

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REPLIMUNE LIMITED AND REPLIMUNE, INC.,
Petitioners,

v.

AMGEN INC.,
Patent Owner.

IPR2023-00106
Patent 10,034,938 B2

Before KRISTIL R. SAWERT, CYNTHIA M. HARDMAN, and
JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Replimune Limited and Replimune, Inc. (collectively, “Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1, 2, 4–8, 10, 11, and 14–19 of U.S. Patent No. 10,034,938 B2 (Ex. 1001, “the ’938 patent”). Amgen Inc. (“Patent Owner”) filed a Preliminary Response (Paper 8, “Prelim. Resp.”). With the Preliminary Response, Patent Owner filed a Statutory Disclaimer of claims 2, 10, 14, and 17–19 of the ’938 patent. Prelim. Resp. 1, n.2; Ex. 2005. With Board authorization, Petitioner filed a Reply (Paper 9, “Reply”), and Patent Owner filed a Sur-reply (Paper 10, “PO Sur-reply”) limited to addressing whether the Board should exercise its discretion and deny review under 35 U.S.C. § 325(d).

Under 35 U.S.C. § 314(a), the Board “may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” After considering the Petition, the Preliminary Response, the Reply, the PO Sur-reply, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1, 4–8, 11, 15, and 16 of the ’938 patent, based on all of the grounds identified in the Petition.

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any

arguments not raised by Patent Owner in a timely-filed Response may be deemed waived, even if they were presented in the Preliminary Response.

II. BACKGROUND

A. Real Parties-in-Interest

Petitioner identifies Replimune Limited and Replimune, Inc. as the real parties-in-interest. *See* Pet. 4. Patent Owner identifies Amgen Inc. as the real party-in-interest. Paper 3, 1.

B. Related Matters

The parties do not identify any pending related matters.

C. The '938 Patent (Ex. 1001)

The '938 patent is titled “Method for Treating Melanoma Using a Herpes Simplex Virus and an Immune Checkpoint Inhibitor.” Ex. 1001, code (54). Melanoma is a tumor of melanocytes, mostly arising in the skin. *Id.* at 1:19–22. “Melanoma is the fifth most common cancer in men and the sixth most common cancer in women in the United States” and its incidence increased rapidly worldwide between 1973 and 2002. *Id.* at 2:4–20. According to the '938 patent, “[m]elanoma that has spread to distant sites (Stage IV) is infrequently curable with standard therapy” although new therapies, including ipilimumab and vemurafenib, offer survival benefits. *Id.* at 1:65–2:3, 2:26–30. Other known therapies for unresectable or advanced melanoma in adults include administering chemotherapy or interleukin-2. *Id.* at 2:21–24. According to the '938 patent, despite existing nonsurgical therapies, “[t]here is a need for additional melanoma treatments.” *Id.* at 2:31–33.

The '938 patent describes “a method for the treatment of melanoma comprising administering to a patient with stages IIIb to IV melanoma an effective amount of an immune checkpoint inhibitor and a herpes simplex

virus.” Ex. 1001, 5:20–23. The specification defines “immune checkpoint inhibitor” as “molecules that totally or partially reduce, inhibit, interfere with or modulate one or more checkpoint proteins.” *Id.* at 5:49–51. Known checkpoint proteins include cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1). *Id.* at 9:15, 36–37. According to the ’938 patent, blocking CTLA-4 with anti-CTLA-4 antibodies has been shown to augment T-cell activation and proliferation. *Id.* at 9:19–21. Known anti-CTLA-4 antibodies include ipilimumab, “a fully human monoclonal IgG antibody” that “is marketed under the name YervoyTM and has been approved for the treatment of unresectable or metastatic melanoma.” *Id.* at 9:30–35.

The ’938 patent describes combining an immune checkpoint inhibitor with a herpes simplex virus that lacks a functional ICP34.5 gene, lacks a functional ICP47 gene, and includes a gene encoding human granulocyte macrophage colony stimulating factor (“GM-CSF”). *Id.* at 7:41–44; 10:8–10. Deleting the ICP34.5 gene renders the virus avirulent. *Id.* at 7:47–49. Deleting the ICP47 gene allows greater antigen processing within the infected cell resulting in an increase in the immune response. *Id.* at 7:54–56. Encoding GM-CSF produces a cytokine that stimulates the immune response. *Id.* at 7:56–62. Known herpes simplex viruses lacking ICP34.5 and ICP47 genes and encoding GM-CSF include “Talimogene laherparepvec, HSV-1 [strain JS1] ICP34.5-ICP47-/hGM-CSF (previously known as OncoVEX^{Gm-CSF}),” an intratumorally delivered oncolytic virus that selectively replicates in solid tumor cells. *Id.* at 7:62–67.

The ’938 patent explains that the combination of an immune checkpoint inhibitor, e.g., ipilimumab, with herpes simplex virus, e.g., talimogene laherparepvec, “may result in enhanced destruction of injected

tumors as well as uninjected/distant tumors . . . to improve the rate of overall tumor response and duration of response.” Ex. 1001, 10:8–26. More specifically, the combination of talimogene laherparepvec with an immune checkpoint inhibitor “is intended to enhance T-cell activation through different mechanisms, respectively augmenting dendritic cell-mediated tumor antigen presentation . . . following the release of tumor antigens by lytic virus replication, enhanced through the local expression of GM-CSF, and antagonizing immune tolerance by blocking inhibitor signals mediated by a immune checkpoint inhibitor, such as CTLA-4.” *Id.* at 10:27–37.

The ’938 patent describes a study to “determine the safety and tolerability of talimogene laherparepvec in combination with ipilimumab as assessed by incidence of dose-limiting toxicities (DLT) in subjects with previously untreated, unresectable, stages IIIb to IV melanoma.” Ex. 1001, 18:34–19:37. Specifically, talimogene laherparepvec was administered by intratumoral injection “at a dose of up to 4.0 ml of 10^6 plaque forming unit/mL (PFU/mL) at day 1 of week 1 followed by a dose of up to 4.0 ml of 10^8 plaque forming unit/mL (PFU/mL) at day 1 of week 4 and every 2 weeks (± 3 days) thereafter.” *Id.* at 18:42–47. “Ipilimumab was administered intravenously at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 6 (i.e., at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15.” *Id.* at 18:47–52. No dose-limiting toxicities were observed in the patients completing the dose-limiting toxicity time evaluation, including patients that received at least 4 doses of talimogene laherparepvec and 2 doses of ipilimumab. *Id.* at 19:13–25. No efficacy data is reported for this phase of the study.

The '938 patent also describes Phase 2 of the study as a prophetic protocol “to estimate the safety and efficacy of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone as assessed by overall survival in subjects with previously untreated, unresectable, stages IIIb to IV melanoma.” Ex. 1001, 19:38–21:23.

D. Statutory Disclaimer

After the filing of the Petition in this proceeding, Patent Owner filed a statutory disclaimer, disclaiming claims 2, 10, 14, and 17–19 of the '938 patent, effective February 17, 2023. Prelim. Resp. 1, n.2; Ex. 2005, 1. “No *inter partes* review will be instituted based on disclaimed claims.” 37 C.F.R. § 42.107(e). We do not analyze the patentability of claims 2, 10, 14, and 17–19 because these claims have been statutorily disclaimed.

E. Challenged Claims

Of the remaining non-disclaimed claims, Petitioner challenges claims 1, 4–8, 11, 15, and 16 of the '938 patent. Claim 1, which is the only challenged independent claim of the '938 patent, is illustrative of the challenged claims, and is reproduced below:

1. A method for the treatment of melanoma, said method comprising administering to a patient with stages IIIb to IV melanoma:

- (i) an effective amount of an anti-PD-1 antibody or anti-CTLA-4 antibody; and
- (ii) a herpes simplex virus, wherein said herpes simplex virus:
 - lacks a functional ICP34.5 encoding gene;
 - lacks a functional ICP47 encoding gene; and
 - comprises a gene encoding human GM-CSF.

Ex. 1001, 21:26–36. Challenged claims 4–8, 11, 15 and 16 depend from claim 1, either directly or indirectly.

A. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 4–8, 11, 15, and 16 of the ’938 patent (“the challenged claims”) are unpatentable in view of the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1	1, 4–8, 11, 15, 16	102	Natarajan ²
2	1, 4–8, 11, 15, 16	103	Natarajan

Pet. 4. Petitioner submits the Declaration of Jeffrey A. Sosman, M.D. (Ex. 1002) in support of institution of *inter partes* review.

B. Asserted Prior Art

1. Natarajan (Ex. 1003)

Natarajan, titled “Novel Immunotherapeutic Agents and Small Molecule Antagonists of Signalling Kinases for the Treatment of Metastatic Melanoma,” is a review article discussing the rationale and recent trial results for treating unresectable stage III and IV melanoma. Ex. 1003, 1233–34.³ Natarajan discloses that the agents discussed in the article “are enabling the rational design of novel combination trials to simultaneously increase antigen presentation, deplete regulatory T cells and block immune

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. § 103, was effective on March 16, 2013. Because the ’938 patent claims priority to a provisional application that has a filing date before March 16, 2013, and Petitioner does not currently contest this priority date, we apply the pre-AIA version of § 103. We note that our analysis in this Decision would not change under AIA law.

² Natarajan et al., *Novel Immunotherapeutic Agents and Small Molecule Antagonists of Signalling Kinases for the Treatment of Metastatic Melanoma*, DRUGS 71(10):1233–1250 (2011) (Ex. 1003, “Natarajan”).

³ The cited page numbers in Exhibit 1003 refer to original page numbers at the top of the reference.

check-points in order to activate melanoma antigen-specific immunity.” *Id.* at 1233.

Natarajan discloses therapeutic options for unresectable stage III and IV melanoma, including ipilimumab and OncoVEX^{GM-CSF}. Ex. 1003, 1237–1240. Natarajan describes ipilimumab as “a human monoclonal antibody that blocks the T-cell negative regulator, CTLA-4.” *Id.* at 1238. Natarajan also describes dosing of ipilimumab at 10 mg/kg having an 11.1% overall response rate and at 3 mg/kg having a 4.2% overall response rate. *Id.* at 1239.

Natarajan describes OncoVEX^{GM-CSF} as an oncolytic herpes simplex virus “that has been engineered to be both non-pathogenic and immunogenic through multiple genetic alterations.” Ex. 1003, 1240. The alterations include: “(i) deletion of ICP34.5,” “(ii) deletion of ICP47,” and “(iii) insertion of the open-reading frame of GM-CSF which promotes the differentiation of monocytic progenitor cells into DCs [dendritic cells].” *Id.* Natarajan describes dosing unresectable stage IIIc and IV melanoma patients with “intratumoral injections of up to 4 mL of 10⁶ plaque forming units (pfu)/mL of OncoVEX^{GM-CSF} followed 3 weeks later by up to 4 mL of 10⁸ pfu/mL every 2 weeks for up to 24 treatments,” resulting in a 26% overall response rate. *Id.*

Natarajan discloses that “[c]linical trialists now have the unique opportunity to develop novel protocols to test immunotherapeutic agents with an emphasis on rational combinations, scheduling and dosing in patients with melanoma.” Ex. 1003, 1242. Natarajan notes that “no study in humans has been conducted to analyze the effects of combined administration of gp100 (antigen), GM-CSF . . . , denileukin diftitox . . . , [and] anti-CTLA-4 (e.g., ipilimumab) to prevent negative feedback of the

effector phase (figure 1).” *Id.* Natarajan specifically identifies incorporating OncoVEX^{GM-CSF} for targeted delivery of GM-CSF. *Id.*

Natarajan’s Figure 1 is reproduced below.

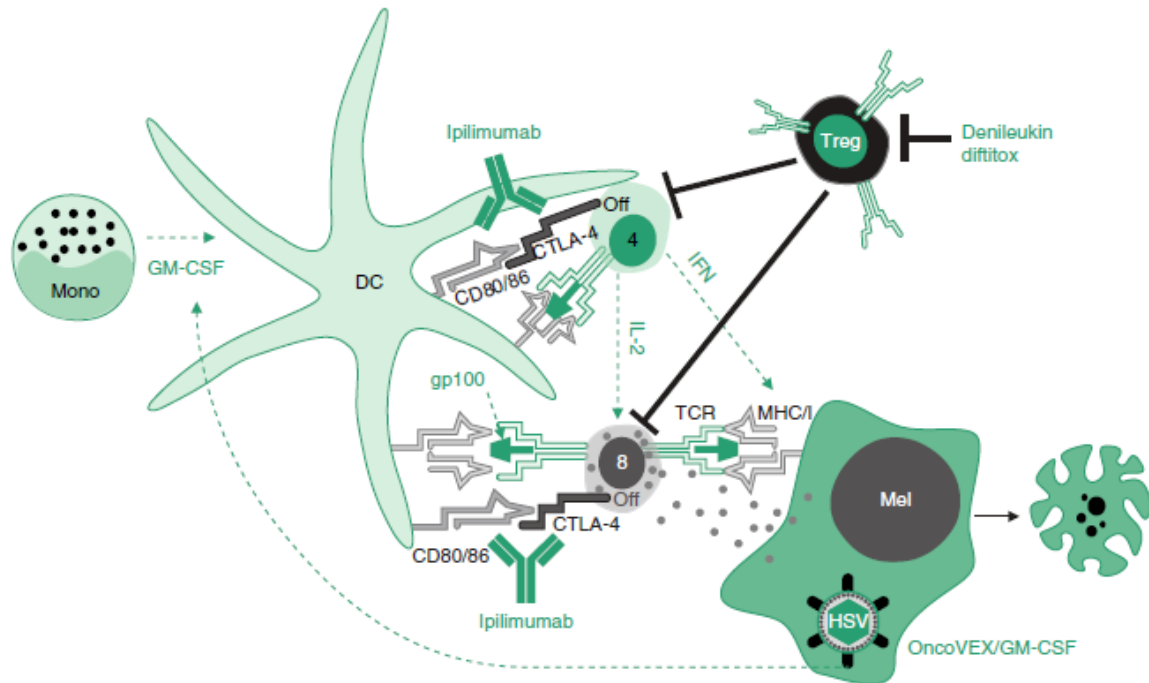


Figure 1 is a biological diagram illustrating “combination immunotherapy for the treatment of unresectable melanoma.” Ex. 1003, 1243. The biological diagram includes a dendritic cell (DC) priming naïve CD4+ and CD+8 T-cells to become activated against melanoma cells (Mel). *Id.* The melanoma cell is illustrated as a circle being infected with a herpes simplex virus (“HSV”), specifically, OncoVEX/GM-CSF. *Id.* OncoVEX/GM-CSF that has infected melanoma cells expresses GM-CSF that can promote differentiation of monocytes (shown as “Mono”) into DCs. *Id.* The DC interacts with the CD4+ and CD8+ T-cells through cluster of differentiation 80 and 86 (CD80/86) on the DC and CTLA-4 on the T cells. *Id.* Ipilimumab is shown as an antibody that “interrupts the physical interaction between CD80/86 and the T-cell negative regulator CTLA-4.” *Id.* Accordingly, the T-cell receptor (“TCR”) recognizes the “specific peptide

antigens presented by [major histocompatibility complex (‘MHC’)] class I molecules on the surface of melanoma cells.” *Id.*

III. DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Petition presents substantially the same art and arguments that the Office previously analyzed and fails to show that the Office erred during prosecution. *See* Prelim. Resp. 58–68.

We have discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d) (“Section 325(d)”). In that respect, Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.⁴ *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating the exercise of discretion to deny institution under Section 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

⁴ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”).

Factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* “At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9.

A. The '938 Patent Prosecution History

The original application for the '938 patent was filed with a preliminary amendment listing twenty-three claims. Ex. 2004, 12–16.⁵ Claim 1 recited an “immune checkpoint inhibitor” and dependent claims 7 and 11 recited an “anti-CTLA-4 antibody” and a “PD-L1 blocker,” respectively. *Id.* at 13–14.

In a Non-Final Office Action on February 19, 2016, the Examiner rejected claim 1 as anticipated by or, in the alternative, obvious over Eagle.⁶ Ex. 2004, 1021–1024. The Examiner found that Eagle teaches a method for treating melanoma by “administering to a patient a combination treatment of a therapeutically effective amount of an intralesional chemoablative pharmaceutical composition along with a therapeutically effective amount of a systemic immunomodulatory anticancer agent.” *Id.* at 1023. The Examiner also found that Eagle teaches the use of an immune checkpoint-inhibitor, such as the anti-CTLA-4 antibody ipilimumab and an oncolytic herpes simplex virus (“HSV”) comprising a gene encoding human GM-CSF (OncoVEX). *Id.* The Examiner maintained this rejection in an August 1, 2016 Office Action. *Id.* at 1119–1123.

In response, the applicant argued that “Eagle refers to combinations of [1] an intralesional chemoablative pharmaceutical composition; and [2] a systemic targeted anticancer agent” but “*defines and characterizes* both anti-CTLA-4 antibodies . . . and OncoVex *solely* as ‘systemic immunomodulatory anticancer agents.’” *Id.* at 1167–68. Therefore,

⁵ The cited page numbers in Exhibit 2004 refer to the page numbers added by Patent Owner in the bottom-right corner of the page.

⁶ Eagle et al., US 2012/0263677 A1, published Oct. 18, 2012 (Ex. 1027, “Eagle”).

according to the applicant, “Eagle clearly fails to anticipate the instant claims . . . because nothing in Eagle teaches or even suggests combining two systemic immunomodulatory anticancer agents (i.e., combining [1] an immune checkpoint inhibitor; and [2] a modified [HSV]).” *Id.* at 1169.

In response to the applicant’s arguments, the Examiner withdrew the anticipation and obviousness rejections over Eagle and issued a new rejection of claim 1 as obvious over Eagle, Eshun⁷, and Zhang.⁸ Ex. 2004, 1216–1221. The Examiner found that, although Eagle focuses on the combination of a chemical agent with a systemic agent, e.g., anti-CTLA-4 antibody, “delivery of an oncogenic HSV with an anti-cancer antibody was a combination treatment modality that was known in the art at the time of filing and would be obvious to try, as evidenced by the teachings of Zhang and Eshun.” *Id.* at 9.

In response to the new rejection, the applicant argued that “nothing in Eagle, Eshun, or Zhang, either alone or in combination, would have led the skilled artisan to the claimed method of treating a patient with stages IIIb to IV melanoma with the [claimed] combination.” Ex. 2004, 1265. The applicant further argued “that the combination of HSV and immune checkpoint inhibitor recited in the claims, when administered to patients

⁷ Eshun et al., *VEGF blockade decreases the tumor uptake of systemic oncolytic herpes virus but enhances therapeutic efficacy when given after virotherapy*, GENE THERAPY 17(7):922–929 (2010) (Ex. 1022, “Eshun”).

⁸ Zhang et al., *Bevacizumab with angiostatin-armed oHSV increases antiangiogenesis and decreases bevacizumab-induced invasion in U87 glioma*, MOLECULAR THERAPY 20(1):37–45 (2012) (Ex. 1023, “Zhang”).

with stages IIIb to IV melanoma, demonstrates an improved systemic immune response that is neither taught nor suggested in the cited art.”

Id. at 23. Specifically, the applicant argued that “the combination of T-VEC + [ipilimumab] yields an unexpected superior increase in systemic effect (35.5%), as compared to either drug alone (15% and 13.6%, respectively).”

Id. at 1267 (citing to studies from Chesney⁹ and Andtbacka¹⁰). The applicant submitted the summary table below showing visceral lesion response rate:

Visceral Lesion Response Rate		
T-VEC (Andtbacka)	T-VEC + ipi (Chesney)	Ipi (Chesney)
15%	35.5%	13.6%

Id. at 1267.

In a November 22, 2017 Final Rejection, the Examiner maintained all the same rejections against the claims. Ex. 2004, 1423–1425. The Examiner determined that “the argument of unexpected and/or surprising results are not entirely commensurate in scope with the instantly claimed invention, as a specific immune checkpoint inhibitor is not presently claimed, nor is a specific outcome of said method.” *Id.* at 1425. The Examiner further determined that “the 6.9% increase in effect could be due to synergism of the two therapies, or could be due to a simple additive effect

⁹ Chesney et al., *Primary results from randomized (1:1), open-label phase II study of talimogene laherparepex (T) and ipilimumab (I) vs I alone in unresected stage IIB-IV melanoma*, JOURNAL OF CLINICAL ONCOLOGY, Vol. 35(15):9509–9509, 2017 (Ex. 1008, “Chesney”).

¹⁰ Andtbacka et al., *Talimogene Laherparepvec Improves Durable Response Rate in Patients with Advanced Melanoma*, JOURNAL OF CLINICAL ONCOLOGY, Vol. 33(25):2780–2788, 2015 (Ex. 1007, “Andtbacka”).

of the two therapies in line with a natural standard deviation Therefore, it is **not** clear and convincing that 1) this is a synergistic (and not additive) effect of the two therapies, 2) the additive effect of combining these two therapies would be unexpected in view of Eagle, Eshun, and Zhang.” *Id.*

In response to the Examiner’s rejection, in a February 14, 2018, response, the applicant argued that updated data from Chesney 2¹¹ showed “an even greater visceral lesion response rate of 52% . . . with the combination of T-VEC + [ipilimumab] compared to 23% for ipilimumab melanoma monotherapy,” and argued that this combination “yields an unexpected superior increase in systemic effect (52%), as compared to either drug alone.” Ex. 2004, 1439–1441. The applicant also submitted data from Ribas¹² showing that the combination of T-VEC with another checkpoint inhibitor (the anti-PD-1 antibody pembrolizumab (“pembro”)) showed that the combination resulted in a >50% reduction in 33% of visceral lesions. *Id.* at 1140. The applicant presented the summary table below:

Visceral Lesion Response Rate			
T-VEC monotherapy (Andtbacka)	Ipi monotherapy (Chesney 2)	T-VEC + ipi (Chesney 2)	T-VEC + pembro (Ribas)
15%	23%	52%	33%

¹¹ Chesney et al., *Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination with Ipilimumab Versus Ipilimumab Alone in Patients with Advanced, Unresectable Melanoma*, JOURNAL OF CLINICAL ONCOLOGY, Vol. 36(17):1658–1667, 2018 (Ex. 1006, “Chesney 2”).

¹² Ribas et al., *Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy*, CELL, 170:1109–1119, 2017 (Ex. 1009, “Ribas”).

Id. at 1441.

However, in a February 21, 2018 supplemental response, the applicant “clarif[ied]” that the 52% and 23% lesion response rates cited for Chesney 2 in the February 14, 2018 response, referred “to visceral lesions where *any* change in tumor area from baseline was observed” and the response rate for visceral lesions where $\geq 50\%$ change in tumor area from baseline for the combination of T-VEC + ipilimumab was 36% (i.e., substantially the same as that reported in Chesney). *Id.* at 1487–1488 (emphasis added). The applicant then presented the revised summary table:

Visceral Lesion Response Rate ($\geq 50\%$ change in tumor area)			
T-VEC monotherapy (Andtbacka)	Ipi monotherapy (Chesney 2)	T-VEC + ipi (Chesney/Chesney 2)	T-VEC + pembro (Ribas)
15%	14%	36%	33%

Id. at 1489.

In a March 9, 2018 Advisory Action, the Examiner noted that:

Applicants supplemental response expands upon the teachings of Chesney, Ribas, and Chesney 2, the latter 2 submitted with the 2/14/2018 after final response. Applicant notes that the unexpected results in Chesney 2 show that the visceral lesion response rates, which refer to any change in tumor area from baseline, clearly shows that the claimed combination has an unexpected benefit over T-VEC or ipilimumab monotherapy.

Ex. 2004, 1504. The Examiner also noted that, “these unexpected and/or surprising results noted by applicant are not commensurate in scope with the breadth of the claimed invention.” *Id.* In response, the applicant amended claim 1 by replacing “immune checkpoint inhibitor” with “anti-PD-1 antibody or anti-CTL4-A antibody” in a March 13, 2018 response. *Id.* at 1509.

The Examiner then issued a Notice of Allowance. Ex. 2004, 1561–1571. In the reasons for allowance, the Examiner stated:

[I]n light of the amendments presented on 03/13/2018 which bring the arguments presented regarding the surprising and unexpected nature of the method into the scope of the claimed invention, it is the opinion of the Office that the method had surprising synergistic effect when treating stages IIIb to IV melanoma using both the oncolytic HSV with an anti-PD1 or anti-CTLA-4 antibody.

Id. at 1569–1570.

B. Same or Substantially the Same Art or Arguments Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office.

Advanced Bionics, Paper 6 at 8. Patent Owner contends that Petitioner’s reliance on the Natarajan reference simply “swap[s] in for, and play[s] the same role as, the Eagle reference considered, argued, and overcome during prosecution.” Prelim. Resp. 59. Petitioner argues that Natarajan was not considered during prosecution and is not cumulative to Eagle. Reply 1–2.

Eagle discloses a method for treating melanoma by administering a therapeutically effective amount of an intralesional chemoablative pharmaceutical composition along with a therapeutically effective amount of a systemic immunomodulatory anticancer agent. Ex. 1027, code (57). As argued by Patent Owner during prosecution, Eagle characterizes both anti-CTLA-4 antibodies and OncoVEX “**solely** as systemic immunomodulatory anticancer agents,” and nothing in Eagle suggests combining two systemic immunomodulatory anticancer agents. See Ex. 2004, 1168–1169; Ex. 1027 ¶¶ 13, 14, Table 1, claims 3, 32. Further, Eagle lists over 40 such systemic immunomodulatory anticancer agents. Ex. 1027, Table 1. In contrast,

Natarajan discloses combining ipilimumab with OncoVEX for the treatment of melanoma. Ex. 1003, 1243, Fig. 1 (“Combination immunotherapy for the treatment of unresectable melanoma” and depicting ipilimumab and OncoVEX together in the tumor microenvironment). Natarajan also discusses the “combined administration of gp100 [], GM-CSF..., denileukin diftitox ... and, ... anti-CTLA-4” and notes that “[c]ertainly, one could imagine the promising OncoVEX^{GM-CSF} agent as the targeted delivery source for the GM-CSF.” *Id.* at 1242. Therefore, we agree with Petitioner that Natarajan is not substantially the same as Eagle at least because it teaches combining ipilimumab and OncoVEX for the treatment of melanoma, while Eagle does not disclose such a combination.

Due to these differences in the disclosures of Natarajan and Eagle, we also find that the arguments regarding Natarajan in this proceeding are not substantially the same as those during prosecution regarding Eagle. For example, there is no argument that Natarajan fails to disclose combining OncoVEX^{GM-CSF} and ipilimumab (only that there is no disclosure of combining *only* these two agents). Further, even assuming arguendo that the arguments regarding Natarajan are substantially the same as those regarding Eagle considered by the Examiner during prosecution, we find that Petitioner has demonstrated that the Examiner materially erred for the reasons discussed below.

C. Whether the Office Erred in a Manner Material to Patentability

As discussed above, regardless of whether we were to find that the same or substantially the same art or arguments were previously presented, we find that Petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24. Specifically, we

agree with Petitioner that the Examiner appears to have overlooked the applicant's clarification regarding data submitted in support of its arguments of unexpected results.

In response to the Examiner's obviousness rejection over Eagle, Eshun, and Zhang, the applicant presented evidence of alleged unexpected results. Specifically, the applicant presented data showing that when T-VEC and ipilimumab were both administered to patients, 35.5% of the visceral lesions had a >50% decrease in size compared to the visceral lesion response rate of using either drug alone (15% and 13.6%, respectively). Ex. 2004, 1266–1267. In the next Office Action, the Examiner maintained the obviousness rejection and noted that this increased effectiveness could be due to an additive effect and would not have been unexpected. Ex. 2004, 1425. In response to this rejection, the applicant presented additional data from Chesney 2, which applicant said had an “even greater visceral lesion response rate of 52%.” *Id.* at 1439–40. However, in a Supplemental Response, the applicant “clarif[ied]” that the response rate of 52% in Chesney 2 referred to visceral lesions where *any* change from baseline was observed, while, in the context of visceral lesions where there was $\geq 50\%$ change in tumor area from baseline, the response rate was actually 36%, which the applicant acknowledged was “substantially the same as that reported in Chesney.” *Id.* at 1488.

In an Advisory Action, the Examiner referred to the applicant's assertion that “the unexpected results in Chesney 2 show that the visceral lesion response rates, which refer to any change in tumor area from baseline, clearly shows that the claimed combination has an unexpected benefit over T-VEC or ipilimumab monotherapy.” Ex. 2004, 1504. However, the Examiner did not acknowledge that the clarified efficacy data from

Chesney 2 is substantially the same as the data from Chesney, as clarified by applicant in its supplemental response, which the Examiner previously found to be merely additive. Instead, the Examiner only found that the evidence of unexpected results was not commensurate in scope with the claims, a rejection that was withdrawn once the claims were amended. *Id.* Thus, the Examiner appears to have overlooked the applicant's clarification in the supplemental response or misunderstood the data of unexpected results presented by the applicant during prosecution. And as discussed below in Section IV.D.4.a., we are not persuaded by Patent Owner's arguments that the data submitted during prosecution demonstrates unexpected results. Because the Examiner relied on that unexpected results data in allowing the claims, we determine that Petitioner has sufficiently shown that the Office erred in a manner material to the patentability of challenged claims.

D. Conclusion as to Section 325(d)

For the reasons set forth above, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. ANALYSIS

A. Person of Ordinary Skill in the Art

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

Petitioner asserts that a person of ordinary skill in the art ("POSA") at the time of the invention would have "been an individual with an M.D. specializing in the treatment of melanoma and having five or more years of experience treating patients with melanoma, or an individual with an M.D.

and/or Ph.D. having five or more years of experience researching treatments for melanoma.” Pet. 18. Patent Owner does not contest the characterization offered by Petitioner. *See* Prelim. Resp. 5.

For purposes of this Decision, we adopt Petitioner’s characterization because it is consistent with the level of skill in the art at the time of the invention as reflected by the ’938 patent and the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Interpretation

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner provides a proposed construction for two terms in claim 1: (1) the preamble reciting a “method for the treatment of melanoma,” and (2) an “[e]ffective amount of an anti-PD-1 antibody or anti-CTLA-4 antibody.” Pet. 18–24. Patent Owner provides alternative constructions of these terms. Prelim. Resp. 12–17. Patent Owner also provides a proposed construction for the limitation “wherein [the/said] anti-PD1 antibody is,” recited in claims 8, 15, and 16.

While we address below Patent Owner’s proposed construction for “wherein [the/said] anti-PD1 antibody is,” upon review of the parties’

arguments and the evidence of record, we determine that the other claim terms do not require express construction for purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

1. “wherein [the/said] anti-PD1 antibody is”

Claims 8, 15, and 16 depend from claim 1 and include additional limitations regarding the anti-PD-1 antibody. For example, claim 8 recites “[t]he method according to claim 1, wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, lambrolizumab, CT-011, and AMP-224.” Ex. 1001, 22:14–16. Petitioner contends that nothing in claim 8 restricts the alternative of an anti-PD-1 antibody or anti-CTLA-4 antibody recited in claim 1. Pet. 42. Accordingly, Petitioner argues that claim 8 should be construed to mean:

“[a] method for the treatment of melanoma, said method comprising administering to a patient with stages IIIb to IV melanoma: (i) an effective amount of an anti-PD-1 antibody [wherein the anti-PD-1 antibody is selected from the group consisting of nivolumab, lambrolizumab, CT- 011, and AMP-224] *or* anti-CTLA-4 antibody . . .”

Id.

Patent Owner contends that “wherein [the/said] anti-PD-1 antibody is” should be construed to require that the claimed method include one of the anti-PD-1 antibodies recited in dependent claims 8, 15, and 16. Prelim. Resp. 18–20. Patent Owner also argues that the prosecution history supports this construction because during prosecution, an earlier version of current

claim 8 (original claim 14), recited only anti-PD-1 antibodies. *Id.* (citing Ex. 1014, 54–55, 116–117). While we recognize that claim 8 may have been limited to anti-PD-1 antibodies at some point during prosecution, the current claim at issue does not so limit claim 8. According to the plain language of claim 8, there is nothing in the claim that omits the alternate use of anti-CTLA-4 antibodies. Therefore, we construe claim 8 to include the use of the specifically recited anti-PD-1 antibodies *or* an anti-CTLA-4 antibody, as proposed by Petitioner. We construe claims 15 and 16 similarly.

C. Asserted Anticipation of Claims 1, 4–8, 11, 15, and 16 by Natarajan

Petitioner contends that claims 1, 4–8, 11, 15, and 16 are anticipated by Natarajan. Pet. 26–40. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 20–29.

1. Principles of Law

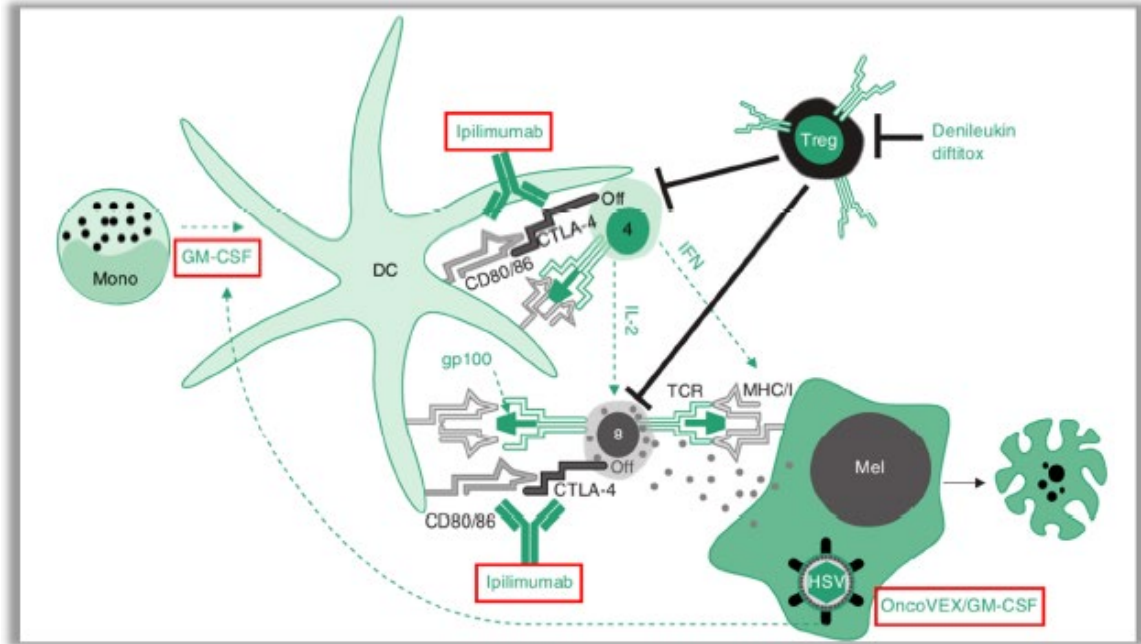
To establish anticipation under 35 U.S.C. § 102, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). Each element of the challenged claim must be found, either expressly or inherently, in the single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). When evaluating a prior art reference in the context of anticipation, the reference must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA 1978)). “[A] reference can anticipate a claim even if it ‘d[oes] not expressly

spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

In order to be anticipatory, a prior art reference must enable a person of ordinary skill in the art to make the invention without undue experimentation. *See Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008). A sufficiently enabling anticipatory reference must put the invention “in the possession” of the person of ordinary skill in the art. *See Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1315 (Fed. Cir. 2008).

2. Petitioner’s Position

Petitioner contends that the limitations of claim 1 are disclosed in Natarajan and that Natarajan’s disclosure is enabling. Pet. 33–34. Specifically, Petitioner contends that Natarajan discloses the combined administration of “(i) an ‘effective amount’ of ipilimumab to stage IIIb to IV melanoma patients and (ii) OncoVEX^{GM-CSF} to stage III(b) to IV melanoma patients.” *Id.* at 36. Petitioner contends that “Figure 1 of Natarajan, entitled ‘**Combination immunotherapy for the treatment of unresectable melanoma**,’ depicts the combined administration of ipilimumab and OncoVEX^{GM-CSF}.” *Id.* at 36–37 (citing Ex. 1003, 1242, Figure 1). Petitioner’s annotation of Natarajan Figure 1 is reproduced below.



Id. at 37. Petitioner’s annotated figure shows Figure 1 from Natarajan with the “OncoVEX/GM-CSF”, “Ipilimumab”, and “GM-CSF” labels boxed in red. Petitioner further contends that “[a]lthough it describes a prospective study of this combination, Natarajan anticipates because it describes and depicts combining OncoVEX^{GM-CSF} and ipilimumab for the treatment of stage IIIb to IV melanoma as recited in claim 1.” *Id.* at 38 (citing Ex. 1002 ¶¶ 52–54).

Petitioner also contends that “[i]ndependent claim 1 only requires the steps of administering the claimed anti-CTLA-4 or anti-PD-1 antibody and the claimed HSV—without requiring any efficacy showing for or clinical results of the combined monotherapies.” *Id.* at 39 (citing Ex. 1002 ¶ 30). According to Petitioner, the ’938 patent specification also “contains ***no*** clinical efficacy data for the claimed method.” *Id.* at 39–40 (citing Ex. 1001, 18:29–19:37, 19:38–21:23).

3. Patent Owner's Position

Patent Owner contends that Natarajan does not disclose combination treatment of OncoVEX^{GM-CSF} and ipilimumab and is not an enabling reference. Prelim. Resp. 20–29. Specifically, Patent Owner contends that Natarajan Figure 1 refers to “Potential Future Directions,” and “illustrates *at least seven* agents/monotherapies (*e.g.*, GM-CSF, OncoVEX^{GM-CSF}, IFN, IL-2, gp100, denileukin diftitox, and ipilimumab).” *Id.* at 21 (citing Ex. 1003, 1243). According to Patent Owner, “it is unclear whether the Petition relies on a combination of *all* agents in Figure 1, or a combination of some *subset*.” *Id.* at 22. Patent Owner further contends that Petitioner points to no disclosure of a combination of only OncoVEX^{GM-CSF} and ipilimumab. *Id.*

Patent Owner further asserts that Natarajan does not disclose the claimed combination for treating melanoma as recited in the preamble. Prelim. Resp. 24. Rather, Patent Owner contends that Natarajan discloses monotherapies (*i.e.*, novel immunotherapeutic agents), not combinations. *Id.* at 24–25. Patent Owner further contends that Natarajan does not disclose effective amounts of ipilimumab and OncoVEX^{GM-CSF} for combination therapy for stages IIIb-IV melanoma. *See id.* at 25–27.

Patent Owner also argues that Petitioner has “not presented a *prima facie* [sic] case of anticipation or (more particularly) a Natarajan disclosure to which” a presumption of enablement could attach. Prelim. Resp. 27. Instead, Patent Owner contends that “Natarajan affirmatively *disavows* any working treatment,” by advocating for novel protocols to test immunotherapeutic agents. *Id.* at 28 (citing Ex. 1003, 1242). Patent Owner further contends that Natarajan does not offer a functional regimen and

instead instructs that “major clinical effort” would be required to study the immunocorrelates and clinical response. *Id.*

4. Analysis

a) Claims 1, 4–7, and 11

On the current record, we find that Natarajan discloses the limitations of claim 1 of the '938 patent. First, we find that Natarajan, which is entitled, “Novel Immunotherapeutic Agents and Small Molecule Antagonists of Signalling Kinases for the Treatment of Metastatic Melanoma,” discloses a method for the treatment of melanoma. Ex. 1003, 1233. Natarajan discusses the “rationale and recent trial results of several novel immunotherapeutic approaches and small molecule inhibitors of signalling kinases,” and states that “these studies reveal that, for the first time, several immunotherapeutic and targeted agents are yielding dramatic clinical responses and improvements in overall survival in patients with unresectable stage III and IV melanoma.” *Id.* at 1233–1234. Figure 1 of Natarajan also discloses “[c]ombination immunotherapy for the treatment of unresectable melanoma” and depicts usage of OncoVEX^{GM-CSF} and ipilimumab. *Id.* at 1243.

On the current record, we find that Natarajan also discloses “administering to a patient with stages IIIb and IV melanoma an effective amount of an anti-PD-1 antibody or anti-CTLA-4 antibody.” Section 2 of Natarajan discusses “Therapeutic Options for Unresectable Stage III and IV Melanoma and notes the “remainder of this review” describes “exciting new immunotherapeutic and targeted approaches for the treatment of advanced unresectable melanoma.” Ex. 1003, 1237. Natarajan also discloses that “[a] randomized, double-blind, phase II trial ... recently evaluated the effects of ipilimumab [an anti-CTLA-4 antibody]” in “previously treated patients with

stage III (unresectable) or stage IV melanoma.” *Id.* at 1238–1239.

According to Natarajan, administering ipilimumab at a 10 mg/kg dose yielded a 11.1% overall response rate while administering at a 3 mg/kg dose yielded a 4.2% overall response rate. *Id.* at 1238–1239.

Natarajan also discloses “[administering to a patient with stages IIIb to IV melanoma] a herpes simplex virus,” having the characteristics recited in claim 1. Natarajan discloses that OncoVEX^{GM-CSF} is “an oncolytic herpes simplex virus type 1 (HSV-1) [strain JS1] that has been engineered” to include “deletion of ICP34.5”; “deletion of ICP47”; and “insertion of the open-reading frame of GM-CSF” and discusses the results of clinical trials of OncoVEX^{GM-CSF} administered to patients with stages IIIc to IV melanoma. Ex. 1003, 1240. Natarajan describes dosing unresectable stage IIIc and IV melanoma patients with “intratumoral injections of up to 4 mL of 10⁶ plaque forming units (pfu)/mL of OncoVEX^{GM-CSF} followed 3 weeks later by up to 4 mL of 10⁸ pfu/mL every 2 weeks for up to 24 treatments,” resulting in a 26% overall response rate. *Id.*

We are not persuaded by Patent Owner’s argument that Petitioner points to no disclosure of a combination of *only* OncoVEX^{GM-CSF} and ipilimumab. Challenged claim 1 recites a method of treatment “*comprising*” administration of the recited agents, such that the use of additional agents is encompassed by the claim. Patent Owner contends that Figure 1 of Natarajan illustrates at least seven agents/monotherapies and the sentence citing Figure 1 lists four agents: GM-CSF, anti-CTLA-4, denileukin diftitox, and gp100, but not OncoVEX^{GM-CSF}. Prelim. Resp. 21 (citing Ex. 1003, 1243). However, as Patent Owner acknowledges, the next sentence in Natarajan states that, “[c]ertainly, one could imagine the incorporation of the promising OncoVEX^{GM-CSF} agent as the targeted delivery source for the GM-

CSF.” Ex. 1003, 1242. Therefore, Natarajan discloses use of OncoVEX^{GM-CSF} with three other possible agents, including an anti-CTLA-4 antibody.¹³ Given this disclosure, and on the current record, we find that one of skill in the art would be able to “at once envisage” the use of an anti-CTLA-4 antibody combined with OncoVEX^{GM-CSF} for the treatment of stage III and IV melanoma. *See Kennametal*, 780 F.3d at 1381.

Patent Owner also argues that Natarajan does not disclose treating a patient with the combination of both claimed drugs in an amount that would be effective to treat melanoma. As discussed above, Natarajan discloses clinical trial results showing the effective use of OncoVEX^{GM-CSF} and ipilimumab monotherapies, including specific dosage amounts, for the treatment of patients with stage III and IV melanoma. Ex. 1003, 1238–1240. Natarajan also discusses the prospects of “rational combinations” of these therapies in order to treat melanoma. *Id.* at 1242. “[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).

¹³ We are also not persuaded by Patent Owner’s argument that Petitioner “do[es] not address how such a treatment regimen would be administered given Natarajan’s statements that anti-CTLA-4 should not be administered until after ‘the expansion of gp100-specific CD8+ T cells . . . to prevent negative feedback of the effector phase (figure 1).’” Prelim. Resp. 22 (citing Ex. 1003, 1242). Natarajan’s disclosure of the administration of anti-CTLA-4 “after 2 weeks to allow for the expansion of gp100-specific CD8+ T cells,” is provided as just one example as to how these agents can be administered. Further, such administration would be encompassed by the challenged claims, which include the open-ended “comprising” transitional phrase.

On the issue of enablement, on the current record, we first note that prior art publications are presumed enabled. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012); *Apple Inc. v. Corephotonics, Ltd.*, 861 Fed. App'x 443, 450 (Fed. Cir. 2021). We also credit the unrebutted testimony of Dr. Sosman that “Natarajan is enabling because it describes ipilimumab and OncoVEX^{GM-CSF} in detail, including their successes as monotherapies, and all that a POSA needs to do to practice the claimed method is to administer the two drugs in combination, which would have been routine to a POSA in August 2012.” Ex. 1002 ¶ 54. Although Natarajan indicates that “[t]he timing of administration of each of the agents and the study of immunocorrelates and clinical responses will require a major clinical trials effort,” this statement does not necessarily indicate that undue experimentation would be needed to practice the claimed invention and Patent Owner has not presented any evidence of such undue experimentation at this stage of the proceeding. We also note that the '938 patent itself does not disclose any clinical efficacy data for the claimed method. Rather, the '938 patent includes a prophetic example of treating patients with talimogene latherpareopvec and ipilimumab. Ex. 1001, 19:37–21:23. Thus, on the current record, we find that Petitioner has shown that Natarajan is an enabling disclosure. These arguments can be more fully developed on a complete trial record.

Accordingly, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claim 1 of the '938 patent is anticipated by the disclosure of Natarajan. Petitioner also presents evidence and arguments as to how Natarajan anticipates dependent claims 4–7 and 11. Pet. 40–41, 43. Other than the arguments discussed above, Patent Owner does not separately argue the patentability of these claims. We have

reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has also demonstrated a reasonable likelihood that claims 4–7 and 11 of the '938 patent are anticipated by the disclosure of Natarajan.

b) Claims 8, 15, and 16

Petitioner contends that dependent claims 8, 15, and 16 are anticipated because they encompass the combined administration of ipilimumab and OncoVEX^{GM-CSF} (e.g., talimogene laherparepvec), which Petitioner contends is disclosed in Natarajan. Pet. 42, 43, 44 (citing Ex. 1002 ¶ 62). Patent Owner argues that these claims are not anticipated because the claims require particular anti-PD-1 antibodies and Petitioner only identifies Natarajan's disclosure of anti-CTLA-4 antibodies. Prelim. Resp. 30. Because we have construed these claims to encompass use of anti-CTLA-4 antibodies, we find that, on the current record and for the reasons discussed for claim 1, Petitioner has demonstrated a reasonable likelihood that claims 8, 15, and 16 of the '938 patent are anticipated by the disclosure of Natarajan.

D. Asserted Obviousness of Claims 1, 4–8, 11, 15, and 16 by Natarajan

Petitioner contends that claims 1, 4–8, 11, 15, and 16 would have been obvious over Natarajan. Pet. 47–70. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 30–57.

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 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. *See also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the answer depends on “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 417. It is generally obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) (“[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another.”); *see also Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (the combination of known elements and substitution of one well known agent for another is obvious).

2. *Petitioner’s Position*

Petitioner contends that, “[b]ased on Natarajan, a POSA would have been motivated to combine OncoVEX^{GM-CSF} with ipilimumab for the treatment of a patient with stage IIIb to IV melanoma, and she would have had a reasonable expectation of success in doing so.” Pet. 47–48 (citing

Ex. 1002 ¶¶ 73–85). Petitioner provides three reasons for why a skilled artisan would have been motivated to perform the claimed method.

First, Petitioner contends that Natarajan proposes the combined administration of ipilimumab with GM-CSF and further teaches incorporating “the promising OncoVEX^{GM-CSF} agent as the targeted delivery source for the GM-CSF.” Pet. 48–49 (citing Ex. 1003, 1242–43; Ex. 1002 ¶ 73). According to Petitioner, Natarajan’s Figure 1 “*explicitly* depicts this combination.” *Id.*

Second, Petitioner contends, with supporting testimony from Dr. Sosman, that “a POSA would have been motivated to combine OncoVEX^{GM-CSF} with ipilimumab because she would have known, among other things, their respective biological compositions, mechanisms of action, common target patient population, successful clinical trial results, and dosing regimens.” Pet. 50 (citing Ex. 1002 ¶ 74). Specifically, Petitioner contends that a skilled artisan would have known of OncoVEX^{GM-CSF} as an oncolytic virus and ipilimumab as an anti-CTLA-4 antibody. *See id.* at 50–52 (citing Ex. 1002 ¶¶ 75, 76; Ex. 1034; Ex. 1003, 1239–1240; Ex. 1026, 5; Ex. 1037).

Third, Petitioner contends that “a POSA would have considered the claimed combination therapy to have the added benefit of increased killing of melanoma cells.” Pet. 52 (citing Ex. 1002 ¶ 77). Specifically, Petitioner contends, with supporting testimony from Dr. Sosman, that a skilled artisan would have known of the different mechanisms of ipilimumab and OncoVEX^{GM-CSF} for enhancing T-cell activation. *Id.* at 52–53 (citing Ex. 1002 ¶¶ 77–78). Finally, Petitioner contends that “the POSA would have been aware of OncoVEX^{GM-CSF} low toxicity profile making it a prime

candidate for combination therapy.” *Id.* at 53 (citing Ex. 1002 ¶ 79; Ex. 1043, 295).

Furthermore, Petitioner contends that a POSA would have had a reasonable expectation of success in the combination therapy because “the literature had already shown that monotherapy with either ipilimumab or OncoVEX^{GM-CSF} was clinically effective.” Pet. 54 (citing Ex. 1002 ¶ 81; Ex. 1001, 10:38–48; 8:33–35; Ex. 1003, 1238–40). Petitioner also contends that “ipilimumab had previously been combined with other immunostimulatory drugs,” reinforcing the POSA’s reasonable expectation of success. *Id.* at 55–56 (citing Ex. 1003, 1239, 1241; Ex. 1040, 602). According to Petitioner, the known combinations included combining GM-CSF with an anti-CTLA-4 antibody, such as ipilimumab, resulting in improved anti-tumor effects. *Id.* at 57 (citing Ex. 1038; Ex. 1039; Ex. 1002 ¶ 84).

3. Patent Owner’s Position

Patent Owner contends that Petitioner’s obviousness ground (1) does not clearly articulate their obviousness argument (Prelim. Resp. 31–34), (2) fails to establish a motivation to combine (*id.* at 35–42), and (3) fails to establish a reasonable expectation of success (*id.* at 43–49).

First, Patent Owner contends that Petitioner does not clearly articulate its obviousness ground. For example, Patent Owner argues that “it is [] not clear whether Petitioners’ ultimate combination includes *only* OncoVEX^{GM-CSF} and ipilimumab, or whether they are proposing a four- or more-way combination that *also* includes gp100 and denileukin difttox (and possibly IFN and IL-2).” Prelim. Resp. 33 (citing Pet. 48–52). Patent Owner further argues that “with respect to Petitioners’ argument for ‘efficacious[ness],’ it is also not clear *which limitation* Petitioners are

referencing in their argument—*e.g.*, whether Petitioners are purporting to address the preamble, or, instead, the requirement for ‘an effective amount.’” *Id.* at 34.

Second, Patent Owner contends that Petitioner’s motivations to combine fail “because they do not relate to the obviousness of an ‘efficacious’ requirement, and because they are conclusory and insufficiently explained.” Prelim. Resp. 35. Patent Owner contends that “Petitioners do not identify *any* art showing administration (let alone *effective* administration) of the claimed combination for *any* purpose, and ignore reasons POSA might *not* combine the individual therapies.” *Id.* at 37. Instead, Patent Owner contends that Natarajan acknowledges no combination study has been conducted of the proposed combinations. *See id.* (citing Ex. 1003, 1242).

Patent Owner further contends that knowing the properties of the individual monotherapies does not provide a motivation to combine, nor show that the combination would be efficacious. Prelim. Resp. 38. According to Patent Owner, “Petitioners also never address how the mechanisms of action for the individual therapies would *impact the other(s) in combination* when administered to a patient with stage IIIb-IV melanoma.” *Id.*

Patent Owner also asserts that “Petitioners do not explain *why* combining different mechanisms of action would ‘enhance T-cell activation,’ connect that to ‘increased killing of melanoma cells,’ or identify any prior art recognizing [] the mechanisms of action” of the combination. Prelim. Resp. 39–40. According to Patent Owner, Petitioner disregards the significant toxicity profile of ipilimumab and of the other therapies in

Natarajan’s potential combinations. *Id.* at 40 (citing Pet. 52–53; Ex. 1003, 1237, 1239; Ex. 1037, 1; Ex. 2006, 1; Ex. 2007, 1; Ex. 2008, 1).

Third, Patent Owner contends that “Petitioners ignored Natarajan’s own teachings that cast doubt on Petitioners’ [reasonable expectation of success] theory and assertion that anti-CTLA-4 would ‘enhance activation of T-cells.’” Prelim. Resp. 44 (citing Pet. 56). Specifically, Patent Owner cites to Natarajan’s teaching “that identifying the right combinations ‘will require a major clinical trials effort.’” *Id.* at 44 (citing Ex. 1003, 1242). According to Patent Owner, Petitioner has not shown that the treatments were predictable in combination, nor that immunotherapy was predictable as of the August 2012 priority date. *Id.* at 45. Instead, Patent Owner contends that “*Petitioners’ own references* here demonstrate both that: ipilimumab and other agents in the multi-way combination presented substantial toxicity concerns; and combinations were unpredictable.” *Id.* at 45–46 (citing Pet. 54–57; Ex. 1003, 1239).

4. Analysis

a) Claims 1, 4–7, and 11

We find, on the current record, that Petitioner has sufficiently articulated its obviousness arguments. For example, Petitioner sufficiently shows where Natarajan discloses the use of OncoVEX^{GM-CSF} and ipilimumab for the treatment of patients with stage III and IV melanoma, as well as Natarajan’s suggestion to combine these treatments.¹⁴ *See, e.g.*, Pet. 48–49

¹⁴ We understand Petitioner’s arguments regarding “efficacious[ness]” to relate to the preamble language regarding “[a] method for the treatment of melanoma.” On the current record, we find these arguments to be persuasive as discussed *infra* in the context of a POSA having a reasonable expectation of success in practicing the claimed method.

(citing Ex. 1003, 1242–43; Ex. 1002 ¶ 73). Further, as explained with respect to Petitioner’s anticipation arguments, the claims recite a method of treatment “comprising” administration of the recited agents, such that the use of additional agents is encompassed by the claims.

We also find that, on the current record, Petitioner has provided sufficient evidence of a motivation to combine the administration of OncoVEX^{GM-CSF} and ipilimumab for the treatment of patients with stage III and IV melanoma. First, as discussed above in the anticipation section, Natarajan expressly discloses combining these two therapies for the treatment of melanoma. Ex. 1003, 1242–1243. Second, we credit the unrebutted testimony of Dr. Sosman that “a POSA would have been motivated to combine OncoVEX^{GM-CSF} and ipilimumab because she would have known, among other things, their respective biological compositions, mechanisms of action, common patient population, successful clinical trial results, and dosing regimens.” Ex. 1002 ¶¶ 74–76 (citing references disclosing the properties of these agents).¹⁵ We are not persuaded by Patent Owner’s unsupported contention that knowing the properties of the individual monotherapies does not provide a motivation to combine. Further, we credit the unrebutted testimony of Dr. Sosman that knowledge of the use of these agents in clinical trials for the treatment of melanoma would, in fact, provide a POSA with a motivation to combine the two therapies.

¹⁵ Patent Owner asserts that the Petition and Dr. Sosman’s Declaration cite to references that are not part of the Petition grounds; however, it is permissible for Petitioner to cite to references showing the state of the art at the relevant time. *See, e.g., Genzyme Therapeutic Prods. Ltd. P’ship v. Biomarin Phar. Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016).

We also credit the testimony of Dr. Sosman that “a POSA would have known that combining immunotherapeutic agents with different mechanisms of action may enhance efficacy.” Ex. 1002 ¶ 77. We are not persuaded by Patent Owner’s contention that Petitioner does not explain why combining different mechanisms of action would “enhance T-cell activation,” because Dr. Sosman discusses OncoVEX^{GM-CSF}’s ability to augment tumor-specific immune responses and ipilimumab’s ability to enhance the action of OncoVEX^{GM-CSF} to “further boost the anti-tumor response by enhancing the priming and activation of T cells by dendritic cells presenting tumor-derived antigens.” *Id.* at ¶¶ 77–78. We further credit Dr. Sosman’s testimony that “this is precisely the mechanism of action proposed in Figure 1 of Natarajan.” *Id.* at ¶ 78 (citing Ex. 1003, Figure 1).

We are also not persuaded by Patent Owner’s unsupported argument that the alleged toxicity of ipilimumab would deter a POSA from using it in a combination therapy. *See* Prelim. Resp. 38, 40, 46, 47. As acknowledged by Patent Owner, Natarajan recognizes the potential toxicity of ipilimumab; however, Natarajan still recommends the use of ipilimumab in a combination therapy to treat melanoma. *See* Ex. 1003, 1239, 1242–1243.

We further find that, on the current record, Petitioner has provided sufficient evidence that a POSA would have had a reasonable expectation of success in the administration of OncoVEX^{GM-CSF} and ipilimumab for the treatment of patients with stage III and IV melanoma. We credit the un rebutted testimony of Dr. Sosman that it had already been shown that monotherapy with either ipilimumab or OncoVEX^{GM-CSF} was clinically effective. Ex. 1002 ¶ 81 (citing Ex. 1003, 1239–1240; Ex. 1001, 10:34–43). We also credit the testimony of Dr. Sosman that “the fact that ipilimumab had previously been combined with other immunostimulatory drugs would

have provided the POSA with a further reasonable expectation of success.” *Id.* at ¶ 82 (citing Ex. 1003, 1040). We are also persuaded by Dr. Sosman’s testimony that “the literature taught that combining GM-CSF with an anti-CTLA-4 antibody, such as ipilimumab, results in improved anti-tumor effects.” *Id.* at ¶ 84 (citing Exs. 1038, 1039, 1040). Standing alone, Natarajan’s statement “that identifying the right combinations ‘will require a major clinical trials effort,’” does not persuade us on this record that a POSA would not have had a reasonable expectation of success in combining these two therapies, which were known to be effective in treating melanoma.

Overall, on the current record, we determine that Petitioner sufficiently explains why an ordinarily skilled artisan would have been motivated to combine OncoVEX^{GM-CSF} with ipilimumab for the treatment of a patient with stage IIIb to IV melanoma based on the disclosure in Natarajan, and would have had a reasonable expectation of success in doing so.

(1) Objective Evidence of Non-Obviousness

In determining whether a claim is obvious in light of the prior art, we also consider any relevant evidence of secondary considerations of non-obviousness. *See Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to one of ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of non-obviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984).

Patent Owner contends that the Examiner allowed the claims of the ’938 patent based on “strong objective indicia of nonobviousness,” that Petitioner has not overcome. Prelim. Resp. 49–57. Petitioner contends that

Patent Owner’s evidence of unexpected results presented during prosecution does not weigh in favor of patentability because they do not show unexpected results and are not commensurate in scope with the claims.

Pet. 60–70.

As discussed above, the applicant presented evidence of unexpected results during prosecution of the ’938 patent. For example, the applicant presented the following summary table in support of its argument that the combination of T-VEC and ipilimumab yielded an unexpectedly superior increase in systemic effect (36%), as compared to either drug alone (15% and 14%, respectively), and that the combination of T-VEC and pembro also yielded an unexpectedly superior increase in systemic effect (33%), as compared to T-VEC alone (15%):

Visceral Lesion Response Rate ($\geq 50\%$ change in tumor area)			
T-VEC monotherapy (Andtbacka)	Ipi monotherapy (Chesney 2)	T-VEC + ipi (Chesney/Chesney 2)	T-VEC + pembro (Ribas)
15%	14%	36%	33%

Ex. 2004, 1489.

We acknowledge Petitioner’s arguments regarding potential weaknesses of this data. First, according to Dr. Sosman, this data represents a comparison across multiple different clinical trials, with differences in clinical trial stage, lesion criteria for enrollment, distribution of patients across disease stages, and primary endpoint. Ex. 1002 ¶¶ 91–93. On this record, we credit Dr. Sosman’s opinion that these differences may have affected the results of the compared studies, especially given Patent Owner’s statements in another document that “comparisons across trials should be interpreted with caution.” Ex. 1042, 690; *see also* Ex. 1002 ¶ 93.

Second, on this record, we credit the testimony of Dr. Sosman that the visceral lesion response rates reported in Andtbacka and those reported in Chesney/Chesney 2 were computed differently, and thus may lack persuasive value. According to Dr. Sosman:

[T]he visceral response rates for the combination of T-VEC and ipilimumab, and ipilimumab alone in Chesney 2 are based on the percentage of *patients* in which visceral lesions decreased in size by $\geq 50\%$, whereas in Andtbacka, the response rate for T-VEC alone is based on the percentage of *visceral lesions* that decreased in size by $\geq 50\%$ —a meaningless apples-to-oranges comparison that fails to support Amgen’s allegation of unexpected results.

Id. at ¶ 95 (emphases added).

Further, we credit the testimony of Dr. Sosman on this record that “the data represent at most a difference in degree in efficacy which would have been expected since both T-VEC and ipilimumab had been shown individually to be effective at treating melanoma.” Ex. 1002 ¶ 96. Patent Owner argues that Petitioner provides no explanation or evidence for this argument and offers “no basis to disturb the Examiner’s conclusion” that the claimed invention exhibits unexpected results. However, as discussed above with respect to the § 325(b) arguments, we find that the Examiner erred in her consideration of this data. These arguments can be more fully developed on a complete trial record.

For these reasons, on the current record, we are not persuaded by Patent Owner’s arguments that unexpected results weigh toward the non-obviousness of the claimed subject matter.

*(2) Conclusions as to obviousness of claim 1
over Natarajan*

In sum, we find that the disclosure of Natarajan teaches or suggests each and every element of claim 1. We find that an ordinarily skilled artisan would have been motivated to combine OncoVEX^{GM-CSF} with ipilimumab for the treatment of a patient with stage IIIb to IV melanoma, and would have had a reasonable expectation of success in doing so. On the current record, we also find that the evidence of secondary considerations of non-obviousness is not persuasive as discussed above.

Thus, after carefully considering the arguments and evidence, we determine that, on this record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claim 1 of the '938 patent would have been obvious over the disclosure of Natarajan. Petitioner also presents evidence and arguments as to how Natarajan renders obvious dependent claims 4–7 and 11 of the '938 patent. Pet. 40–41, 43, 58. Other than the arguments discussed above, Patent Owner does not separately argue the patentability of these claims. We have reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 4–7 and 11 of the '938 patent is rendered obvious by the disclosure of Natarajan.

b) Claims 8, 15, and 16

Petitioner contends that claims 8, 15, and 16 are unpatentable as obvious because they encompass the combined administration of ipilimumab and OncoVEX^{GM-CSF} (e.g., talimogene laherparepvec), which is disclosed in Natarajan. Pet. 42, 43, 44, 58 (citing Ex. 1002 ¶ 62). Patent Owner argues that these claims would not have been obvious because the claims require

particular anti-PD-1 antibodies and Petitioners “make throwaway obviousness arguments regarding substitution of anti-PD-1 for claim 1” that “should be disregarded because they identified no ground and performed no analysis for any such obviousness argument.” Prelim. Resp. 49 (citing Pet. 54, n. 17). Because we have construed these claims to encompass use of anti-CTLA-4 antibodies, we find, on the current record and for the reasons discussed for claim 1, that Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 8, 15, and 16 of the ’938 patent are unpatentable as obvious over the disclosure of Natarajan.

V. CONCLUSION

For the forgoing reasons, Petitioner has demonstrated a reasonable likelihood that at least one challenged claim of the ’938 patent would have been anticipated by and/or obvious over the prior art of record. Accordingly, we institute an *inter partes* review on claims 1, 4–8, 11, 15, and 16 for all grounds set forth in the Petition.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review is instituted on claims 1, 4–8, 11, 15, and 16 for all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the ’938 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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