UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Pfizer Inc., Petitioner

v.

Genentech, Inc., Patent Owner.

United States Patent No. 9,795,672

Case No. IPR2018-00373

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,795,672

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Exhibit 1055	Declaration of Vanessa Park-Thompson, dated Jan. 5, 2018.	

I. INTRODUCTION

Pfizer Inc. ("Petitioner" or "Pfizer") requests *inter partes* review of Claims 1 to 18 (the "Challenged Claims") of U.S. Patent No. 9,795,672 (the "'672 patent"; Ex1001), assigned to Genentech, Inc. ("Patent Owner" or "Genentech").

The Challenged Claims relate to a method of treating cancer with bevacizumab, and specifically, to managing a well-known bevacizumab side effect, grade III hypertension (*i.e.*, hypertension requiring therapy). The Challenged Claims require managing such hypertension with a sufficient amount of an antihypertensive agent and maintaining the bevacizumab dosing regimen. Maintaining the bevacizumab dosing regimen while treating hypertension falls short of invention; it merely follows the standard of care at the time.

The Challenged Claims are anticipated and rendered obvious by the prior art. Published clinical trial summaries, some co-authored by the named inventors, demonstrate that clinicians were practicing the claimed invention years before the patent filing. In particular, Kabbinavar (Ex1011) and Yang (Ex1016) teach that grade III hypertension can be managed with standard antihypertensive medication and without altering bevacizumab dosing. Kabbinavar and Yang were both published before the earliest priority date to which the patent is entitled (May 28, 2004), and are prior art to the '672 patent.

The Challenged Claims are also rendered obvious by WO 01/74360 ("PCT'360"; Ex1006), in combination with Presta (Ex1033). PCT'360 explains the scientific rationale, grounded in preclinical data, behind why anti-vascular endothelial growth factor ("VEGF") agents like bevacizumab cause hypertension. It teaches treating such hypertension with standard antihypertensives and without altering the anti-VEGF therapy. PCT'360 specifically identifies a Genentech anti-VEGF antibody that can be used in this way, and Presta teaches how that antibody was humanized to become bevacizumab.

PCT'360, like Kabbinavar and Yang, would also have been considered in the context of standard clinical care at the time: oncologists assessed each patient individually to determine whether to maintain, reduce, or suspend bevacizumab after hypertension arose. For patients with milder forms of hypertension, oncologists would have maintained bevacizumab dosing and reasonably expected to control hypertension with an antihypertensive.

Only after ***thirteen years*** of prosecution and nine continuation applications did Genentech first claim a method of treating grade III hypertension while maintaining bevacizumab therapy. Before filing a Preliminary Amendment with the Challenged Claims in 2016, Genentech never indicated or even suggested to the Patent Office that this was an invention. In fact, at the time the 2003 Provisional Application (Ex1003) was filed, Genentech itself and various other

clinicians published that bevacizumab-related hypertension was "easily managed" with antihypertensive agents. ***Nothing*** changed in the art over those thirteen years that transformed two standard treatments – one for cancer and one for grade III hypertension – into a patentable invention.

The prior art renders each of the Challenged Claims anticipated and/or obvious under pre-AIA[1] 35 U.S.C. §§102 and 103. The Board should grant this Petition and institute trial on all of the Challenged Claims.

II. MANDATORY NOTICES

A. Petitioner and Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

Pfizer is the Real Party-in-Interest. Pfizer is a corporation organized and existing under the laws of Delaware. Its principal place of business is at 235 East 42nd Street, New York, New York 10017.

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

Petitioner identifies the following litigation that may affect, or be affected by, a decision in this *Inter Partes* Review:

- *Amgen Inc. v. Genentech, Inc. and City of Hope*, No. 17-7349 (C.D. Cal.)
- *Genentech, Inc. and City of Hope v. Amgen, Inc.*, No. 17-1407 (D. Del.)
- *Genentech, Inc. and City of Hope v. Amgen, Inc.*, No. 17-1471 (D. Del.)

[1] For this Petition only, Petitioner challenges the 2003 priority claim and treats the '672 patent as governed by pre-AIA standards. Petitioner reserves all rights to challenge the 2004 priority claim.

C. Counsel and Service Information (37 C.F.R. § 42.8(b)(3)-(4))

Pfizer's lead and backup counsel are shown below:

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Please address all correspondence to lead and backup counsel. Pfizer consents to service by email at the following addresses: rcounihan@whitecase.com and joelke@whitecase.com. A power of attorney is being filed concurrently with the designation of counsel in accordance with 37 C.F.R. § 42.10(b).

III. FEES (37 C.F.R. § 42.15(A))

Pfizer authorizes the United States Patent and Trademark Office ("USPTO") to charge $24,200 from Deposit Account No. 503672 for the fee set forth in 37 C.F.R. § 42.15(a), and authorizes charging any additional fees associated with this Petition to the same account.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '672 patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the Challenged Claims on the grounds identified in this Petition.

B. Statement of Relief Requested (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review, under 35 U.S.C. §§ 311-318 and 37 C.F.R. §§ 42.100-42.123, and cancellation of the Challenged Claims as unpatentable on the following grounds:

- **Ground 1**: Kabbinavar anticipates Claim 1 or, in the alternative, renders Claim 1 obvious; Kabbinavar anticipates or renders obvious dependent Claims 2-18.

- **Ground 2:** Chen (Ex1012) anticipates Claim 1; Chen anticipates or renders obvious dependent Claims 2-18.

- **Ground 3**: Yang anticipates Claim 1; Yang anticipates or renders obvious dependent Claims 2-18.

- **Grounds 4 & 5**: PCT'360 in combination with Presta (Ex1033), or in further combination with prior art clinical practice, renders Claim 1 obvious.

Under either ground, PCT'360 renders obvious dependent Claims 2-18 in further combination with Chen.

The full statement of reasons for the relief requested is set forth in detail below. In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith and a Table of Exhibits is provided above. The Expert Declaration of Ronald Bukowski, M.D., on behalf of Pfizer, accompanies this Petition. (*See* Bukowski (Ex1009)) Dr. Bukowski has extensive experience in the relevant field and is qualified to provide opinions regarding what a person of skill in the art ("POSA") would have known or concluded at the relevant time. (*See id.* and Exhibit A thereto)

V. THE LEVEL OF ORDINARY SKILL IN THE ART

The '672 patent relates to the treatment of human cancer using anti-VEGF antibodies. A POSA as of the applicable priority date (either May 30, 2003 or May 28, 2004) would have had a medical degree, with a specialization in oncology and at least five years of clinical experience in cancer diagnosis and treatment. (Bukowski ¶22) A POSA would consider both clinical and preclinical teachings in the art related to cancer treatment. (*Id.*) Medical oncologists (*i.e.*, POSAs) were (and are today) trained as internists, and were qualified to treat cancer therapy-related hypertension. (Bukowski ¶34)

VI. THE ’672 PATENT

The ’672 patent, entitled “Treatment with Anti-VEGF Antibodies,” issued October 24, 2017. It is directed to the treatment of cancer using the anti-VEGF antibody bevacizumab. It is assigned to Genentech.

The ’672 patent issued from U.S. Patent Application No. 15/198,769 (the “’769 application”), dated June 30, 2016. It claims priority through a series of continuations to U.S. Provisional Application No. 60/474,480 (the “Provisional Application”), filed May 30, 2003.

A. The Claims

All of the claims depend from a single independent claim, Claim 1, which reads:

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

(’672 patent, 53:8-16)

To this concept, the dependent claims identify specific cancer types or add requirements for cancer therapy that were common at the time (Bukowski ¶61; *see also* ¶¶86, 93, 104, 123):

- Claims 2-6 and 17 add the step of administering chemotherapeutic agents, including agents commonly used with bevacizumab at the time.

- Claims 7-14 list cancer types in which the method of Claim 1 can be used; by May 2003, studies with bevacizumab or other anti-VEGF antibodies were on-going or had been successfully completed in each of the listed cancers.

- Claims 15 and 18 specify bevacizumab dosage regimens common at the time.

- Claim 16 requires that, prior to bevacizumab administration, the patient does not have clinically significant cardiovascular disease – a common screening in view of bevacizumab's well-known hypertensive side effects.

B. The Disclosure

The ’672 patent explains that “a variety of therapeutic strategies aimed at blocking VEGF or its receptor signaling system are currently being developed for the treatment of neoplastic diseases,” such as cancer. (’672 patent, 3:17-23) The specification identifies bevacizumab, an anti-VEGF antibody, and describes briefly how it was generated. (*Id.* at 3:29-41) The ’672 patent acknowledges that using bevacizumab with chemotherapy to treat cancer was known and previously described in numerous publications. (*Id.* at 3:41-47)

The disclosure of the ’672 patent regarding grade III hypertension is sparse. The patent explains that grade III hypertension was a common, “well-described bevacizumab-associated adverse event” (*id*. at 52:41-45), referring to previous clinical trials that had identified hypertension as a side effect of bevacizumab treatment (*id*. at 43:20-23; 46:56-58; 47:56-61; 49:35-38). It cites two publications in particular, Kabbinavar and Yang, which are further discussed below.

The ’672 patent includes two examples about managing bevacizumab-related hypertension. Both are clinical trials of bevacizumab plus chemotherapy in metastatic colorectal cancer patients. Example 1 reports that bevacizumab doses were not reduced in any patients (*id.* at 43:2-3), no patients discontinued bevacizumab therapy due to hypertension and that “[a]ll episodes of hypertension were manageable with standard oral antihypertensive agents” (although neither the

agents nor their amounts are specified) (*id*. at 46:61-67). Example 2 reports that "grade 3 hypertension was seen in 16% of the 5-FU/LV/bevacizumab group versus 3% in the 5-FU/LV/placebo group," but it does not say how the hypertension was treated, whether bevacizumab doses were modified or suspended, or give any further details about this side effect. (*Id*. at 52:41-45) None of these statements are found in the Provisional Application; in fact, Example 2 is not disclosed at all.

C. The Prosecution History

The '672 patent stems from a long chain of continuations, all filed with identical claims to methods, articles of manufacture and kits for treating cancer with anti-VEGF antibodies.

The 2003 Provisional Application contained no claims related to hypertension. It provided clinical trial results in Example 1 and explained, regarding grade III hypertension, that "***the symptom was easily managed with oral medications.***" (Provisional Application at 82 (emphasis added)) This statement was removed one year later, on May 28, 2004, in U.S. Application No. 10/857,249 (the "'249 application" (Ex1004)), which claims priority to the Provisional Application. The '249 application replaced the assertion that grade III hypertension was "easily managed" with the clinical trial results of Examples 1 and 2 in the'672 patent, and similarly had no claims related to hypertension. (*See generally id.*)

In February 2004, between filing the Provisional Application and the '249 application, Genentech received approval to sell bevacizumab in the United States under the brand name Avastin™. After the '249 application, Genentech filed ***nine*** continuation applications over the next ***twelve*** years. None of the applications, as filed or as amended, included any claims directed to hypertension.

In July 2016, after obtaining only one patent through all of these applications, ***for the first time***, Genentech amended the '769 application to include claims to hypertension. (Prosecution History (Ex1002), at 1577-82)

i. <u>The Examiner Rejected the Claims as Anticipated and Obvious</u>

On January 10, 2017, the Examiner rejected the hypertension-related claims as being anticipated and obvious over the prior art. The Examiner rejected the claims under pre-AIA 35 U.S.C. §102(a) as anticipated by Kabbinavar (Office Action (Ex1007) at 3)), which Genentech disclosed in an Information Disclosure Statement ("IDS") (Prosecution History at 3327, 3371-76). The Examiner explained that Kabbinavar teaches every requirement of the impugned claims, namely:

> "[A] method treating a metastatic colorectal cancer patient comprising:
>
> a) administering biweekly to the patient 5 mg/kg bevacizumab;

b) further administering fluorouracil (5-FU) and leucovorin (LV);

c) detecting Grade 3 hypertension in the patient and treating orally with antihypertensive agents;

d) continuing bevacizumab treatment for six cycles; wherein the patient does not have clinically significant cardiovascular disease."

(Office Action at 3)

The Examiner also rejected the claims under pre-AIA 35 U.S.C. §103(a) as obvious over Kabbinavar in view of Sica (Ex1034). According to the Examiner, Sica added to Kabbinavar "numerous known and clinically used oral calcium channel blocking antihypertensive agents for treating hypertension in patients." (*Id*. at 3-4)

Finally, the Examiner rejected the claims under 35 U.S.C. §103(a) as obvious over Chen, which Genentech disclosed in an IDS (Prosecution History at 3312, 3362-70), in view of Sica and Bergsland 2000 (Ex1020). (Office Action at 5) The Examiner explained that:

"Chen et al teach a method treating (sic) cancer patients including metastatic colorectal cancer patients comprising:

a) administering biweekly to the patients 5 mg/kg bevacizumab;

b) further administering fluorouracil (5-FU) and leucovorin (LV);

c) commonly detecting hypertension in the patient, attributable to bevacizumab, that was controllable with medication."

(*Id*.)

The Examiner stated that, "Bergsland et al, the clinical study cited by Chen et al, teach that the treatment regimen for metastatic colorectal cancer patients comprised administering 5-FU + LV plus 5mg/kg bevacizumab biweekly until progressive disease occurred, therefore was a continuing treatment regimen." (*Id*. at 6)

ii. Applicant Overcame the Examiner's Rejections with Unsupported Inventor and Expert Declarations

In response to these rejections, Applicant did not attempt to distinguish Kabbinavar or argue that Kabbinavar did not render the claims unpatentable. (*See* Patentee Response (Ex1008)) Instead, Applicant argued that Kabbinavar was not available as prior art because it described the '672 patent inventors' own work and was published less than one year before the 2003 Provisional Application was filed. (*Id*. at 4-5) Applicant's only support was a terse, six paragraph declaration by a named inventor of the patent, Dr. William Novotny (the "Novotny Declaration"). (*Id*.)

Regarding Chen, Applicant disagreed with the Examiner about how a POSA would read the statement in Chen that hypertension was "in most cases… controllable with medication." Applicant argued that bevacizumab and its side effects were so unpredictable that a POSA would interpret "controllable" to actually require "administ[ering] an antihypertensive agent ***in conjunction with an alteration in the bevacizumab dosing regimen***, either by holding the drug or reducing the dose, or both." (*Id*. at 8 (emphasis in original))

Applicant based its arguments on the opinions of Dr. Ivy Altomare, who admitted in her declaration that she was not practicing in the field when the Provisional Application was filed, and was not certified in Medical Oncology until years later. (*See* Altomare (Ex1054) ¶2, Exhibit B thereto) Dr. Altomare cited no documentary support for her views about how a medical oncologist would have administered bevacizumab in 2003; she simply stated her personal opinion. (*Id.*)

Applicant also submitted Gotlib (Ex1046), a report of clinical trial results published five months after the May 2003 priority date. (Prosecution History at 3440-41) Applicant argued that Gotlib is "strong objective evidence" teaching away from the subject matter of the claims because it "confirms that medical practitioners at that time, confronted with grade III hypertension resulting from bevacizumab administration, would alter the bevacizumab dosing regimen." (Patentee Response at 9) Applicant omitted that one of Gotlib's co-authors was a

named inventor of the '672 patent, Dr. Novotny. Applicant did not explain why (or even acknowledge that) Dr. Novotny publicly disclosed a method of treatment inconsistent with his alleged invention ***five months*** after filing the Provisional Application, when he allegedly already had the invention in hand.

Based on Applicant's representations and arguments, the Examiner withdrew her objections and allowed the claims on September 7, 2017. (Prosecution History at 4130-37)

VII. THE SCOPE AND CONTENT OF THE PRIOR ART AS OF MAY 30, 2003

A. Bevacizumab Was a Publicly Known Cancer Treatment

The formation of new blood vessels (angiogenesis) is essential for the growth of cancerous tumors. (*See, generally,* Barbera-Guillem (Ex1038); Achen (Ex1037)) The human body produces a molecule called VEGF that regulates angiogenesis. (*Id.*)

In the 1990s, VEGF became a target for new cancer treatments. (*See* Barbera-Guillem at 7042; *see also* Bukowski ¶26) Scientists developed drugs that block VEGF or its receptor signaling system. (Bukowski ¶26) For example, Genentech researchers developed the anti-VEGF drug bevacizumab (also known as "rhuMAb VEGF" or "Avastin™"). (*See* '672 patent, 3:29-31) Bevacizumab is an antibody that binds to and neutralizes VEGF. (*Id.*) It was generated from a murine antibody called A.4.6.1, as described in Presta. (*Id.*)

As of May 30, 2003 (the filing date of the Provisional Application), several clinicians had reported success using bevacizumab to treat various cancer types, including metastatic colorectal, breast, non-small-cell lung and renal cancers. (*See, e.g.*, Chen (summarizing on-going clinical trials); Bergsland 2000; Cobleigh 2001 (Ex1017); Burstein 2002 (Ex1022); Langmuir (Ex1024); Yang 2002 (Ex1015); Kabbinavar (Ex1011); *see also* '672 patent, 3:41-47; Bukowski ¶27) VEGF had also been identified as clinically relevant to a variety of other cancer types, including ovarian and cervical cancers, (*see, e.g.*, Mesiano (Ex1052); Yamamoto (Ex1051); Hashimoto (Ex1050)), and bevacizumab clinical trials targeting those cancer types were underway (*see* Chen at 1024).

B. Hypertension Was a Known Side Effect of Cancer Therapy That Was Treated With Standard Anti-Hypertensives

In 2003, POSAs, and the patent itself, classified cancer treatment toxicities according to version 2 of the National Cancer Institute's ("NCI's") Common Toxicity Criteria ("CTC"). (CTC (Ex1040); Trotti 2002 (Ex1036) at 2; '672 patent, 37:4-8, 43:13-19, 49:31-35) Published in 1998, version 2 of the CTC included hypertension as a known toxicity associated with cancer treatment, as follows (*id.* at 5):

	Grade				
Adverse Event	0	1	2	3	4
Hyper-tension	None	Asympto-matic, transient increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring Treatment	recurrent or persistent or symptom-matic increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	Hyper-tensive crisis

**Note: For pediatric patients, use age and sex appropriate normal values >95th percentile ULN.*

Grade III hypertension is a discretionary measure where the physician decides whether therapy is required. It encompasses a range of conditions from less to more severe, depending on the physician's treatment preferences and the specific patient's symptoms. (Bukowski ¶31; *see also* CTCAE Guide (Ex1042), slide 15)

As of May 2003, there were no specific guidelines for treating grade III hypertension arising during cancer treatment. (*Id.*; *see also* Martel (Ex1013) 2006 at 92, remarking that even in 2006, "recommendations for the management of hypertension and proteinuria related to bevacizumab have been vague," with no

specific guidelines from Genentech at all.) While the CTC provides criteria to grade adverse events, it does not provide guidance on how to treat them. (CTC Manual at 5; Bukowski ¶33) The CTC manual warns against using CTC criteria in this manner: "Although it would be convenient to assume that all Grade 3 adverse events represent dose limiting toxicities, ***this is not appropriate***." (CTC Manual at 18 (emphasis added); Bukowski ¶48)

Given the lack of specific guidelines, a POSA treating grade III hypertension arising during cancer treatment would have followed standard teachings from internal medicine, a field where the signs, symptoms and standard treatments for hypertension were well-known and well-documented. (Bukowski ¶34) One relevant standard internal medicine reference used in 2003 (and commonly consulted today) was Harrison's: Principles of Internal Medicine. (*Id.* at ¶35) The edition of Harrison's available in 2003 teaches that hypertension should be treated on a patient-by-patient basis, and that a POSA should consider all factors, including the severity of the hypertension and the physician's sense of the patient's overall condition. (Harrison's at 1420-29; Bukowski ¶35-38)

In terms of when hypertension requires therapy (*i.e.*, grade III hypertension in the CTC), Harrison's teaches, under "R_x Treatment: Indications for Therapy":

> "A reasonable guideline would be that all patients with a diastolic pressure repeatedly >90 mmHg or systolic pressure > 140 mmHg ***should be treated***

> unless specific contraindications exist. Patients with isolated systolic hypertension (levels > 160 mmHg with diastolic pressure < 89 mmHg) ***should also be treated*** if they are over age 65."

(*Id*. at 1420 (emphasis added)) Harrison's provides a sample treatment plan, showing that drug treatment should be used for patients with relatively low blood pressure who have other risk factors or do not respond to lifestyle measures after 3-6 months. (*Id*. at Figure 246-1) Harrison's advises beginning with a low dose of a single antihypertensive agent and monitoring the patient's response. (*Id*. at 1425-26; Bukowski ¶36) Harrison's gives suggested antihypertensive medications, along with recommended doses, indications and contraindications. (*Id.* at 1421-29)

As taught by Harrison's and explained by Dr. Bukowski, the POSA's standard treatment plan for hypertension involved consideration of the relevant factors before deciding how to proceed. (Bukowski ¶38) Regarding grade III hypertension in particular, clinicians would prescribe antihypertensive agents in a variety of circumstances, including when the patient's blood pressure was elevated, but not significantly so, if there were other risk factors present. (*Id*.)

C. Bevacizumab-Related Hypertension Was "Easily Managed" with Medication

By May 30, 2003, medical oncologists understood that antiangiogenic cancer treatments, including VEGF inhibitors like bevacizumab, may be associated

with hypertension. (PCT'360 at 4:1-5; Malik (Ex1039) at 52; Hartman (Ex1019) at 742, citing PCT'360, Yang 1996 (Ex1048) and Ku (Ex1049); Bukowski ¶28-38)

PCT'360. One patent application that renders the Challenged Claims obvious is PCT'360, entitled "Therapeutic Combinations of Antihypertensive and Antiangiogenic Agents" and published in October 2001. PCT'360 describes how VEGF was believed to cause blood vessel dilation through nitric oxide release and, conversely, that VEGF inhibition had been shown to cause an increase in blood pressure. (PCT'360 at 2:9-24, 4:3-5, 5:24-6:2; *see also* Malik at 52) Therefore, as PCT'360 explains, VEGF inhibitors were expected to cause hypertension. (*Id.*)

PCT'360 also explains how to manage hypertension caused by VEGF inhibitors; namely, by combining the VEGF inhibitor with an antihypertensive agent. (*Id.* at 4:5-11; 5:10-20) To demonstrate this concept, PCT'360 discloses the results of a trial in rats that received a VEGF inhibitor for 10 days, causing their blood pressure to increase. (*Id.* at 28:26-30:22 (Example 1); *see in particular* 30:12-13, Figure 1) This blood pressure increase was reversed with an antihypertensive drug (captopril), while the rats continued to receive the VEGF inhibitor without any change in dosing. (*Id.* at 30:13-15, 20-21, Figure 1)

PCT'360 identifies, as a type of antiangiogenic agent that can be used in the manner taught, the "anti-VEGF receptor antibody (Genentech, Canadian Patent Application No. 2213833)." (*Id.* at 15:11-17) Canadian Patent Application No.

2213833 discloses the results of various tests with the anti-VEGF antibody A.4.6.1, including its inhibitory effect on human VEGF and the growth of human cancer cells in mice. (*See* '833 Application (Ex1005) at Examples 1-6, Figures 1-10) A.4.6.1 is the murine anti-VEGF antibody humanized to become bevacizumab. (*See generally* Presta; *see also* '672 patent, 3:29-40)

It is not surprising, then, that hypertension, and specifically grade III hypertension, was a well-documented side effect of bevacizumab by May 2003. (*See, e.g.*, Chen at 1020; Eskens (Ex1026) at S12; Langmuir; Kabbinavar at 63; Maung (Ex1027) at 376; *see also* '672 patent, 52:41-45 (acknowledging the "well-described bevacizumab-associated adverse event of grade 3 hypertension."); Bukowski ¶40)

Also unsurprisingly, by May 30, 2003, researchers had repeatedly published that bevacizumab-related hypertension could be "easily managed" with standard hypertensive medications. For example, in 2000, Genentech published that "[t]he majority of these [adverse] events [including hypertension] were Grade 1/2 and ***all were transient and reversible***." (May 23, 2000 Press Release (Ex1044) at 3) In an April 2003 review, Genentech employees reported that, across ***six*** bevacizumab Phase II trials, "[a]ll but two cases of hypertension… were ***manageable with antihypertensive treatment***." (Malik at 52 (emphasis added)) And, two weeks before filing the Provisional Application, Genentech proclaimed that "***grade 3***

hypertension, easily managed with oral medications, was clearly increased in this Phase III study." (May 19, 2003 Press Release (Ex1045) at 2 (emphasis added))

Chen. One publication of particular relevance is Chen, published in 2001. (*See, infra,* §X.C) Chen reviewed bevacizumab clinical trials as of that time, reporting that, across seven published trials, "[h]ypertension attributable to bevacizumab was common (about 20%) but ***in most cases, was mild or controllable with medication***." (Chen at 1020) (emphasis added))

Kabbinavar. Another publication that anticipates the '672 patent is Kabbinavar, published in January 2003. (*See, infra,* §X.B) Kabbinavar reports the results of a Phase II trial comparing three treatment arms in colorectal cancer patients. The patients received chemotherapy alone, or chemotherapy and either 5 mg/kg or 10 mg/kg of bevacizumab every two weeks. Kabbinavar discloses that 16 patients experienced bevacizumab-related hypertension that was treated with oral antihypertensive therapy (*i.e.*, grade III hypertension). (*Id.* at 63) Kabbinavar teaches that bevacizumab treatment was continued for six cycles, that only one patient discontinued bevacizumab because of hypertension (and angina), and it gives no indication that any patient required a reduced bevacizumab dose because of hypertension. (*Id.* at 63, Table 2)

In fact, none of the above publications indicate that grade III hypertension required a reduction or discontinuation in bevacizumab dosing. While certain

patients discontinued bevacizumab because of a grade IV event (*see, e.g.*, Cobleigh 2001; Sledge (Ex1030)), the majority of hypertensive patients appear to have been treated with antihypertensives without any alteration in bevacizumab dosing. (Bukowski ¶51, 55)

Between the filing of the Provisional Application on May 30, 2003 and the '249 application on May 28, 2004, additional publications confirmed that bevacizumab-associated hypertension was "easily managed" with standard oral hypertensives without modifying bevacizumab dosing. For example, a Phase II bevacizumab trial presented at the May 2003 American Society of Clinical Oncology annual meeting explained that "4 [patients] had worsening of pre-existing hypertension that was ***easily managed***." (Carson (Ex1028)) In October 2003, yet another team of researchers remarked that, even though the mechanism of hypertension was not clearly understood, even bevacizumab-associated hypertension classified as "serious adverse events" were "***easily managed***." (Cobleigh 2003 (Ex1018) at 121-123)

***Yang*.** An additional publication that anticipates the '672 patent (because Genentech is not entitled to the May 2003 priority date; *see, infra*, §X.A) was published in July 2003. Yang disclosed the results of a Phase II trial comparing placebo with bi-weekly bevacizumab doses of 3 or 10 mg/kg in metastatic renal cancer. (Yang at 430) Yang teaches that "[t]ypically, hypertension… was treated

by the patients' private physicians with standard regimens for essential hypertension." (*Id*. at 430) Bevacizumab dosing was only modified if the hypertension was not completely controlled by one standard medication; otherwise, all doses were given as planned. (*Id.* at 430, Table 2)

Yang is also relevant because the clinical trial began in October 1998, almost five years before the Provisional Application was filed. No purported inventor is named as an author. Yang therefore teaches what those in the field (other than the inventors) were doing well before May 2003: managing treatment-related grade III hypertension with standard antihypertensives and without altering bevacizumab dosing. (*Id.* at 430, Table 2) This fact is reinforced by a separate trial begun in March 2001, where "[p]atients who developed hypertension… were advised to initiate or add antihypertensive therapy" without bevacizumab dose reduction or discontinuation, except under extreme circumstances. (Burstein 2008 (Ex1023) at 7872, listing none of the '672 inventors as authors)

D. <u>The Standard of Care for Bevacizumab-Related Hypertension</u>

Based on the clinical and preclinical teachings summarized above, a POSA observing grade III hypertension resulting from bevacizumab would ***not*** have automatically reduced or suspended the bevacizumab dose. (Bukowski at ¶48) The POSA would recognize that they had three options regarding bevacizumab: (1) reduce the dose, (2) suspend the dose, or, as Genentech claimed in the '672 Patent,

(3) maintain the dose. (*Id.* at ¶47) Before selecting one of these options, the POSA would evaluate all the facts and circumstances regarding the patient's condition. (*Id.* at ¶46-51) This consideration would include, *inter alia*, the numerous clinical reports that bevacizumab-related hypertension was "easily managed." (*See, supra*, §VII.C; Bukowski ¶49) A POSA taking all factors into account would determine, in certain circumstances, that maintaining the bevacizumab dosing regimen while administering antihypertensive therapy was clinically appropriate for some patients, and would have reasonably expected to succeed with that approach. (*Id.* at ¶50-51)

E. Genentech's Characterization of Clinical Practice During Prosecution Should be Accorded Little Weight

During the '672 patent prosecution, Genentech and its expert, Dr. Altomare, argued that "given the unpredictability associated with bevacizumab in 2003, a medical practitioner, when confronted with a patient exhibiting a grade III hypertensive event resulting from bevacizumab administration, would not have continued treatment according to the original bevacizumab dosage regimen." (Patentee Response at 7-8; Altomare ¶10) Petitioner and its expert, Dr. Bukowski, disagree with Genentech's and Dr. Altomare's depiction of the standard of care in 2003 and how a POSA would respond to bevacizumab-related grade III hypertension. (*See, supra*, §VI.C; Bukowski ¶46-57)

As the only documentary support for "unpredictability," Genentech and Dr. Altomare cited abstracts reporting that bevacizumab was discontinued for ***grade IV*** events (one case of malignant hypertension (Sledge), one of hypertensive encephalopathy and nephrotic syndrome (Cobleigh 2001), and one of hemorrhages unrelated to hypertension (Johnson (Ex1047)). (Patentee Response at 6-7; Altomare ¶¶5-6; *see* Bukowski ¶55 (explaining these are grade IV events)) However, Genentech did not disclose the full picture to the Patent Office. For example, the full publication of the Cobleigh trial explains that, aside from the one case of hypertensive encephalopathy, "[h]ypertension was treated successfully with a variety of antihypertensive medications" and "***easily managed***." (Cobleigh 2003 at 121-122) Thus, while these anecdotes about grade IV events may have caused a physician to exercise caution, they would not overcome the individual patient's diagnosis, especially milder forms of hypertension appropriate for antihypertensive therapy. (Bukowski ¶57; *see*, *supra,* §VII.D)

Regarding grade III events, Genentech relied solely on Dr. Altomare's personal opinion to argue that, "in conjunction with antihypertensive therapy, the practitioner ***would have altered the bevacizumab dosage regimen***… until resolution of the hypertensive event." (Patentee Response at 6-7, citing Altomare ¶¶10-11 (emphasis in original)) Dr. Altomare cited no underlying facts or documentary support for her view, which is directly contradicted by the warning in

the CTC Manual that treatment doses should ***not*** automatically be altered for grade III events. (CTC Manual at 18) Dr. Altomare's "[o]pinions expressed without disclosing the underlying facts or data may be given little or no weight." U.S. Patents and Trademark Office Trial Practice Guide, 77 Fed. Reg. 48756, 48763 (Aug. 14, 2012), citing *Rohm & Haas Co. v. Brotech Corp*., 127 F.3d 1089, 1092 (Fed. Cir. 1997) (nothing in the Federal Rules of Evidence or Federal Circuit jurisprudence requires the fact finder to credit unsupported assertions of an expert witness).

Dr. Altomare's views should further be accorded little weight because she was not practicing oncology when the Provisional Application was filed, and was not board-certified until ***five years later***. (*See* Altomare ¶2, Exhibit B); *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1556 (Fed. Cir. 1983) (rejecting an invalidity argument, in part because the supporting expert "was still in school at that time.").

Genentech's arguments during prosecution regarding clinical practice in 2003 should be granted little weight, if any.

VIII. CLAIM CONSTRUCTION

The term "***grade III hypertensive event***" should be construed to mean "hypertension requiring therapy or more intensive therapy than previously." (*See* Bukowski ¶58-70)

The term should be construed according to its broadest reasonable interpretation, consistent with its plain meaning in the context of the written description and the prosecution history. 37 C.F.R. § 42.100(b) (2012); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016); *Medrad, Inc. v. MRI Devices Corp*., 401 F.3d 1313, 1318 (Fed. Cir. 2005).

Petitioner's proposed construction is taken from the CTC, which provided guidance to medical oncologists observing adverse events during cancer treatment in 2003. (*See* Bukowski ¶59; Trotti 2000 at 15) The '672 patent describes two clinical trials, both of which define "grade III hypertension" by the CTC. ('672 patent, 37:4-8, 43:13-19, 49:31-35; *see, supra,* §VI.B) These trials are the only instances in the '672 patent where the term "grade III hypertension" is used. Accordingly, the specification has defined "grade III hypertensive event" by the CTC terminology, and the court should "rely heavily on the written description for guidance as to the meaning of the claims." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005).

The CTC definition of grade III hypertension was also expressly followed by Genentech and its expert during prosecution, although neither explicitly cited the CTC. (Patentee Response at 7 ("[T]he claims refer to grade III hypertension, which is hypertension that requires therapeutic intervention or more intensive therapeutic intervention than was previously prescribed"); *see also* Altomare ¶4

(same)) Prosecution statements defining a claim term, such as here, are binding on the applicant. *Typhoon Touch Techs., Inc. v. Dell, Inc.*, 659 F.3d 1376, 1381 (Fed. Cir. 2011).

Pfizer's proposed construction should be adopted, as it is consistent with the '672 patent and the POSA's understanding, as well as Genentech's representations during prosecution.

IX. LEGAL STANDARDS

To claim priority to an earlier-filed provisional application, there must be a sufficient written description in the application to support the issued claims. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011).

A patent is invalid for anticipation where a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *Brassica Protection Prods. LLC v. Sunrise Farms* (*In re Cruciferous Sprout Litig.*), 301 F.3d 1343, 1349 (Fed. Cir. 2002). "[I]n considering the disclosure of a reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968).

A patent is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a) (2012). "Obviousness does not require absolute predictability of success," only "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). A method of treatment claim is obvious where it merely confirms a result in humans that was observed and predicted from animal testing. *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007).

X. DETAILED STATEMENT OF GROUNDS FOR INVALIDITY

This Petition must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a) (2012). As described below, this Petition meets and exceeds this threshold.

A. The '672 Patent is Entitled to a Priority Date No Earlier than May 28, 2004

The '672 patent is entitled to a priority date no earlier than May 28, 2004, the filing date of its earliest non-provisional application, the '249 application. The '672 patent purports to claim an earliest effective filing date under 35 U.S.C. § 119 of May 30, 2003, when the Provisional Application was filed. However, the

Challenged Claims are not supported by the written description of the Provisional Application. *Centocor*, 636 F.3d at 1348.

i. The Provisional Application Does Not Provide A Written Description of the Claimed Invention

The Provisional Application provides practically no information regarding hypertension or its management. (*See generally* Provisional Application) In fact, in almost 100 total pages, hypertension is only mentioned five times:

- In the background section, the Provisional Application mentions that previous clinical studies with anti-VEGF antibodies had shown a variety of side effects, including hypertension (*id.* at 64);

- Regarding Example 1 (the only example in the application), the Provisional Application states:

    - Uncontrolled hypertension was an exclusion criterion in the described clinical trial (*id.* at 71);

    - Subjects and investigators were queried regarding a list of adverse events, including hypertension (*id.* at 77);

    - Summaries of those adverse events, including hypertension, were tabulated (*id.*);

- "The addition of rhuMAb VEGF to bolus-IFL chemotherapy resulted in a small increase in grade 3 hypertension (2.3% vs. 10.9%), but ***the symptom was easily managed with oral medications***" (*id.* at 82; emphasis added).

Because all of the other statements merely provide context, only the statement that hypertension "was easily managed with oral medications" could potentially provide written description support for the alleged invention of the '672 patent. (Bukowski ¶62-65) This statement is, on its face, not sufficient to support Claim 1, nor the seventeen claims dependent upon Claim 1.

Specifically, the Provisional Application provides no information about whether bevacizumab doses were altered or discontinued because of hypertension, and it cannot be assumed or inferred that the bevacizumab dose was maintained after a grade III hypertensive event, as Claim 1 requires. (*Id.* at ¶65) The treatment plan of the example in the Provisional Application does not provide this information, as it only describes how to manage "toxicity due to chemotherapy" (Provisional Application at 68) and "infusion-associated adverse events (fever and/or chills)" (*id.* at 72), not hypertension. Similarly, this information is missing from the results section, which reports adverse event details, including discontinuations, but does not specifically state whether any patients discontinued due to hypertension. (*Id.* at 81-82)

Further, the Provisional Application does not explain what is hypertension "resulting from the bevacizumab administration," what oral medications may be used, or what is "an amount [of medication] sufficient to manage" the hypertension. The bare statement that hypertension was "easily managed" (removed in subsequent applications in the '672 patent chain), without any further detail, reveals that even the inventors themselves thought there was nothing novel or inventive about the now-claimed "invention" or that they believed they possessed an "invention." The Provisional Application does not provide adequate support for the Challenged Claims.

ii. Genentech's Arguments Distinguishing Chen Foreclose Any Argument that the Provisional Application Provides a Written Description of the Claimed Invention

Genentech's prosecution arguments about Chen demonstrate that the '672 patent's disclosure cannot adequately support the Challenged Claims.

Chen reviews bevacizumab clinical trials and concludes that "[h]ypertension attributable to bevacizumab was common (about 20%) but in most cases, was mild or controllable with medication." (Chen at 1020) During prosecution, Genentech argued that Chen "falls far short of suggesting or motivating the presently claimed method" (Patentee Response at 8) because the phrase "controllable with medication" "would not have indicated to medical practitioners in 2003 (or when published in 2001) that bevacizumab treatment should be continued following a

hypertensive event without alteration of the dosage regimen." (*Id*, citing Altomare ¶¶13-14) Genentech argued that a POSA, in response to grade III hypertension, would have reduced or discontinued bevacizumab. (*Id.*)

The Provisional Application's disclosure, including that hypertension could be "easily managed with oral medications," says nothing more than Chen's teaching that hypertension was "controllable with medication." Notably, the Provisional Application does not say how hypertension was managed, what medications were used or whether bevacizumab therapy was altered. Accordingly, by Genentech's own reading of clinical disclosures, the Provisional Application does not convey that the inventors maintained the bevacizumab dose and the Provisional Application fails to show they possessed the claimed invention. *Centocor*, 636 F.3d at 1348.

Below, Petitioner explains the flaws in Genentech's arguments that a POSA would automatically reduce or discontinue bevacizumab for grade III hypertension. (*See, infra,* §X.B.i(b)) In any event, Genentech "is bound by representations made and actions that were taken in order to obtain the patent." *Typhoon Touch Techs*., 659 F.3d at 1381. It cannot now argue that its Provisional Application provides adequate written description support.

iii. Genentech's Arguments Regarding Gotlib Confirm the Lack of Written Description Support

The Gotlib article Genentech relied on during prosecution confirms that the purported inventors were not in possession of their alleged invention when the Provisional Application was filed. During prosecution, Genentech argued that "Gotlib and his colleagues, when managing grade III toxicities, elected to dose reduce, rather than continue bevacizumab treatment without an alteration in dosage regimen. This represents strong, objective evidence that Applicant's approach was not obvious." (Patentee Response at 9) Genentech omitted that one of Gotlib's "colleagues," and co-author of the article, was Dr. Novotny, the '672 patent inventor who submitted a declaration during prosecution to overcome Kabbinavar. (Patentee Response at 4-6)

Taking Genentech's statements at face value, if Gotlib is "strong, objective evidence" of anything, it is that a purported inventor did not possess the alleged invention as of November 2003, if indeed he ever thought that treating an "easily managed" side effect was an invention. Such an admission confirms that the Provisional Application does not provide written description support for the Challenged Claims, and that Genentech cannot show it is entitled to a priority date before May 28, 2004.

B. Ground 1: Kabbinavar Anticipates or Renders Obvious the Challenged Claims

Kabbinavar was published on January 1, 2003. Genentech submitted Kabbinavar during prosecution (Prosecution History at 3327, 3371-76) and it was overcome with an inventor declaration as described above in §VI.C.

Because the '672 patent is entitled to a priority date no earlier than May 28, 2004 (*see*, *supra*, §X.A), and Kabbinavar is a printed publication accessible to the public more than one year before that date (Bukowski ¶71; *see also* Kabbinavar at 8, showing Library of Congress's January 1, 2003 publication date), Kabbinavar is §102(b) prior art.

i. Kabbinavar Anticipates Claim 1

As found by the Examiner during prosecution (*see* Office Action at 3), and not contested on these merits by Genentech (*see* Patentee Response at 4-5), Kabbinavar discloses every requirement of Claim 1, as follows (*see also* Bukowski ¶73-79):[2]

Claim 1 claims "[a] method of treating cancer in a patient with bevacizumab..."[3] Kabbinavar teaches a method of treating colorectal cancer with

[2] For ease of reference, the Bukowski Declaration provides charts showing how all claims are anticipated or rendered obvious by each Ground in this Petition. The Bukowski Declaration contains no obviousness or anticipation arguments not presented in this Petition.

[3] This requirement is a preamble, and therefore may not need to be disclosed for a prior art reference to anticipate the Challenged Claims. *See, e.g.*, *Marrin v. Griffin*,

bevacizumab. (*See, e.g.*, Kabbinavar at 64)

Claim 1 then recites "wherein the patient has a grade III hypertensive event resulting from the bevacizumab administration…" Kabbinavar states: "[s]ixteen of the 19 patients [with hypertension] required oral antihypertensive therapy" (*id.*), a disclosure consistent with how "grade III hypertension" should be construed (*see, supra*, §VIII).[4] Kabbinavar teaches that several patients had grade III hypertensive events resulting from bevacizumab administration during the clinical trial. (Bukowski ¶74)

Claim 1 next recites "the method further comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event…" Kabbinavar teaches that "[s]ixteen of the 19 patients [with hypertension] required oral antihypertensive therapy," and only one patient discontinued bevacizumab because of hypertension (and angina). (Kabbinavar at 63) Kabbinavar also states that hypertension was generally "manageable." (*Id.* at 64) If the Board finds that Kabbinavar must identify specific dosages and antihypertensive agents to be anticipatory, Kabbinavar renders this claim obvious in view of standard clinical practice. (*See, infra*, §X.B.ii)

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599 F.3d 1290, 1295 (Fed. Cir. 2010). In any event, Kabbinavar discloses this requirement, as do the other references discussed in §X.C-E.

[4] Kabbinavar's use of CTC version 1 (*id.* at 63) is irrelevant, as Kabbinavar teaches that 16 patients received antihypertensives, consistent with the proper construction of "grade III hypertension." (*See, supra*, §VIII; Bukowski ¶79)

Finally, Claim 1 claims "while continuing to treat the patient with bevacizumab, the continued bevacizumab treatment being carried out without altering the dosage regimen." Kabbinavar provides explicit instructions for managing hypertension and teaches that the bevacizumab dosage regimen need not be altered. Kabbinavar explains that only one patient experiencing hypertension discontinued bevacizumab. (Kabbinavar at 63) No other patients are indicated to have had their bevacizumab dosing altered; instead, Kabbinavar explicitly teaches continuing bevacizumab treatment for six cycles. (*Id.* at 63, Table 2)

For a detailed peer-reviewed clinical trial publication like Kabbinavar, standard practice dictates that any reductions, discontinuations, or other alterations in the dosage regimen be reported. (Bukowski ¶77) Kabbinavar followed this standard practice, reporting only one discontinuation for hypertension. Moreover, as Kabbinavar compares the efficacy of two doses (5 and 10 mg/kg), a dose reduction would particularly need to be reported, as that information affects the conclusions that can be drawn from the study (*Id.*)

Consequently, a POSA would reasonably understand or infer from Kabbinavar that the dosage was not altered (other than the one discontinuation), rendering this final claim requirement anticipated. (*Id.* at ¶78); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) ("the dispositive question regarding anticipation [is] whether one skilled in the art would reasonably

understand or infer from a [prior art reference] that every claim requirement is disclosed in that reference.") (quoting *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991)).

A POSA cannot draw the same inference from the Provisional Application. It is not a peer-reviewed clinical trial publication, and the trial in the Provisional Application does not compare different dosage amounts; it compares bevacizumab to placebo. (*See, e.g.,* Provisional Application at 79-81 (efficacy results)) Unlike Kabbinavar, which compares two dosages, a dose reduction in a trial against placebo may not affect the investigators' conclusions. (Bukowski ¶66) Kabbinavar also provides more detail than the Provisional Application, such as the specific number of patients who suffered grade III hypertension and discontinued bevacizumab as a result, which again would cause a POSA to reasonably conclude that any dose reductions would have been expressly disclosed if they had occurred. (*Id.* at ¶76-78)

ii. <u>In the Alternative, Kabbinavar Renders Claim 1 Obvious</u>

As described above, Kabbinavar discloses every requirement of Claim 1. If the Board finds that Kabbinavar fails to disclose any requirement, then the claimed invention would have been obvious over Kabbinavar in view of the standard clinical care for hypertension. (Bukowski ¶80-85); *Ormco Corp. v. Align Tech. Inc.*, 463 F.3d 1299, 1307-08 (Fed. Cir. 2006) ("A claim can be obvious even

where all the claimed features are not found in specific prior art references. . . 'the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references.'") (quoting *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006))

A POSA managing bevacizumab-related hypertension in May 2003 or May 2004, upon considering Kabbinavar, would have followed standard clinical practice, which is taught, for example, by the authoritative text on hypertension, Harrison's. (*See, supra,* §VII.B, VII.D; Bukowski ¶81) Harrison's is a printed publication accessible to the public in 2001 (Bukowski ¶81; *see also* Harrison's at 22, showing Library of Congress's January 8, 2001 publication date) and is prior art under §102(b) regardless of whether the '672 patent is entitled to the May 30, 2003 priority date.

Standard clinical practice was to treat hypertension on an individual patient basis. (Bukowski ¶35-38, 82) For example, Harrison's teaches that antihypertensive agents should be considered if a patient has blood pressure of 140/90 or greater, and has other risk factors, such as smoking, obesity, or being male. (Harrison's at 1425, Figure 246-1) Accordingly, hypertension meeting the '672 patent's definition of a grade III hypertensive event (*i.e.*, "requiring therapy or more intensive therapy than previously") may be relatively mild. (Bukowski ¶38, 83) A POSA would have readily expected to be able to manage this hypertension

with standard medications, such as those Harrison's describes. (Bukowski ¶35-38, 83-85)

Depending on the patient's prognosis, a treatable condition like grade III hypertension might be of decreased importance compared to the patient's advanced malignancies. (Bukowski ¶83) If the patient was experiencing severe side effects without any significant clinical benefit, a POSA may be inclined to discontinue bevacizumab immediately, until the patient's blood pressure returned to normal, or reduce the bevacizumab dose. (*Id*.) However, if the POSA believed that the hypertension was treatable with standard antihypertensives, it would have been obvious to the POSA to continue bevacizumab treatment without altering the dosage regimen. (*Id*.) In the latter situation, the POSA would reasonably expect both treatments to succeed in line with the normal rates of success associated with each treatment. (*Id*.) These options – stopping (either temporarily or permanently), reducing, or maintaining bevacizumab dosing – were the POSA's only options regarding bevacizumab, as Genentech acknowledged during prosecution. (*Id*.; Patentee Response at 8)

A POSA considering Kabbinavar would know and adhere to this standard of care. (Bukowski ¶84) Kabbinavar lacks any teaching that dose alteration was implemented or necessary, and, to the contrary, strongly indicates that dosing was ***maintained*** for all hypertensive patients except one. (Kabbinanvar at 63, Table 2;

Bukowski ¶84) Kabbinavar therefore reinforced a POSA's reasonable expectation that an antihypertensive would successfully treat grade III hypertension. Consequently, it would have been obvious to maintain the bevacizumab dosage in response to a grade III hypertensive event, as required by the final requirement of Claim 1.

Further, consistent with the claim requirement "an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event," a POSA would have selected an antihypertensive and its amount based on the teachings of Harrison's. (Harrison's at 1421-29; Bukowski ¶35-38, 83) The claimed invention is obvious.

iii. Kabbinavar is Also Prior Art Under 35 U.S.C. §102(a)

Kabbinavar also qualifies as §102(a) prior art, regardless of the priority date of the '672 patent, as it was published five months before May 30, 2003. *See Celorio Garrido v. Holt*, 547 Fed. Appx. 974, 978 (Fed. Cir. 2013) (affirming Board's decision that prior art found not to be a §102(b) reference was available as prior art under §102(a).).

Kabbinavar was raised by the Examiner as §102(a) art during prosecution, but Genentech overcame the rejection by submitting a declaration by Dr. Novotny (the only named inventor who is also a co-author of Kabbinavar) pursuant to *In re Katz*, 687 F.2d 450 (C.C.P.A. 1982). (*See* Patentee Response at 4-5; Prosecution

History at 3458-59 ("Novotny Declaration")) That the Novotny Declaration carried the '672 patent through prosecution does not relieve Genentech of their burden ***in this proceeding***.

The six cursory paragraphs in the Novotny Declaration are deficient to overcome Kabbinavar, as they are nothing more than the inventor's "naked assertions," with no corroboration. *EmeraChem Holdings, LLC v. Volkswagen Group of Am., Inc.*, 859 F.3d 1341, 1346, 1347 (Fed. Cir. 2017) ("*Katz* required more than a naked assertion by the inventor" and "corroborating an inventor's testimony is a well-established principle in [Federal Circuit] law."); *see also Finnegan Corp. v. U.S. ITC*, 180 F.3d 1354, 1367 (Fed. Cir. 1999) ("[T]he case law is unequivocal that an inventor's testimony respecting facts surrounding [any of the §102 subsections] cannot, standing alone, rise to the level of clear and convincing proof.") (quoting *Price v. Symsek*, 988 F.2d 1187, 1194 (Fed. Cir. 1993)).

Moreover, the surrounding evidence shows that Dr. Novotny did not believe he had invented anything, even months after Kabbinavar published. For example, Dr. Novotny's Provisional Application stated that hypertension was "***easily managed***." (Provisional Application at 82) And, almost a year after Kabbinavar published, Dr. Novotny and others published the Gotlib reference that is, according to Genentech, "strong, objective evidence" "confirm[ing] that medical

practitioners" – including Dr. Novotny, apparently – "***would alter the bevacizumab dosing regimen***." (Patentee Response at 9) (emphasis in original))

Even if the Board finds that the '672 patent is entitled to claim priority to the Provisional Application (which it is not), Kabbinavar is §102(a) prior art because the Novotny Declaration fails to meet the requirements of *In re Katz* and anticipates Claim 1 as explained above.

iv. Kabbinavar Anticipates or, in Combination with Chen, Renders Obvious Each Dependent Claim

Kabbinavar discloses or, in combination with Chen and the references summarized in Chen, renders obvious every requirement of the dependent claims. Chen is prior art to the '672 patent under §102(b). (*See* §X.C) Because Chen provided an overview of bevacizumab clinical trials over a year before Kabbinavar was published, it would have been obvious to a POSA to combine Kabbinavar's teachings with Chen and the references cited therein. (*See* Bukowski ¶86)

Dependent Claims	***Kabbinavar and Chen***
2. The method of claim **1**, wherein the method further comprises administering one or more chemotherapeutic agents.	Kabbinavar teaches the method of Claim 1 (*see, supra,* §X.B.i; Bukowski ¶73-79) where the patient is administered "one or more chemotherapeutic agents," such as fluorouracil and leucovorin. (*See, e.g.,* Kabbinavar at 61)

Dependent Claims	***Kabbinavar and Chen***
3. The method of claim **2**, wherein the one or more chemotherapeutic agents is one or more of an alkylating agent, antimetabolite, pyrimidine analog, vinca alkyloid, epipodophyllotoxin, antibiotic, topoisomerase inhibitor, interferon, platinum coordination complex, or taxoid.	*See id.* 5-FU, taught by Kabbinavar (*see id.*), is an example of an anti-metabolite. ('672 patent at 12:2-3, 40-41)
4. The method of claim **3**, wherein the one or more chemotherapeutic agents is one or more of a pyrimidine analog, 5-fluorouracil (5-FU), leucovorin, irinotecan, paclitaxel, oxaliplatin, carboplatin, cisplatin, doxorubicin, topotecan, or interferon-alpha.	*See* Claim 2, *supra* describing the use of 5-FU and leucovorin.
5. The method of claim **4**, wherein the one or more chemotherapeutic agents is one or more of 5-FU, leucovorin, irinotecan, or oxaliplatin.	*See* Claims 2 and 4, *supra.*
6. The method of claim **5**, wherein the one or more chemotherapeutic agents is 5-FU, leucovorin, and irinotecan.	*See* Claims 2 and 5, *supra.*
7. The method of claim **2**, wherein the cancer is colorectal cancer, rectal cancer, glioblastoma, non-small cell lung cancer, cervical cancer, peritoneum cancer, renal cancer, ovarian cancer, or mesothelioma.	Kabbinavar teaches the method of Claim 2 in colorectal cancer. (Kabbinavar at 60)
8. The method of claim **5**, wherein the cancer is metastatic colorectal cancer.	*See* Claims 5 and 7, *supra.*
9. The method of claim **6**, wherein the cancer is metastatic colorectal cancer.	*See* Claims 6 and 7, *supra.*

Dependent Claims	***Kabbinavar and Chen***
10. The method of claim **4**, wherein the cancer is metastatic non-small cell lung cancer.	Kabbinavar teaches the method of Claim 4 (*see* Claim 4, *supra*) in colorectal cancer. (Kabbinavar at 60) The '672 Patent only contains data regarding the use of the alleged invention in colorectal cancer. (*See* Examples 1 and 2) If the Board determines that the '672 Patent enables the subject matter of Claims 7-14, then Kabbinavar's disclosure regarding colorectal cancer renders Claims 7-14 anticipated. (Bukowski ¶86) If the Board determines that Kabbinavar does not anticipate Claim 10, then Kabbinavar, in combination with Chen, renders it obvious. (Bukowski ¶86) Chen teaches the method of Claim 4 (Chen at 1020) and describes and cites to the results of bevacizumab trials in patients with advanced non-small-cell lung cancer. (*See* Chen at 1020, citing DeVore; Novotny; Gordon)

Dependent Claims	***Kabbinavar and Chen***
11. The method of claim **4**, wherein the cancer is metastatic cervical cancer.	*See id*. If the Board determines that Kabbinavar does not anticipate Claim 11, then Kabbinavar read with Chen renders it obvious, because Chen cites an ongoing trial of bevacizumab in cervical cancer. (Chen at 1024; *see* Bukowski ¶86) Furthermore, before May 2003, clinicians had identified an association between cervical cancer and VEGF and predicted that "[n]eutralization of VEGF activity may have clinical application in inhibiting malignant ascites formation in ovarian cancer." (Mesiano at Abstract; *see also* Yamamoto at Abstract) Chen also discloses that bevacizumab was an effective treatment for cancers with a known association to VEGF, and that a cervical cancer clinical trial with bevacizumab was underway. (Chen at 1020, 1024) Kabbinavar in combination with Chen renders Claim 11 obvious. (Bukowski ¶86)

Dependent Claims	***Kabbinavar and Chen***
12. The method of claim **4**, wherein the cancer is metastatic ovarian cancer or metastatic peritoneum cancer.	*See* Claim 10, *supra*. If the Board determines that Kabbinavar does not anticipate Claim 12, then Kabbinavar read with Chen renders it obvious, because Chen cites an ongoing trial of bevacizumab in ovarian and peritoneal cancers. (Chen at 1024; ; *see* Bukowski ¶86) Furthermore, before May 2003, clinicians had identified an association between ovarian cancer and VEGF. (*See, e.g.,* Hashimoto at Abstract) Chen also discloses that bevacizumab was an effective treatment for cancers with a known association to VEGF, and that an ovarian cancer clinical trial with bevacizumab was underway. (Chen at 1020, 1024) Kabbinavar in combination with Chen renders Claim 12 obvious. (Bukowski ¶86)
13. The method of claim **4**, wherein the cancer is metastatic renal cancer.	*See* Claim 10, *supra*. If the Board determines that Kabbinavar does not anticipate Claim 13, then this claim is obvious over Kabbinavar in view of Chen and/or Gordon (Ex1029). (Bukowski ¶86) Chen cites Gordon (Chen at 1026), which discloses the results of bevacizumab clinical trial in patients with renal cancer (*see* Gordon at Table 1).

Dependent Claims	***Kabbinavar and Chen***
14. The method of claim **1**, wherein the cancer is glioblastoma.	In addition to the bevacizumab-related clinical trials described above (*see* Claims 10-13, *supra*), Chen describes how, in preclinical models, "[a]nti-VEGF MAbs have shown potent growth inhibition in vivo in a variety of human cancer xenograft and metastasis models, including … glioblastoma." (Chen at 1020) A POSA would therefore reasonably expect that bevacizumab would effectively treat glioblastoma, rendering this claim obvious. (Bukowski ¶86)
15. The method of claim **1**, wherein the bevacizumab is administered to the patient bi-weekly at about 10 mg/kg.	Kabbinavar teaches the method of Claim 1 (*see*, *supra*, §X.B.i; Bukowski ¶73-79) where bevacizumab is administered to the patient bi-weekly at 10 mg/kg. (*See* Kabbinavar at 61)
16. The method of claim **4**, wherein the patient does not have clinically significant cardiovascular disease prior to the bevacizumab administration.	Kabbinavar teaches the method of Claim 4 (*see* Claim 4, *supra*) where the patients did not have clinically significant cardiovascular disease before bevacizumab administration. (Kabbinavar at 60)
17. The method of claim **8**, wherein one of the one or more chemotherapeutic agents is 5-FU.	*See* Claims 2 and 8, *supra*.
18. The method of claim **1**, wherein the bevacizumab is administered to the patient bi-weekly at about 5 mg/kg.	Kabbinavar teaches the method of Claim 1 where bevacizumab is administered to the patient bi-weekly at 5 mg/kg. (*See* Kabbinavar at 61)

v. The Examiner's Decision to Allow the Claims Over Kabbinavar Should Not Be Given Deference

The Examiner's ultimate decision to allow the claims over Kabbinavar should not be given deference under 35 U.S.C. §325(d). The Examiner was not presented with and did not consider the argument that the '672 patent is entitled to a priority date no earlier than May 28, 2004. (*See, supra*, §X.A; *see also PowerOasis, Inc. v. T-Mobile USA Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008) ("[s]ince the PTO did not make a determination regarding priority, there is no finding for the district court to defer to.")) Furthermore, Kabbinavar was only avoided by an *In re Katz* declaration insufficient in this proceeding. (*See, supra*, §X.B.iii) As such, Kabbinavar is prior art under §§102(a) and (b) for reasons not considered by the Examiner. Had the Examiner considered the flaws in the priority claim or the Novotny Declaration, she would have maintained her anticipation rejection.

C. Ground 2: Chen Anticipates or Renders Obvious the Challenged Claims

Chen was published on August 1, 2001 and publicly available by August 31, 2001, more than one year prior to the earliest possible priority date of the '672 patent. (Bukowski ¶86; *see also* Chen at 10, showing Library of Congress's August 15, 2001 publication date) It is prior art under §102(b) regardless of whether the '672 patent is entitled to the May 30, 2003 priority date. Genentech

submitted Chen during prosecution (Prosecution History at 3312, 3362-70) and it was overcome as described above in §VI.C.

i. Chen Anticipates Challenged Claim 1

If Genentech backtracks on its prosecution arguments regarding Chen to preserve its claim to the Provisional Application's priority date, then Chen anticipates Claim 1, as follows: (*See* Bukowski ¶87-92)

Claim 1 first claims "[a] method of treating cancer in a patient with bevacizumab…" Chen discloses the results of various Phase I and II clinical trials where bevacizumab was used to treat cancer, with citation to those underlying trials. (*See generally* Chen; Bukowski ¶88)

Claim 1 then recites "wherein the patient has a grade III hypertensive event resulting from the bevacizumab administration…" Chen discloses that, across all of the disclosed clinical trials, "[h]ypertension attributable to bevacizumab was common (about 20%) but in most cases, was mild or controllable with medication." (Chen at 1020) Hypertension "controllable with medication" is, by definition, "a grade III hypertensive event," as that term is used in Claim 1 (*i.e.*, "requiring therapy or more intensive therapy than previously"). (*See, supra*, §VIII; Bukowski ¶89) Chen states that the hypertension was "attributable to bevacizumab," (Chen at 1020) satisfying the requirement that hypertension "result[] from the bevacizumab administration." (Bukowski ¶89)

Claim 1 next recites "the method further comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event…" A POSA reading Chen would understand the phrase "controllable with medication" to mean that grade III hypertension arising from bevacizumab was "sufficiently managed" by administering an antihypertensive agent. (Bukowski ¶90)

The final requirement of Claim 1 is "while continuing to treat the patient with bevacizumab, the continued bevacizumab treatment being carried out without altering the dosage regimen." If Genentech tries to circumvent its prosecution arguments about Chen to argue entitlement to the Provisional Application's priority date, Chen meets this limitation as well, as Chen and the Provisional Application provide the same information. (*See, supra*, §X.A.ii; Bukowski ¶68-69, 91)

Chen states that (at 1020) "[h]ypertension attributable to bevacizumab was … controllable with medication" and the Provisional Application states (at 82) that hypertension "was easily managed with oral medications." Chen indicates (at 1020) that "early stopping rules [were used] to minimize risk to patients" and the Provisional Application discloses (at 81) that adverse events led to discontinuations; neither reference identifies discontinuations due to hypertension. Neither Chen nor the Provisional Application indicates whether a dosage reduction

occurred or was planned in the treatment plan. Consequently, Chen and the Provisional Application disclose the same information.

If the Provisional Application is found to have an adequate written description, then Chen anticipates Claim 1.

ii. Chen Anticipates or Renders Obvious the Dependent Claims

As described below, Chen and the references described therein anticipate or render obvious each of the dependent claims. (*See* Bukowski ¶93)

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
2. The method of claim **1**, wherein the method further comprises administering one or more chemotherapeutic agents.	Chen teaches the method of Claim 1 (*see, supra*, §X.C.i; Bukowski ¶88-92), and describes and cites publications of bevacizumab clinical trials with chemotherapeutic agents such as 5-FU, leucovorin, carboplatin and paclitaxel (Chen at 1020).
3. The method of claim **2**, wherein the one or more chemotherapeutic agents is one or more of an alkylating agent, antimetabolite, pyrimidine analog, vinca alkyloid, epipodophyllotoxin, antibiotic, topoisomerase inhibitor, interferon, platinum coordination complex, or taxoid.	*See id.* 5-FU, taught by Chen (*see id.*), is an example of an anti-metabolite. ('672 Patent at 12:2-3, 40-41 ("Examples of chemotherapeutic agents include… anti-metabolites such as … 5-fluorouracil (5-FU)…"))
4. The method of claim **3**, wherein the one or more chemotherapeutic agents is one or more of a pyrimidine analog, 5-fluorouracil (5-FU), leucovorin, irinotecan, paclitaxel, oxaliplatin, carboplatin, cisplatin, doxorubicin, topotecan, or interferon-alpha.	*See* Claims 2 and 3, *supra*.

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
5. The method of claim **4**, wherein the one or more chemotherapeutic agents is one or more of 5-FU, leucovorin, irinotecan, or oxaliplatin.	*See* Claims 2 and 4, *supra*.
6. The method of claim **5**, wherein the one or more chemotherapeutic agents is 5-FU, leucovorin, and irinotecan.	*See* Claims 2 and 5, *supra*.
7. The method of claim **2**, wherein the cancer is colorectal cancer, rectal cancer, glioblastoma, non-small cell lung cancer, cervical cancer, peritoneum cancer, renal cancer, ovarian cancer, or mesothelioma.	Chen teaches the method of Claim 2 (*see* Claim 2, *supra*) and describes and cites to clinical trials in various cancers, including metastatic colorectal cancer, non-small-cell lung cancer and metastatic breast cancer. (*See* Chen at 1020, 1026, citing, *inter alia*, DeVore (Ex1031) (non-small-cell lung cancer); Bergsland 2000 (Ex1020) (metastatic colorectal cancer); Bergsland 2001 (Ex1021) (metastatic colorectal cancer); Kabbinavar 2001 (Ex1010) (metastatic colorectal cancer); Sledge (Ex1030) (metastatic breast cancer); Novotny (Ex1032) (non-small-cell lung cancer))
8. The method of claim **5**, wherein the cancer is metastatic colorectal cancer.	*See* Claims 5 and 7, *supra*.
9. The method of claim **6**, wherein the cancer is metastatic colorectal cancer.	*See* Claims 6 and 7, *supra*.
10. The method of claim **4**, wherein the cancer is metastatic non-small cell lung cancer.	*See,* Claims 4 and 7, *supra*.

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
11. The method of claim **4**, wherein the cancer is metastatic cervical cancer.	Chen teaches the method of Claim 4 (*see* Claim 4, *supra*) and cites an ongoing trial of bevacizumab in cervical cancer. (Chen at 1024) If the Board determines that Chen does not anticipate Claim 11, then Chen renders it obvious. (Bukowski ¶93) Before May 2003, clinicians had identified an association between cervical cancer and VEGF and predicted that "[n]eutralization of VEGF activity may have clinical application in inhibiting malignant ascites formation in ovarian cancer." (Mesiano at Abstract; *see also* Yamamoto at Abstract) Chen also discloses that bevacizumab was an effective treatment for cancers with a known association to VEGF, and that a cervical cancer clinical trial with bevacizumab was underway. (Chen at 1020, 1024)

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
12. The method of claim **4**, wherein the cancer is metastatic ovarian cancer or metastatic peritoneum cancer.	Chen teaches the method of Claim 4 (*see* Claim 4, *supra*) and cites ongoing trials of bevacizumab in ovarian and peritoneal cancers. (Chen at 1024) If the Board determines that Chen does not anticipate Claim 12, Chen renders it obvious. (Bukowski ¶93) Before May 2003, clinicians had identified an association between ovarian cancer and VEGF. (*See*, *e.g.*, Hashimoto at Abstract) Chen also discloses that bevacizumab was an effective treatment for cancers with a known association to VEGF, and that an ovarian cancer clinical trial with bevacizumab was underway. (Chen at 1020, 1024)
13. The method of claim **4**, wherein the cancer is metastatic renal cancer.	Chen teaches the method of Claim 4 (*see* Claim 4, *supra*) and cites Gordon (Ex1029). (Chen at 1026) Gordon discloses the results of a bevacizumab clinical trial in patients with renal cancer. (Gordon Ex1029 at Table 1) Claim 13 is therefore anticipated by Chen and/or rendered obvious by Chen in view of Gordon. (Bukowski ¶93)
14. The method of claim **1**, wherein the cancer is glioblastoma.	In addition to the bevacizumab-related clinical trials described above (*see* Claims 7-13), Chen describes how, in preclinical models, "[a]nti-VEGF MAbs have shown potent growth inhibition in vivo in a variety of human cancer xenograft and metastasis models, including … glioblastoma." (Chen at 1020) A POSA would therefore reasonably expect that bevacizumab would effectively treat glioblastoma.

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
15. The method of claim **1**, wherein the bevacizumab is administered to the patient bi-weekly at about 10 mg/kg.	Chen teaches the method of Claim 1 (*see*, *supra*, §X.C.i; Bukowski ¶88-92) and discloses that "[r]ecommended doses for further studies are 5 or 10 mg every 2 weeks..." (Chen at 1020) Chen also cites trials investigating that dosing regimen, such as Bergsland 2000 (Ex1020). (Chen at 1026)
16. The method of claim **4**, wherein the patient does not have clinically significant cardiovascular disease prior to the bevacizumab administration.	Chen teaches the method of Claim 4 (*see* Claim 4, *supra*), and renders this claim obvious in view of clinical practice. (Chen at 1020; (Bukowski ¶93)) As hypertension was a well-known side effect of bevacizumab, a POSA would recognize that patients with pre-existing cardiovascular disease may not be suitable candidates for bevacizumab treatment. It was also a POSA's standard clinical practice to consider and screen for pre-existing cardiovascular disease when determining how to treat hypertension in a particular patient. (*See, e.g.,* Harrison's at 1420, Figure 246-1) Thus, it would have been obvious to a POSA that the method of claim 4 should be applied to patients who did not have clinically significant cardiovascular disease before bevacizumab administration. (Bukowski ¶93)
17. The method of claim **8**, wherein one of the one or more chemotherapeutic agents is 5-FU.	*See* Claims 2 and 8, *supra.*

Dependent Claims	***Chen and Underlying Clinical Trial Reports***
18. The method of claim **1**, wherein the bevacizumab is administered to the patient bi-weekly at about 5 mg/kg.	Chen teaches the method of Claim 1 (*see*, *supra*, §X.C.i; Bukowski ¶88-92) and discloses that "[r]ecommended doses for further studies are 5 or 10 mg every 2 weeks..." (Chen at 1020) Chen also cites trials investigating that dosing regimen, such as Bergsland 2000 (Ex1020). (Chen at 1026)

D. Ground 3: Yang Anticipates or Renders Obvious the Challenged Claims

Yang was published on July 31, 2003. Genentech submitted Kabbinavar during prosecution (Prosecution History at 3344), though it was not discussed by Genentech or the Examiner. Because the '672 patent is entitled to a priority date no earlier than May 28, 2004 (*see*, *supra*, §X.A), and Yang is a printed publication accessible to the public more than one year before that date (Bukowski ¶94; *see also* Yang at 10, showing Library of Congress's July 31, 2003 publication date), Yang is §102(a) prior art.

i. Yang Anticipates Claim 1

Yang discloses the results of a Phase II trial initiated more than four years before the 2003 Provisional Application was filed. (*See*, *supra*, §VII.D) Yang discloses every requirement of Claim 1, as follows (*see also* Bukowski ¶96-102):

Claim 1 first claims, "[a] method of treating cancer in a patient with bevacizumab…" Yang teaches a method of treating renal cancer with bevacizumab. (*See, e.g.*, Yang abstract; Bukowski ¶96)

Claim 1 next recites, "wherein the patient has a grade III hypertensive event resulting from the bevacizumab administration…" Yang teaches that 15 patients who received bevacizumab experienced hypertension, reporting a median time to onset for "newly diagnosed hypertension" of 131 days. (Yang at 430, Table 2) Yang explains that "hypertension during the study was treated… with standard regimens for essential hypertension." (*Id.* at 430) Hypertension requiring treatment is, by definition, "grade III hypertension" in Claim 1. (*See, supra*, §VIII) Yang teaches that grade III hypertensive events resulted from bevacizumab administration. (*Id.*; Bukowski ¶97)

Claim 1 next recites, "the method further comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event…" Yang teaches that patients with grade III hypertension (according to the definition in Claim 1) were managed "by the patients' private physicians with standard regimens for essential hypertension." (Yang at 430) The standard regimen for treating hypertension included antihypertensive medication. (*Id.* at Table 2; Bukowski ¶98)

Finally, Claim 1 recites, "while continuing to treat the patient with bevacizumab, the continued bevacizumab treatment being carried out without altering the dosage regimen." Regarding hypertension, Yang teaches that "[a]ll planned doses of the study drug were given unless grade 3 toxic effects occurred, in which case doses were withheld as specified by the study protocol." (Yang at 430) Notably, Yang uses the term "grade 3 hypertension," but gives it a ***different*** definition than Claim 1. Yang defines grade III hypertension as "hypertension not completely controlled by ***one standard medication***" (*id.* at 430, Table 2 (emphasis added)), whereas grade III hypertension in Claim 1 is "hypertension requiring therapy or more intensive therapy than previously" (*see, supra,* §VIII). Yang discloses that bevacizumab was withheld only if Yang's higher standard was met; for all other patients whose hypertension "was treated… with standard regimens for essential hypertension" (*i.e.*, for patients with "grade III hypertension" *per* Claim 1), the bevacizumab dosage regimen was ***not*** altered. (*Id.* at 430; Bukowski ¶99-102)

Yang teaches that, in response to a grade III hypertensive event, an antihypertensive agent was administered and bevacizumab dosing was maintained. As with Kabbinavar, these explicit instructions are absent from the Provisional Application. Yang anticipates Claim 1.

ii. Yang Anticipates or Renders Obvious Each Dependent Claim

Chen summarizes clinical trial information available as of its publication in August 2001. (*See, supra*, §X.C.ii) A POSA who had reviewed Yang and sought additional bevacizumab clinical trial information would have combined Yang with the teachings of Chen and the clinical trial publications it describes. (Bukowski ¶103) Yang (which anticipates Claim 1), in combination with Chen and/or the underlying clinical trial publications (which disclose every requirement of the dependent claims (*see, supra,* §X.C.ii)), renders obvious each of the dependent claims. (Bukowski ¶104) Without restating the entire claim chart provided above in connection with Chen (§X.C.ii), a summary is provided here.

Claims 2-6 and 17 add the step of administering one or more specific chemotherapeutic agents. While the Yang trial did not use a chemotherapeutic agent, Yang concludes by suggesting the combination of bevacizumab with non-anti-VEGF agents. (Yang at 433) Chen describes combining bevacizumab with chemotherapeutic agents such as 5-FU, leucovorin, carboplatin and paclitaxel (Chen at 1020), none of which are anti-VEGF agents. Yang, in combination with Chen, renders Claims 2-6 and 17 obvious. (Bukowski ¶104)

Claims 7-14 list various cancers in which the method of Claim 1 can be used. Chen describes and cites clinical trials with bevaciumab or other anti-VEGF antibodies in at least one cancer required by each of Claims 7-14. (*See, supra,*

§X.C.ii) Yang, in combination with Chen, renders Claims 7-14 obvious. (Bukowski ¶104)

Claims 15 and 18 require bevacizumab administration bi-weekly at about 10 mg/kg and 5 mg/kg. Yang discloses that bevacizumab was administered bi-weekly at 10 mg/kg, anticipating Claim 15. Chen discloses both claimed dosage regimens. (*See, supra,* §X.C.ii) Yang, in combination with Chen, renders Claim 18 obvious. (Bukowski ¶104)

Claim 16 adds to Claim 4 that, prior to bevacizumab administration, the patient does not have clinically significant cardiovascular disease. Because hypertension was a well-known side effect of bevacizumab, a POSA would recognize that patients with pre-existing cardiovascular disease may not be suitable for bevacizumab treatment. (Bukowski ¶¶61(d), 104) It was also standard clinical practice to consider and screen for pre-existing cardiovascular disease before treating hypertension. (*Id.*; *see also* Harrison's at 1420, Figure 246-1; *supra,* §X.C.ii) Yang, in combination with Chen, renders Claim 16 obvious.

E. Grounds 4 & 5: PCT'360 Renders Obvious the Challenged Claims

PCT'360 and Presta, published October 11, 2001 and October 15, 1997 respectively, were publicly available more than one year before the earliest possible priority date for the '672 patent. Both references are prior art under §102(b) regardless of whether the '672 patent is entitled to the May 30, 2003

priority date. To Petitioner's knowledge, PCT'360 was not cited during prosecution. Genentech submitted Presta during prosecution (Prosecution History at 3336), though it was not discussed by Genentech or the Examiner.

i. Ground 4: PCT'360, in Combination with Presta, Renders Obvious the Challenged Claims

A method of treatment claim is obvious where it merely confirms a result in humans that was observed and predicted from animal testing. *Pharmastem Therapeutics,* 491 F.3d at 1363-64. Through animal testing, PCT'360 advised that hypertension may occur with bevacizumab treatment, confirming clinical observations, and described the mechanism by which anti-VEGF agents like bevacizumab have this effect. (*Id*. at 2:27-3:24; *see, supra,* §VII.C) It also taught the POSA how to treat that hypertension and that bevacizumab treatment could be continued during this treatment. (*Id.*) Thus, PCT'360, when read with Presta, renders Claim 1 obvious, as follows (*see* Bukowski ¶106-123):

Claim 1 claims, "[a] method of treating cancer in a patient with bevacizumab…" PCT'360 teaches a method of treating cancer with anti-VEGF therapy (*id.* at 1:29-31), and identifies the antibody A.4.6.1 as one anti-VEGF therapy (*id.* at 15:11-17 ("[Antiangiogenic] [a]gents which inhibit the action of growth factors include… an anti-VEGF receptor antibody (Genentech, Canadian Patent Application No. 2213833) [A.4.6.1]."). (Bukowski ¶113-114)

Presta describes the humanization of A.4.6.1 into bevacizumab (referred to as "rhuMAb"). (*See generally* Presta) Presta concludes that "[bevacizumab] is suitable for clinical trials to test the hypothesis that inhibition of VEGF action is an effective strategy for the treatment of cancer and other disorders in humans." (*Id.* at 4593)

Claim 1 next recites, "wherein the patient has a grade III hypertensive event resulting from the bevacizumab administration…" PCT'360 states that anti-VEGF therapy causes hypertension. (*See id.* at 4:3-5; *see also* Figure 1, showing that an anti-VEGF agent increases blood pressure in rats.) A POSA would understand that such hypertension includes grade III hypertension because, *inter alia*, PCT'360 teaches administering an antihypertensive medication to treat the hypertension (*id.* at 8:23-29), which meets the Claim 1 definition of grade III hypertension (*see, supra*, §VIII). A POSA would have combined these preclinical teachings with their clinical experience and knowledge of internal medicine to determine when hypertension required treatment. (*See, supra,* §VII; Bukowski ¶115) PCT'360 teaches that a patient may have grade III hypertension resulting from bevacizumab administration.

Claim 1 next recites, "…the method further comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event…" PCT'360 teaches administering an antihypertensive to

manage the grade III hypertension. For example, in Example 1 of PCT'360, the increase in blood pressure from the anti-VEGF agent was reversed by adding the antihypertensive agent captopril. (*Id.* at 30:20-21, Figure 1) PCT'360 gives exemplary antihypertensives that can be used to control hypertension related to antiangiogenic agents like bevacizumab. (*See id.* at 8:23-15:10)

The final part of Claim 1 recites, "…while continuing to treat the patient with bevacizumab, the continued bevacizumab treatment being carried out without altering the dosage regimen." PCT'360 teaches combining anti-VEGF agents, like bevacizumab, and antihypertensive agents, where the anti-VEGF dosage regimen is continued and not altered. In the Example 1 preclinical study, "[the anti-VEGF compound] was dosed p.o. at 12.5 mg/kg once daily for 10 days. For the next 4 days (i.e. days 11 to 14 of compound dosing) the rats were dosed with the ACE inhibitor captopril at 30 mg/kg p.o. once daily ***in addition to the [anti-VEGF compound]***." (*See id.* at 30:12-15) In other words, the anti-VEGF treatment was maintained at its initial dosage regimen. (Bukowski ¶117) Claim 1 is obvious in view of the teachings of PCT'360 and Presta.

ii. Ground 5: Claim 1 is Rendered Obvious by Prior Art Clinical Practice

The obviousness of Claim 1 in view of PCT'360 and Presta is reinforced by the standard of care for hypertension and clinical practice involving bevacizumab and hypertension. (Bukowski ¶119-121); *Ormco,* 463 F.3d 1299, 1307-08.

As described above in §§VII.D and X.B.ii, the standard clinical practice as of May 30, 2003 (and May 28, 2004) was to treat hypertension on an individual patient basis. (*See also* Harrison's at 1425, Figure 246-1) A POSA would consider all relevant factors, including the severity of the hypertension and the patient's overall condition, before designing a treatment plan. (Bukowski ¶46-51, 120) Because even mild hypertension may be considered a "grade III hypertensive event" at the POSA's discretion, a POSA would reasonably expect that administering an anti-VEGF therapy with an antihypertensive treatment would succeed in line with the normal rates of success associated with each treatment. (*Id.* at 120) This expectation is consistent with and bolstered by the preclinical results described in PCT'360.

While a POSA would have had a reasonable expectation of success based on PCT'360 alone, clinical practice from before May 30, 2003 would have further bolstered that expectation of success. (Bukowski ¶121)

iii. Grounds 4 & 5: PCT'360, in Combination with Chen, Presta, and/or Clinical Practice, Renders Obvious the Dependent Claims

A POSA who had reviewed PCT'360 and sought additional bevacizumab clinical trial information would have consulted Chen and the clinical trial publications it describes. (Bukowski ¶122) PCT'360, Presta and prior art clinical practice (which render Claim 1 obvious (*see, supra,* §X.E.i-ii)), in combination

with Chen and/or the underlying clinical trial publications (which disclose every requirement of the dependent claims (*see, supra,* §X.C.ii)), render obvious each of the dependent claims. (Bukowski ¶123) Without restating the entirety of the claim chart provided above in connection with Chen (§X.C.ii), a brief summary is provided here.

Claims 2-6 and 17 add the step of administering one or more specific chemotherapeutic agents. Chen teaches administering chemotherapeutic agents such as 5-FU, leucovorin, carboplatin and paclitaxel (Chen at 1020), meeting the requirements of Claims 2-6 and 17. (*See, supra,* §X.C.ii) Claims 2-6 and 17 are obvious. (Bukowski ¶123)

Claims 7-14 list various cancers in which the method of Claim 1 can be used. Chen describes and cites clinical trials with bevaciumab or other anti-VEGF antibodies in at least one cancer required by each of Claims 7-14, satisfying the requirements of those claims. (*See, supra,* §X.C.ii) Claims 7-14 are obvious. (Bukowski ¶123)

Claims 15 and 18 require that bevacizumab is administered bi-weekly at about 10 mg/kg and 5 mg/kg. Chen discloses that these dosage regimens were used at the time. (*See, supra,* §X.C.ii) Claims 15 and 18 are obvious. (Bukowski ¶123)

Claim 16 adds to Claim 4 that, before bevacizumab administration, the

patient does not have clinically significant cardiovascular disease. Because hypertension was a well-known side effect of bevacizumab, a POSA would recognize that patients with pre-existing cardiovascular disease may not be suitable for bevacizumab treatment. (Bukowski ¶¶61(d), 123) It was also standard clinical practice to consider and screen for pre-existing cardiovascular disease before treating hypertension. (*Id.*; *see also* Harrison's at 1420, Figure 246-1; *supra*, §X.C.ii) Claim 16 is obvious. (Bukowski ¶123)

F. No Objective Indicia of Non-Obviousness

No objective indicia of non-obviousness are sufficiently probative to overcome the invalidity of the '672 patent under 35 U.S.C. §103. Specifically, there are no secondary factors, such as commercial success, long-felt but unmet need, licensing, unexpected results, professional skepticism, or copying by others sufficiently probative to overcome the clear and convincing case that the Challenged Claims are invalid.

Further, no alleged secondary factor can be attributed to the '672 patent. According to the label for Genentech's bevacizumab product, Avastin®, only 5-18% of patients experience a grade III or IV hypertensive event. (Avastin® Label (Ex 1053) at §5.6) The claimed invention is therefore irrelevant for the significant majority of patients. Moreover, in litigation against others, Genentech has alleged that other unrelated and earlier-expiring patents cover bevacizumab.

(*See, supra*, §II.B) In view of these other patents, Genentech cannot demonstrate a nexus between the Challenged Claims and any alleged objective indicia.

The Challenged Claims are unpatentable and should be cancelled.

Date: January 5, 2018

Respectfully submitted,

/s/ Robert Counihan

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 13,474, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, and appendix listing of exhibits.

Date: January 5, 2018

Signed,

/s/ Robert Counihan
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Counsel for Pfizer Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 5th day of January, 2018, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,795,672 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

Clark & Elbing LLP
101 Federal Street
Boston, Massachusetts 02110

The foregoing Petition and accompanying exhibits referenced therein were also served on this 5th day of January, 2018 via PRIORITY MAIL EXPRESS® for overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

Genentech Inc.
1 DNA Way,
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Date: January 5, 2018

Signed,

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