § 103(a) if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. The obviousness analysis includes the following factors: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the prior art and the claimed subject matter; and (4) any objective evidence of nonobviousness, also known as secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Secondary considerations, including long-felt need, failure of others, unexpected results, commercial success, copying, licensing, and industry praise, may provide "powerful tools for courts faced with the difficult task of avoiding subconscious reliance on hindsight." *Mintz v. Dietz & Watson Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). In addition, the patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the claim. *In re Kao*, 639 F.3d 1057, 1068, 1072 (Fed. Cir. 2011)

2. Ground 5: Kabbinavar Renders Claims 1 to 5 Obvious.

Kabbinavar teaches or suggests every limitation of claims 1 to 5 in view of the knowledge of the skilled artisan. (Ex. 1002, Neugut Decl., ¶ 136.) As explained for Ground 2, Kabbinavar expressly discloses (1) administering an effective amount of bevacizumab to treat cancer patients and (2) assessing the patient for GI perforation during treatment with bevacizumab. To 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.

As explained by Dr. Neugut, the standard of care at the time of the alleged invention was to observe the health of cancer patients undergoing cancer therapy and, in particular, to assess whether the patients were experiencing any adverse events caused by the therapy, including GI perforation. (*Id*. at ¶ 105-108.) As 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 ¶¶ 106-107). The 1999 NCI CTC v.2 is evidence that it was the standard of care at the time to assess patients receiving cancer therapy for GI perforation. (Ex. 1002, Neugut Decl., at ¶ 76; Ex. 1017, at 10-13.) The 1999 NCI CTC v.2 grades GI toxicity a "4" on the

severity scale if the patient has GI perforation and therefore, discloses that GI perforation might occur in patients receiving cancer therapy. (Ex. 1002, Neugut Decl., at ¶¶ 76 and 103; Ex. 1017, at 10-13.) As Dr. Neugut explains, the skilled artisan "would have understood from that teaching that patients receiving cancer therapy should be assessed for GI perforation in order to provide safe treatment and to properly record the severity of GI adverse events." (Ex. 1002, Neugut Decl., at ¶ 103.)

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*.)

The fact that the patients in the two clinical trials described in the '115 Patent were assessed for GI perforation by their physicians provides additional

evidence that assessing cancer patients receiving bevacizumab therapy for adverse events including GI perforation was the standard of care at the time of the invention. As discussed, the '115 Patent discloses that medical professionals identified eight patients who experienced GI perforations in two clinical trials (Ex. 1001, at 46:18-19; 50:49-51), which indicates that physicians at the time of the alleged invention were assessing cancer patients receiving therapy for GI perforation. Although the applicants argued during prosecution that "gastrointestinal perforation was a new potential adverse event that occurred in a few patients" (Ex. 1020, at 113 (emphasis in original)), the '115 Patent indicates that physicians at the time were already assessing patients receiving cancer therapy for GI perforation as a matter of routine practice.

Moreover, physicians would have been particularly concerned with life-threatening complications such as GI perforation. (Ex. 1002, Neugut Decl., at ¶ 90.) It was known at the time that GI perforation was associated with a high rate of death, especially in cancer patients whose physical condition is weakened from the disease and therapy. (*Id*.; Ex. 1012, at 2; Ex. 1007 at 11.) Indeed, the '115 patent reports that two of the eight patients who experienced GI perforations died as a result. (Ex. 1001, at 47:19-22; 50:54.) And it was known at the time that early diagnosis was essential in order to increase the likelihood of survival. (*Id*. at ¶

102; Ex. 1013, at 3.) Therefore, physicians would have observed patients for the possible occurrence of GI perforation.

Also, it was known at the time of the alleged invention that colorectal cancer patients undergoing systemic chemotherapy were at an increased risk of GI perforation. (*Id*. at ¶¶ 96-99; Ex. 1007, at 9; Ex. 1014, Fata at 3.) A physician evaluating a cancer patient would have paid particular attention to complications known to be associated with specific cancer types including colorectal cancer and more generally with chemotherapy treatment. (Ex. 1002, Neugut Decl. at ¶¶ 139-140; Ex. 1014, Fata at 3.) Therefore, a physician would have assessed patients with GI tumors (e.g., colorectal cancer) for GI perforation because it was well-known at the time of the invention that GI cancer patients were at risk of experiencing GI perforation, at least in part, due to tissue damage from infiltrating tumors. (*Id*. at ¶¶ 79, 139-140.) A physician would have similarly 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. (*Id*.)

Furthermore, Kabbinavar teaches that some of the patients receiving bevacizumab experienced symptoms that were known at the time to be associated with GI perforation. For example, the skilled artisan would have known that acute severe abdominal pain, nausea, diarrhea, GI hemorrhaging, and fever were

symptoms associated with GI perforation. (*Id*. at ¶ 92.) In particular, Kabbinavar reported a higher rate of GI hemorrhage, including grade 3 or 4, in patients receiving bevacizumab compared to placebo. (Ex. 1005, at 5, Table 5.) Additionally about 50% of patients in each arm experienced abdominal pain and a higher proportion of patients experienced grade 3 or 4 abdominal pain in the bevacizumab arms. (*Id*.) And a larger proportion of patients in the bevacizumab arm experienced fever compared to placebo. (*Id*.) The skilled artisan would have understood that under the standard of care at the time, the patients who experienced grade 3 or 4 GI hemorrhaging and/or grade 3 or 4 abdominal pain or fever would be assessed for GI perforation as a matter of routine medical practice, especially considering that they were at risk of GI perforation as explained above.

Therefore, it 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.

Additionally, as explained for Ground 2, Kabbinavar also discloses the additional limitations of claims 2 to 5. (Ex. 1002, Neugut Decl., at ¶¶ 113-115.) Therefore, claims 2 to 5 would have also been obvious over the teachings of Kabbinavar in view of the knowledge of the skilled artisan. (*Id*. at ¶¶ 142.)

3. Ground 6: Margolin Renders Claims 1 to 5 Obvious.

Margolin teaches or suggests every limitation of claims 1 to 5 in view of the knowledge of the skilled artisan. (*Id*. ¶¶ 117-121 and 136-137.) As explained for Ground 3, Margolin expressly discloses (1) administering an effective amount of bevacizumab to treat cancer patients and (2) assessing the patient for GI perforation during treatment with bevacizumab. To the extent that Margolin 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.

It would have been obvious to the skilled artisan to assess cancer patients receiving bevacizumab treatment as described in Margolin for GI perforation for the same reasons as explained in detail for Kabbinavar in Ground 5. First, it was the standard of care at the time to assess all cancer patients for any adverse events of therapy. (*Id*. at ¶ 138.) Second, the patients in the study were colorectal cancer patients (Ex. 1005, at 1) who were known to be at risk of GI perforation. (*Id*. at ¶ 139.) Third, the patients received systemic chemotherapy (*Id*. at 1), which was

known to be associated with GI perforation. (*Id*. at ¶ 140.) And fourth, some of the patients exhibited symptoms that were known to be associated with GI perforation. (*Id*. at ¶ 92.)

Additionally, as explained for Ground 3, Margolin also discloses the additional limitations of claims 2 to 5. (*Id*. at ¶¶ 119-121.) Therefore, claims 2 to 5 would have also been obvious over the teachings of Margolin in view of the knowledge of the skilled artisan. (*Id*. at ¶ 142.)

4. Ground 7: The 2000 Press Release Renders Claims 1 to 5 Obvious.

The 2000 Press Release teaches or suggests every limitation of claims 1 to 5 in view of the knowledge of the skilled artisan. (*Id*. at ¶¶ 123-128 and 136-137.) As explained for Ground 1, the 2000 Press Release expressly discloses (1) administering an effective amount of bevacizumab to treat cancer patients and (2) assessing the patient for GI perforation during treatment with bevacizumab. To the extent that the 2000 Press Release 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.

It 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.

First, it was the standard of care at the time to assess all cancer patients for any adverse events of therapy, including GI perforation. (*Id*. at ¶ 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.)

Additionally, as explained for Ground 1, the 2000 Press Release also discloses the additional limitations of claims 2 to 5. (*Id*. at ¶¶ 126-128.) Therefore, claims 2 to 5 would have also been obvious over the teachings of the 2000 Press Release in view of the knowledge of the skilled artisan. (*Id*. at ¶ 142.)

5. Ground 8: The 2000 Press Release Renders Claims 1 to 5 Obvious in View of the 1999 NCI CTC v.2

As explained for Grounds 1 and 5, the 2000 Press Release anticipates claims 1 to 5 and/or renders the claims obvious. To the extent it is found that the 2000 Press Release does not anticipate and/or render claims 1 to 5 obvious, the claims are obvious over the combination of the 2000 Press Release and the 1999 NCI CTC v.2. (*Id*. at ¶¶ 143-145.)

The 2000 Press Release describes administering an effective amount of bevacizumab to treat cancer patients. (*Id*. at ¶¶ 123-124, 144.) And as Dr. Neugut

explains, the skilled artisan would have understood from the teachings of the 1999 NCI CTC v.2 "that patients receiving cancer therapy should be assessed for GI perforation in order to provide safe treatment and to properly record the severity of GI adverse events." (*Id*. at ¶ 103.) For example, the 1999 NCI CTC v.2 grades GI toxicity a "4" on the severity scale if the patient has GI perforation and therefore, discloses that GI perforation might occur in patients receiving cancer therapy. (*Id*. at ¶¶ 76 and 103; Ex. 1017, at 10-13.)

The 1999 NCI CTC v.2 also provides motivation for the skilled artisan to combine the teachings of the 2000 Press Release and the 1999 NCI CTC v.2 because it teaches that patients receiving cancer therapy might experience GI perforation and that GI perforation is relevant to grading the severity of GI toxicity. (Ex. 1002, Neugut Decl., at ¶ 145.) The skilled artisan would have been motivated to combine the references in view of those teachings in order to provide safe treatment with bevacizumab and to properly grade GI toxicity. (*Id*.) Indeed, it was well-known in the art at the time of the alleged invention that the death rate in cancer patients experiencing a GI perforation is high. (Ex. 1007 at 11; Ex. 1002, Neugut Decl., at ¶ 67.) Additionally, it was well-known in the art that GI perforation is an acute medical condition that must be addressed quickly in order to improve the patient's chances of survival. (Ex. 1002, Neugut Decl., at ¶ 102.)

Thus, claim 1 would have been obvious over the teachings of the 2000 Press Release in view of the teachings in the 1999 CTC v.2. (*Id*. at ¶¶ 143-145.)

Additionally, as explained for Ground 1, the 2000 Press Release also discloses the additional limitations of claims 2 to 5. (*Id*. at ¶¶ 126-128.) Therefore, claims 2 to 5 would have also been obvious over the teachings of the 2000 Press Release in view of the teachings of the 1999 CTC v.2. (*Id*. at ¶ 145.)

6. Ground 9: The 2000 Press Release Renders Claims 1 to 5 Obvious in View of Kennedy & Spence

As explained for Grounds 1 and 5, the 2000 Press Release anticipates claims 1 to 5 and/or renders the claims obvious. To the extent it is found that the 2000 Press Release does not anticipate and/or render claims 1 to 5 obvious, the claims are obvious over the combination of the 2000 Press Release and Kennedy & Spence. (*Id*. at ¶¶ 143-144 and 146.)

The 2000 Press Release describes administering an effective amount of bevacizumab to treat cancer patients. (Ex. 1002, Neugut Decl., at ¶¶ 123-124, 144.) And Kennedy & Spence teaches that GI perforation is associated with GI cancers. (*Id*. at 9 ("Gastrointestinal perforation, in the cancer patient, is most often due to weakening of the gut wall at the site of a tumor.").) Kennedy & Spence also teaches that GI perforation is associated with chemotherapy and is therefore a concern in all cancer patients undergoing such treatments:

> Another important cause is tumor necrosis during radiotherapy or cytotoxic chemotherapy. Perforation due to peptic ulceration is also common and is often associated with the use of non-steroidal anti-inflammatory drugs or corticosteroids.

(*Id*.) 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*.) Indeed, it was well-known at the time that GI cancers and systemic chemotherapy each are causally related to GI perforation in cancer patients. (Ex. 1002, Neugut Decl., at ¶¶ 96-99.)

It would have been obvious to the skilled artisan to assess patients receiving bevacizumab for GI perforation because Kennedy & Spence teaches that GI cancer patients are at risk of GI perforation. (Ex. 1007 at 9; Ex. 1002, Neugut Decl., at ¶¶ 98-99.) That teaching would have also provided the skilled artisan with the motivation to combine the two references. The skilled artisan would have been motivated to do so in order to provide safer treatment to cancer patients. (Ex. 1002, Neugut Decl., at ¶ 146.) Indeed, it was well-known in the art at the time of the alleged invention that the death rate in cancer patients experiencing a GI perforation is high. (Ex. 1007 at 11; Ex. 1002, Neugut Decl., at ¶ 67.) Additionally, it was well-known in the art that GI perforation is an acute medical condition that must be addressed quickly in order to improve the patient's chances of survival. (Ex. 1002, Neugut Decl., at ¶ 102.) Therefore, the skilled artisan

would have been motivated by the teachings in Kennedy & Spence to assess cancer patients receiving bevacizumab for GI perforation. (*Id*. at ¶ 146.) Thus, claim 1 would have been obvious over the teachings of the 2000 Press Release in view of the teachings in Kennedy & Spence. (*Id*. at ¶¶ 143-144 and 146.)

Additionally, as explained for Ground 1, the 2000 Press Release also discloses the additional limitations of claims 2 to 5. (*Id*. at ¶¶ 126-128.) Therefore, claims 2 to 5 would have also been obvious over the teachings of the 2000 Press Release in view of the teachings of Kennedy & Spence. (*Id*. at ¶ 146.)

7. Ground 10: The 2000 Press Release Renders Claims 1-5 Obvious in View of Matsui

As explained for Grounds 1 and 5, the 2000 Press Release anticipates claims 1 to 5 and/or renders the claims obvious. To the extent it is found that the 2000 Press Release does not anticipate and/or render claims 1 to 5 obvious, the claims are obvious over the combination of the 2000 Press Release and Matsui. (*Id*. at ¶¶ 143-144 and 147.)

The 2000 Press Release describes administering an effective amount of bevacizumab to treat colorectal cancer patients in combination with chemotherapy. (Ex. 1002, Neugut Decl., at ¶¶ 123-124, 144.) 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, at 4, left-hand column.) Matsui et al. teaches that VEGF, the target protein that is

inactivated by bevacizumab, is involved in the repair of GI tissue damage. (*Id*. at 9, left-hand column ("VEGF appears to be an important endogenous mediator of the healing process for gastric injury.").) Matsui et al. also teaches 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, right-hand column.). Thus, Matsui teaches that VEGF-inactivating antibodies, such as bevacizumab, can impair GI injury repair. (Ex. 1002, Neugut Decl., at ¶¶ 25 and 82; Ex. 1021, at 1, Abstract.)

It would have been obvious to the skilled artisan to assess cancer patients receiving bevacizumab for GI perforation because Matsui teaches that VEGF-inactivating antibodies, such as bevacizumab, could promote GI tissue damage. (*Id*. at ¶¶ 25 and 82.)[3] That teaching would have also provided the skilled artisan with the motivation to combine the two references. The skilled artisan would have been motivated to do so in order to provide safer treatment to cancer patients. (Ex. 1002, Neugut Decl., at ¶ 147.) Indeed, it was well-known in the art at the time of the alleged invention that the death rate in colorectal cancer patients experiencing GI perforation is high. (*Id*. at ¶ 90.) Additionally, it was also well-known in the

[3] That is especially true for colorectal cancer patients also receiving chemotherapy because it was known at the time that both colorectal cancer and systemic chemotherapy were each associated with GI damage, including GI perforation. (*Id*. at ¶¶ 96-99.)

art that GI perforation is an acute medical condition that must be addressed quickly in order to improve the patient's chances of survival. (*Id*. at ¶ 102.) Therefore, the skilled artisan would have been motivated by the teaching in Matsui to assess cancer patients receiving bevacizumab for GI perforation. (*Id*. at ¶ 147.) Thus, claim 1 would have been obvious over the teachings of the 2000 Press Release in view of the teachings of Matsui. (*Id*. at ¶¶ 143-144 and 147.)

Additionally, as explained for Ground 1, the 2000 Press Release also discloses the additional limitations of claims 2 to 5. (*Id*. at ¶ 144.) Therefore, claims 2 to 5 would have also been obvious over the teachings of the 2000 Press Release in view of the teachings of Matsui.

8. Ground 11: The 2003 Press Release Renders Claims 1 to 5 Obvious in View of Kabbinavar.

As explained for Ground 4, the 2003 Press Release anticipates claims 1 to 4. To the extent it is found that the 2003 Press release does not teach "administering an effective amount of bevacizumab" claims 1 to 5 would have been obvious over the combination of the 2003 Press Release and Kabbinavar. (*Id*. at ¶¶ 148-150.)

The 2003 Press Release does not identify the precise amount of bevacizumab administered in the reported clinical trial.[4] But as explained in

[4] As explained for Ground 4, it is Petitioner's position that the skilled artisan would have been enabled to administer an "effective amount" of bevacizumab because effective amounts were known in the art and thus, the 2003 Press Release anticipates claims 1 to 4.

Ground 2, Kabbinavar discloses that 5mg/kg and 10 mg/kg are effective amounts of bevacizumab. (Ex. 1005, at 2, Abstract.) Thus, it would have been obvious to the skilled artisan to apply the effective amounts of bevacizumab taught by Kabbinavar to the method of cancer treatment disclosed in the 2003 Press Release. (Ex. 1002, Neugut Decl., at ¶ 148-149.) Indeed, the skilled artisan would have been motivated to combine the teachings of the 2003 Press Release and Kabbinavar in order to provide effective and safe treatment with bevacizumab to cancer patients. (*Id*.) Therefore, claim 1 would have been obvious over the 2003 Press Release in view of Kabbinavar. (*Id*. at ¶ 148-149.)

Additionally, as explained for Ground 4, the 2003 Press Release also discloses the additional limitations of claims 2 to 4. (*Id*. at ¶ 133-134.) Therefore, claims 2 to 4 would have also been obvious over the 2003 Press Release in view of Kabbinavar. (*Id*. at ¶ 149.)

Lastly, claim 5 depends from claim 1 and further recites "wherein the bevacizumab is administered to the patient at about 5-15mg/kg every 2-3 weeks." (Ex. 1001, at 52:49-51.) The 2003 Press Release does not expressly disclose the additional dosing schedule limitation of claim 5. Kabbinavar, however, teaches administering bevacizumab at 5 to 10 mg/kg every two weeks, which falls within the range recited in claim 5. (Ex. 1005 at 2, Abstract.) It would have been obvious to the skilled artisan to combine the teachings of the 2003 Press Release with the

teachings of Kabbinavar in order to arrive at the optimum dosing schedule for bevacizumab. (Ex. 1002, Neugut Decl. ¶ 150.) Indeed, the skilled artisan would have been motivated to do so in order to achieve the most effective and least toxic dosing schedule. (*Id*.) Therefore, claim 5 would have been obvious over the teachings of the 2003 Press Release in view of the teachings of Kabbinavar.

9. No Secondary Considerations of Non-Obviousness

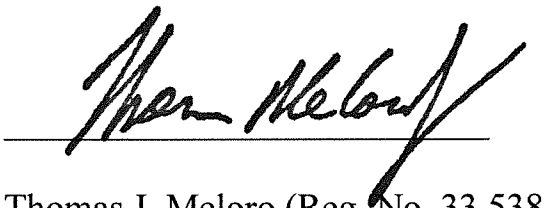
There are no secondary considerations sufficiently probative to overcome the invalidity of the ’115 Patent claims under 35 U.S.C. § 103(a) because they would have been obvious to the skilled artisan in view of the prior art. In particular, there are no secondary factors, such as commercial success, long-felt but unmet need, licensing, professional skepticism and approval, or copying by others that would outweigh the clear and convincing case that the claims of the ’115 patent are invalid because they would have been obvious to the skilled artisan in view of the prior art.

VIII. CONCLUSION

For all of the reasons described above and the attached Declaration of Dr. Neugut, claims 1 to 5 of the ’115 Patent are anticipated and obvious and should be cancelled.

Dated: September 9, 2016

Respectfully submitted,



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CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of this Petition for *Inter Partes* Review of U.S. Patent No. 7,622,115 and all Exhibits and other documents filed together with this Petition were served on the official correspondence address for U.S. Patent No. 7,622,115 shown in PAIR:

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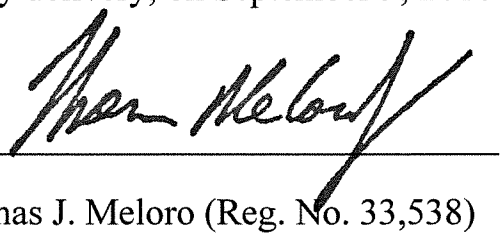
By: 

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Petition complies with the word count limitation of 37 C.F.R. § 42.24(a)(1)(i) because the Petition contains 13,474 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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