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Paper 6
Entered: October 3, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME LLC,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

IPR2024-00648
Patent 11,643,462 B2

Before DEBORAH KATZ, SHERIDAN K. SNEDDEN, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background and Summary

Merck Sharp & Dohme LLC ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–30 of U.S. Patent No. 11,643,462 B2 (Ex. 1001, "the '462 patent"). Petition ("Pet."), Paper 1. The Johns Hopkins University ("Patent Owner") filed a Mandatory Notice identifying itself as the owner of the '462 patent. Paper 3, 1. Patent Owner did not file a Preliminary Patent Owner Response.

To institute an *inter partes* review, we must determine that the information presented in the Petition shows "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) (2018). The Supreme Court has held that a decision to institute under 35 U.S.C. § 314 may not institute on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). After considering the information presented by the parties, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of claims 1–30 of the '462 patent is unpatentable.

B. Real Parties in Interest

Petitioner identifies Merck Sharp & Dohme LLC and Merck & Co., Inc., as its real parties-in-interest. Pet. 64. Patent Owner identifies Johns Hopkins University as its real party-in-interest. Paper 3, 1.

C. Related Matters

The parties indicate that the '462 patent is involved in *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-JRR (D. Md.), filed November 29, 2022. Pet. 64; Paper 3, 1. Petitioner states that the U.S.

District Court for the District of Maryland entered an order granting Petitioner's Motion to Stay on July 1, 2024. Paper 5, 1.

Petitioner has also filed petitions for *inter partes* review of the following patents asserted against Petitioner by Patent Owner: IPR2024-00650 against U.S. Patent No. 11,634,491; IPR2024-00649 against U.S. Patent No. 11,629,187; IPR2024-00647 against U.S. Patent No. 11,649,287; IPR2024-00625 against U.S. Patent No. 11,339,219; IPR2024-00624 against U.S. Patent No. 11,325,975; IPR2024-00623 against U.S. Patent No. 11,325,974; IPR2024-00622 against U.S. Patent No. 10,934,356; and IPR2024-00240 against U.S. Patent No. 11,591,393. Pet. 64; Paper 3, 1. *Inter-partes* reviews in IPR2024-00622, IPR2024-00623, IPR2024-00624, and IPR2024-00625 were instituted on September 23, 2024, and in IPR2024-240, IPR2024-00625, IPR2024-00647, IPR2024-00649, and IPR2024-00650 on September 27, 2024.

D. The '462 patent (Ex. 1001)

The '462 patent is titled "Checkpoint Blockade and Microsatellite Instability." Ex. 1001, code (54). The '462 patent is directed to anti-cancer therapies that block immune system checkpoints, including the programmed death-1 ("PD-1") receptor. *Id.*, Abstract. More specifically, the '462 patent is directed to treating cancer patients with high mutational burdens, such as those found in microsatellite instable ("MSI") cancer, with anti-PD-1 antibodies. *Id.*, 3:38–53. MSI occurs in tumors with deficiency in DNA mismatch repair ("MMR-deficiency"). *Id.*, 1:33–34.

The '462 patent explains that

> [t]he PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or

> excessive immune responses, including auto-immune responses. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors.

Id., 1:55–62. According to the '462 patent, "[h]igh expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types." *Id.*, 2:6–9. However, the specification describes that

> in reports of PD-1 blockade in human tumors, only one of 33 colorectal (CRC) patients responded to this treatment. . . . What was different about this patient? We hypothesized that this patient had MMR-deficiency, because MMR-deficiency occurs in a small fraction of advanced CRCs, . . . somatic mutations found in tumors can be recognized by the patient's own immune system,[] and MMR-deficient cancers have 10- to 100-fold more somatic mutations than MMR-proficient CRC.

Id., 2:63–3:6. After confirming that the tumor of the single CRC patient who responded to PD-1 blockade was MMR-deficient, the '462 patent describes the evaluation of immune checkpoint blockade in patients whose tumors had or did not have MMR-deficiency in a phase 2 clinical trial. *Id.*, 3:14–21. The specification discloses that pembrolizumab is a monoclonal anti-PD-1 antibody, attributed to Merck, which was administered to patients in this clinical trial. *Id.*, 8:52–58. According to the '462 patent, "[t]he data from the small phase 2 trial . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors." *Id.*, 6:53–57.

E. The Challenged Claims

Petitioner challenges claims 1–30. Representative independent claim 1 is reproduced below:

> 1. A method for treating a patient having a solid tumor selected from the group consisting of endometrial cancer,

> small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment, the method comprising:
>
> testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and
>
> in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab.

Ex. 1001, 25:52–26:2.

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1005, MSI-H Study Record, ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1 ("MSI-H Study Record"); also available at *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059-BPG, ECF 1, Complaint, Exhibit B (11/29/22) ("MSI-H Study Record").

Ex. 1007, Chapelle et al., *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. CLIN. ONCOLOGY 3320 (2010) ("Chapelle").

Ex. 1008, Steinert et al., *Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer*, 74(6) CANCER RESEARCH OF1 (March 2014) ("Steinert").

Ex. 1009, Benson et al., *Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology*, 12(7) J. NAT'L COMPREHENSIVE CANCER NETWORK 1028 (July 2014) ("Benson").

Ex. 1011, Hamid et al., *Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma*, 369(2) NEW ENG. J. MEDICINE 134 (July 2013) ("Hamid").

Ex. 1034, Brown et al., *Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival*, 24(5) GENOME RESEARCH 743 (May 2014) ("Brown").

Ex. 1087, Duval et al., *The mutator pathway is a feature of immunodeficiency-related lymphomas*, 101(14) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 5002 (2004) ("Duval").

Ex. 1095, Koh et al., *Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology*, 12(2) J. NAT'L COMPREHENSIVE CANCER NETWORK 248 (February 2014) ("Koh").

Ex. 1096, Ajani et al., *Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines*, 11(5) J. NAT'L COMPREHENSIVE CANCER NETWORK 531 (May 2013) ("Ajani").

Petitioner also relies on the Declaration of Alfred I. Neugut, M.D., Ph.D., M.P.H. (Ex. 1003) to support its contentions.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–30 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 2, 4–7, 9–12, 14–17, 19–30	102	MSI-H Study Record
II	1, 2, 4–7, 9–12, 14–17, 19–30	103	MSI-H Study Record, Brown, Duval, Benson
III	1, 2, 4–7, 9–12, 14–17, 19–24	103	MSI-H Study Record, Brown, Duval, Benson,

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
			Koh
IV	1, 2, 4–7, 9, 11, 12, 14–17, 19, 25, 26	103	MSI-H Study Record, Brown, Duval, Benson, Ajani
V	2, 8, 12, 18	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Chapelle
VI	3, 13	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Steinert
VII	7, 17	103	MSI-H Study Record, Brown, Duval, Benson, Koh, Ajani, Hamid

H. Claim Construction

The challenged claims should be read in light of the Specification, as it would be interpreted by one of ordinary skill in the art. *In re Suitco Surface*, *Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech.*, Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question." (internal quotation marks omitted)); *see also* 37 C.F.R. § 42.100(b) (stating that claims are construed in IPRs according to the same standard as used in federal court).

Petitioner argues that we need not construe any terms of the challenged claims to resolve the issues presented in the Petition. Pet. 10–11.

To the extent we deem it necessary to construe the terms of the challenged claims at this point in the proceeding, we do so in the analysis below. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The Board is required to construe 'only those terms . . . that are in

controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

I. Level of Ordinary Skill in the Art and Declarant

Petitioner presents the testimony of Alfred I. Neugut, M.D., Ph.D., M.P.H., for opinion testimony regarding what one of ordinary skill in the art would have understood at the time of filing. *See* Ex. 1003. Dr. Neugut testifies that he is a medical oncologist with a particular focus on gastrointestinal tract cancers, including colorectal cancers. *Id.* ¶ 4. Dr. Neugut testifies further that he is the Director of the Center for Pharmacoepidemiology and Health Outcomes Research in Columbia's Department of Epidemiology and Director of Global Oncology Research for Columbia's Herbert Irving Comprehensive Cancer Center. *Id.* ¶ 5. Dr. Neugut testifies that he sees approximately 30 patients per week to treat gastrointestinal cancers, including colorectal cancer. *Id.* ¶ 4.

Petitioner argues that one of ordinary skill in the art relevant to the '462 patent would have been a medical doctor or a professional in a related field with at least five years of experience with treating cancer. Pet. 11 (citing Neugut Decl., Ex. 1003 ¶ 19). Petitioner argues further that the ordinarily skilled artisan would have had experience in or access to a person with knowledge of clinical studies for therapeutics and how they work and to a pathologist with comparable experience. *Id.* Patent Owner, having not entered a response, does not dispute Petitioner's proposal about the POSA's qualifications on this record..

For this Decision, we adopt and apply Petitioner's proposal above, which is supported by Dr. Neugut's testimony and does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

II. ANALYSIS

A. Legal Standard

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Moreover, a petitioner should not "place the burden on [the Board] to sift through information presented by the Petitioners, determine where each element [of the challenged claims] is found in [the cited references], and identify any differences between the claimed subject matter and the teachings of [the cited references.]" *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9 at 25 (PTAB May 22, 2014).

Anticipation is a question of fact, as is the question of what a prior art reference teaches. *In re NTP, Inc.*, 654 F.3d 1279, 1297 (Fed. Cir. 2011). "Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). Whether a reference anticipates a claim is assessed from the skilled artisan's perspective. *See Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) ("[T]he dispositive question regarding

anticipation [i]s whether one skilled in the art would reasonably understand or infer from the [prior art reference's] teaching that every claim element was disclosed in that single reference." (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991))).

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 ordinary skill in the art; and (4) objective evidence of nonobviousness.[1] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The obviousness inquiry also typically requires an analysis of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). A petitioner cannot prove obviousness with "mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Rather, a petitioner must articulate a sufficient reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive*, 842 F.3d 1376, 1382 (Fed. Cir. 2016).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

[1] Patent Owner does not present any objective evidence of nonobviousness (i.e., secondary considerations) for the challenged claims at this time.

B. Summary of the Cited Prior Art

1. MSI-H Study Record (Ex. 1005)

The title of the MSI-H Study Record is "Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors." Ex. 1005, 1. MK-3475 is also known as pembrolizumab. *See* Ex. 1054, 3 (disclosing that "Nivolumab . . . and MK-3475 (pembrolizumab formerly lambrolizumab) . . . are humanized MAb that block the interaction between PD-1 and its ligands and demonstrate durable responses in patients with advanced melanoma."); *see also* Ex. 1069 (titled "ANTITUMOR ACTIVITY OF PEMBROLIZUMAB (PEMBRO; MK-3475) . . . .")).

The MSI-H Study Record includes a "Brief Summary," explaining that

> [t]his study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers.

Ex. 1005, 3. Two of the outcome measures reported in the MSI-H Study Record are "Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks" and a determination of "[d]oes MSI as a marker predict treatment response[?]" *Id.*, 4–5. The MSI-H Study Record provides "Arms and Interventions" as follows:

Arms	Assigned Interventions
Experimental: MSI Positive Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Negative Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days
Experimental: MSI Positive Non-Colorectal Cancer	Drug: MK-3475 MK-3475 10 mg/kg every 14 days

Id., 4. The chart above identifies three patient populations and the therapeutic intervention to be provided.

2. Chapelle (Ex. 1007)

Chapelle is an article titled "Clinical Relevance of Microsatellite Instability in Colorectal Cancer." Ex. 1007, 3380. Chapelle discloses that "Microsatellite instability (MSI) is a clonal change in the number of repeated DNA nucleotide units in microsatellites," which "arises in tumors with deficient mismatch repair due to the inactivation of one of the four mismatch repair genes: *MSH2, MLH1, MSH6*, and *PMS2*." *Id.* Chapelle describes the testing of tumor tissue from a patient to determine microsatellite instability in colorectal cancer. *Id.*, 3380, 3383. Chapelle also describes immunohistochemistry techniques to test for microsatellite instability status. *Id.*, 3380, 3384.

3. Steinert (Ex. 1008)

Steinert is an article titled "Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer." Ex. 1008, OF1. Steinert discloses detailed genomic and phenotypic analyses of single colorectal cancer–derived circulating tumor cells (CTC). *Id.* Steinert describes that "[a]mplified gDNA of CTC and tumor tissue samples was tested for microsatellite instability (MSI) using the markers NR21, NR24, and BAT 25." *Id.*, OF2. Steinert describes that the analyses of single cancer-derived

CTC found disparities in key mutations, including MSI, in comparison to the primary tumor. *Id.*, OF4. "MSI at one or more markers . . . was detected in CTC from 2 patients (of 25 with complete MSI data sets; 7.7%, Fig. 2C). In 1 patient, two of 11 tested CTC were MSI despite a microsatellite stable (MSS) tumor (Table 1)." *Id.* In one patient, "[t]hree single CTC were classified as MSI-high level (MSI-H) and showed a mutation in the coding region of the *ELAVL* gene." *Id.*, OF6.

4. Benson (Ex. 1009)

Benson is an article titled "Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology." Ex. 1009, 1028. Benson discloses guidelines that "focus[] on the use of systemic therapy in metastatic disease." *Id.* More specifically, Benson "summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing metastatic CRC, focusing mainly on systemic therapy." *Id.*, 1029. Benson discloses a patient population whose cancer progressed after two previous drug therapies or had metastatic cancer. *Id.*, 1034.

5. Hamid (Ex. 1011)

Hamid is an article titled "Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma." Ex. 1011, 134. Hamid "tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma." *Id.* Hamid discloses administering pembrolizumab intravenously "in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not." *Id.* According to Hamid, "treatment with lambrolizumab resulted in a high rate of sustained tumor regression." *Id.*

6. Brown (Ex. 1034)

Brown is an article titled "Neo-Antigens Predicted by Tumor Genome Meta-Analysis Correlate with Increased Patient Survival." Ex. 1034, 743. Brown discloses that "patients with tumors showing naturally immunogenic mutations and associated [tumor infiltrating lymphocytes] are potential candidates for treatment with immune modulators such as CTLA4- or PDCD1-targeted antibodies," i.e., PD-1 inhibitors. *Id.*, 747. More specifically, Brown teaches that "tumors bearing predicted immunogenic mutations have . . . elevated expression of CTLA4 and PDCD1," i.e., PD-1, "reinforcing the notion that these patients may be optimal candidates for immune modulation." *Id.*, 747–48.

7. Duval (Ex. 1087)

Duval is an article titled "The mutator pathway is a feature of immunodeficiency-related lymphomas." Ex. 1087, 5002. Duval describes that "[c]ancers with a mutator phenotype constitute a frequent subset of solid tumors characterized by mismatch repair deficiency." *Id.* Duval discloses that "[t]hese tumors exhibit a widespread genetic instability at the molecular level that mainly affects microsatellite sequences and are called MSI-H (microsatellite instability-high) tumors." *Id.* According to Duval, the observation that the MSI-H phenotype was specifically associated with immunodeficiency-related lymphomas (ID-RL) "suggests the existence of the highly immunogenic mutator pathway as a novel oncogenic process in lymphomagenesis whose role is favored when host immunosurveillance is reduced." *Id.*

8. Koh (Ex. 1095)

Koh is an article titled "Uterine Neoplasms, Versions 1.2014: Clinical Practice Guidelines in Oncology." Ex. 1095, 248. Koh describes that "[t]he

NCCN Guidelines for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management." *Id.*, Abstract. Koh discloses that patients having endometrial cancer who were enrolled in a clinical study would generally have had a tumor that had progressed after at least one prior cancer treatment and metastatic cancer. *Id.*, 256.

9. Ajani (Ex. 1096)

Ajani is an article titled "Gastric Cancer, Version 2.2013: Featured Updates to the NCCN Guidelines." Ex. 1096, 531. Ajani discloses "evidence- and consensus-based recommendations for a multidisciplinary approach for the management of patients with gastric cancer." *Id.* Ajani discloses that "combined modality therapy has been used as an adjunct to surgery to improve survival rates in patients with localized resectable cancer." *Id.* Because "gastric cancer is often diagnosed at an advanced stage," Ajani describes that "HER2 testing is now recommended for all patients with metastatic disease at the time of diagnosis." *Id.* at 544. According to Ajani, "[t]he selection of appropriate systemic therapy should be based on the patient's performance status and HER2 status." *Id.*

C. Ground 1: Anticipation by MSI-H Study Record

1. Petitioner's Contentions

Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, and 19–30 are anticipated by the MSI-H Study Record. Pet. 13–37. To support its contention, Petitioner directs our attention to the foregoing disclosures of the MSI-H Study Record and provides a detailed claim analysis addressing how each element of claims 1, 2, 4–7, 9–12, 14–17, and 19–30 is disclosed by the MSI-H Study Record. Petitioner supports this interpretation of the MSI-H Study Record with Dr. Neugut's testimony. Ex. 1003 ¶¶ 50–128.

Additionally, Petitioner cites the holding in *Schering Corp. v. Geneva Pharms*., 339 F.3d 1373, 1377 (Fed. Cir. 2003), that "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." Pet. 13–14. Petitioner also cites to *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012), for its holding that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." Pet. 15. Relying on those cases, Petitioner contends that "[t]he MSI-H Study Record inherently anticipates claims 1, 2, 4–7, 9–12, 14–17, and 19–30 of the '462 patent because the claims are directed to the methods disclosed in the MSI-H Study Record." Pet. 16.

Petitioner argues further that the treatment described in the MSI-H Study Record is written description support for the claimed method because the MSI-H Study Record teaches the claimed drug, given at the only therapeutically effective dosage described in the '462 patent, and given to the claimed patient population. *Id.* Petitioner relies on *Schering*, 339 F.3d at 1379, to argue that "[i]f granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated." Pet. 13.

a) Independent Claim 1

Like Petitioner, our analysis focuses on independent claim 1. *See id.* at 30–31 (relying substantially on analysis of claim 1 for independent claim 11). Petitioner's contentions with regard to claim 1 are summarized below.

(1) [1.pre]: "A method for treating a patient"

Petitioner argues that the MSI-H Study Record discloses a method of treating a patient that is the method set forth in this claim. Pet. 16. Specifically, Petitioner cites to the teaching in the Arms and Interventions section of a method of treating patients having non-colorectal MSI-H cancer, as recited in the preamble of claim 1.[2] *Id.* (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria); Ex. 1003 ¶¶ 59–60).

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

(2) [1. pre.b]: "having a solid tumor"

Petitioner contends that the MSI-H Study Record discloses that its patients have both tumors and measurable disease. Pet. 17 (citing Ex. 1005, 2 (Study Identification), 5–6 (Eligibility)). Petitioner contends that "[m]easurability is a property of solid tumors," and that the MSI-H Study Record patients therefore had solid tumors. *Id.* (citing Ex. 1048, 228, 230–31; Ex. 1003, ¶¶ 60–61).

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

[2] We need not decide whether the preamble is limiting as we find that the MSI-H Study Record discloses the preamble.

(3) [1.pre.c]: "selected from the group consisting of endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer"

Petitioner contends that "MSI-H was known to occur commonly in several different types of cancers, including endometrial, small bowel cancer, and gastric cancer." Pet. 17 (citing Ex. 1005, 4 (Arms and Interventions), 2 (Study Identification), 3 (Study Description), 4 (Primary Outcome Measures), 5 (Inclusion Criteria); Ex. 1085, 673, 675; Ex. 1003 ¶¶ 25, 60–61, 63). Petitioner argues that, based on this disclosure, an ordinary skilled artisan would have "envisaged treating patients having endometrial, small bowel, and gastric cancer" using the MSI-H methods. *Id.* at 17–18.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

(4) [1.pre.d]: "that has progressed following at least one prior treatment, the method comprising:"

Petitioner alleges that the MSI-H Study Record discloses that, to participate, eligible patients must have "tumors" and "measurable disease," which Dr. Neugut testifies would include metastatic and advanced non-colorectal cancers in the context of the MSI-H Study Record. Pet. 19–21 (citing Ex. 1005, 2–6 (Study Identification, Study Design, Eligibility) (excluding patients with prior PD-1 and other antibody treatment); Ex. 1003 ¶ 65). According to Dr. Neugut, in the context of the MSI-H Study Record and its disclosures, "the person of ordinary skill would have concluded that patients in the MSI-H study would have generally received a prior cancer

therapy drug and had their solid tumors progress after receiving that prior treatment." Ex. 1003 ¶ 65.

Dr. Neugut further testifies that patients with metastatic and advanced endometrial, small bowel, and gastric cancer "would have generally received at least one other prior drug therapy, such as standard of care chemotherapy, and had their cancers progress following that drug therapy." *Id.* ¶ 67 (citing Ex. 1089 at PDF p. 17 (endometrial); Ex. 1020 at PDF p. 25 (small bowel); Ex. 1094 at PDF p. 12, 15 (gastric cancer patients would generally receive a standard first line therapy, unless diagnosis was late stage)). Dr. Neugut observes that the Eligibility section of the MSI-H Study Record takes care to exclude patients having had prior treatment with certain antibodies. Ex. 1003 ¶ 68. Dr. Neugut interprets this exclusion as supporting his opinion that such patients would have received a prior cancer therapy drug to treat their tumor because otherwise, the study would not have purposefully excluded patients treated with these antibodies. *Id.* Rather, if the prior therapies had worked, these patients would not have participated in the MSI-H Study Record due to their progressing disease. *Id.* Dr. Neugut cites to a poster presentation describing the MSI-H Study Record as requiring that patients have "progressive disease" and have had prior therapies. *Id.* ¶ 70.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses all limitations in the preamble.

> *(5) [1.1]: "testing or having tested a biological sample obtained from the patient to determine whether the solid tumor is microsatellite instability high or DNA mismatch repair deficient; and"*

Petitioner contends that the Arms and Interventions section of the MSI-H Study Record teaches this limitation in claim 1. Pet. 23–25.

Specifically, Petitioner contends that this section of "the MSI-H Study Record discloses three study arms, one of which consists of patients having MSI-H non-colorectal cancer." *Id.* at 23 (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility)). Petitioner contends that "MSI positive" patients identified in the MSI-H Study Record are MSI-H patients as taught by the prior art as affirmed by an inventor during prosecution. *Id.* (citing Exs. 1010, 1193, 1196; Ex. 1018, 293; Ex. 1019, 1065; Ex. 1003, ¶¶ 27, 72; June 28, 2022, Declaration of Dr. Pardoll, 7–8, ¶¶ 21–23). Dr. Neugut testifies that the MSI-H Study Record's description of treating patients with "MSI-H positive" cancer "also discloses treating patients with a mismatch repair deficiency ('dMMR') . . . because MSI-H is caused by dMMR." *Id.* at 24 (citing Ex. 1010, 1192; Ex. 1003, ¶¶ 27–29, 73).

Petitioner also relies on Dr. Neugut's testimony that "the MSI-H Study Record required testing or having tested 'a biological sample obtained from a patient' in order to place the patients into the proper arm." *Id.* (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); Ex. 1003 ¶ 74).

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

> *(6) [1.2]: "in response to determining that the solid tumor microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have a solid tumor that is microsatellite instability high or DNA*

mismatch repair deficient with a therapeutically effective amount of pembrolizumab."

Petitioner argues that the MSI-H Study Record anticipates this limitation in claim 1 because the Arms and Interventions section discloses treating patients having MSI-H non-colorectal cancer with 10 mg/kg of pembrolizumab every 14 days. Pet. 25–26 (citing Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility); *see also* Ex. 1003 ¶¶ 76–79 (Dr. Neugut's testimony that the dosage described in the MSI-H Study Record is the same as the dosage described as being effective in the '462 patent)); *compare* Ex. 1001 4:23–36, 8:51–58, 13:30–37.

In view of the above, on this record, we determine that Petitioner has sufficiently demonstrated that the MSI-H Study Record discloses this limitation.

2. Discussion

At this point in the proceeding, Petitioner has sufficiently shown that there is a reasonable likelihood of a causal relationship in the MSI-H Study Record between treatment of non-colorectal cancer patients and the determination of their MSI status, wherein non-colorectal cancer patients determined to be microsatellite instability high or DNA mismatch repair deficient were placed into a study arm and then treated with pembrolizumab. Ex. 1005, 4. Because treatment of the patients was performed only after MSI-H status was determined, there is evidence that the MSI-H Study Record teaches treating the patients "in response to" determining their MSI-H status.

The MSI-H Study Record describes other patients being enrolled and treated with pembrolizumab, including colorectal cancer patients determined to be MSI-H and colorectal cancer patients determined not to be MSI-H.

See Ex. 1005, 2–6 (Arms and Interventions, Study Identification, Study Design, Eligibility). At this point in the proceeding, we interpret the "in response to" limitation of claim 1 to mean that pembrolizumab is administered to a patient after the patient has been determined to be microsatellite instability high or DNA mismatch repair deficient, regardless of whether pembrolizumab is also administered to other patients. The record is devoid of evidence that one of ordinary skill in the art would have understood treating a patient "in response to" the determination that the patient has a condition to exclude the same treatment of other patients, such as the treatment of control patients not having the condition.

The record before us shows that Petitioner has sufficiently demonstrated a reasonable likelihood that those of ordinary skill in the art would have understood the MSI-H Study Record teaches treatment of non-colorectal cancer patients who have been determined to be microsatellite instability high or DNA mismatch repair deficient because one of the arms of the MSI-H Study Record provides for treatment of patients with "MSI Positive Non-Colorectal Cancer." *See* Ex. 1005, 4. Petitioner points to evidence that those of ordinary skill in the art would have understood that the term "MSI positive" in the MSI-H Study Record means "microsatellite instability high" or "DNA mismatch repair deficient," as recited in claim 1. *See* Neugut Decl., Ex. 1003, ¶¶ 27–29, 73. Petitioner also cites evidence showing that those of ordinary skill in the art would have understood that the term "non-colorectal cancer" in the MSI-H Study Record would include endometrial, small bowel, and gastric cancer. *See* Neugut Decl., Ex. 1003, ¶¶ 25, 60–61, 63. Petitioner cites to further evidence showing that those of ordinary skill in the art would have understood that the MSI-H Study Record uses testing to determine MSI-H status and place patients into a study arm.

Id., ¶ 74. And the Petition cites evidence showing that those of ordinary skill in the art would have understood the treatment in the MSI-H Study Record, administration of 10 mg/kg of pembrolizumab every 14 days, to be treatment with a therapeutically effective dose because it is the only dose used in the '462 patent and the results reported there showed that this does was effective. *Id.*, ¶¶ 76–79.

In light of this evidence, Petitioner has provided sufficient evidence to show there is a reasonable likelihood that the MSI-H Study Record teaches each and every element of claim 1 and, thus, anticipates claim 1 under 35 U.S.C. § 102. We note that "even if [the documents disclosing a planned clinical study] merely proposed the administration of [the drug] for treatment or prevention of [the recited condition] (without actually doing so), it would still anticipate." *In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012).

Accordingly, the evidence of record sufficiently shows that there is a reasonable likelihood Petitioner will prevail with respect to at least one claim challenged under Ground 1 in the Petition.

We have reviewed Petitioner's allegations regarding the MSI-H Study Record's disclosure of the additional limitations of claims 2, 4–7, 9–12, 14–17, and 19–30, and find that Petitioner has sufficiently demonstrated, on this record as supported by the testimony of Dr. Neugut, that the MSI-H Study Record discloses those additional limitations. *See* Pet. 27–37; Ex. 1003 ¶¶ 80–127. Accordingly, we determine that there is sufficient evidence to warrant institution of review on all claims challenged in Ground 1 of the Petition.

3. Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that the challenged claims of the '462 patent are unpatentable. Accordingly, we institute an *inter partes* review of claims 1, 2, 4–7, 9–12, 14–17, and 19–30 of the '462 patent.

D. Ground 2: Obviousness over MSI-H Study Record, Brown, Duval, and Benson

1. Petitioner's Contentions

Petitioner presents alternative grounds of challenge against the patentability of the claims of the '462 patent based on obviousness. *See* Pet. 41–61. In regard to Ground 2, challenging the patentability of claims 1, 2, 4–7, 9–12, 14–17, and 19–30, Petitioner cites to Brown, Duval, and Benson, in addition to the MSI-H Study Record. *Id.*, 41–51.) According to Petitioner, this ground of challenge is raised to address potential arguments by Patent Owner that the MSI-H Study Record cannot anticipate because (1) the MSI-H Study Record does not disclose an improved outcome and that one of ordinary skill in the art would not have expected such efficacy, (2) the MSI-H Study Record does not disclose testing a patient for MSI-H or MMR deficiency status, and/or (3) the MSI-H Study Record does not teach specific types of cancer, as well as arguments that related to dependent claims. Pet. 41.

In regard to the first potential argument, that the MSI-H Study Record does not disclose an improved outcome and/or that such efficacy would not have been expected, Petitioner cites to Brown as teaching that PD-1 inhibitors are inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize. Pet. 42 (citing Ex. 1034, 747). Petitioner argues further that Duval teaches that MSI-H cancers have

cells that are easy for immune cells to recognize. *Id.* (citing Ex. 1087, 5002). Dr. Neugut's testimony supports Petitioner's argument that the cited teachings of Brown and Duval, as well as other references, would have motivated a person of ordinary skill in the art to obtain the results of the MSI-H Study Record. *See* Ex. 1003 ¶¶ 124, 130, 132, 136. Petitioner argues further that Brown and Duval would have motivated one of ordinary skill in the art to obtain the results of the MSI-H Study Record by treating patients with common types of MSI-H cancers, including endometrial, small bowel, and gastric cancers. Pet. 42–43 (citing Ex. 1003, ¶ 136).

Petitioner argues further that the state of the art, as demonstrated by Brown and Duval, as well as other references, would have provided one of ordinary skill in the art with a reasonable expectation of success because physicians were actively treating patients with cancers that were known to be MSI-H with PD-1 inhibitors. Pet. 43 (citing Ex. 1016; Ex. 1017; Ex. 1003 ¶¶ 131–132).

According to Petitioner, these other references would have "independently urged" those of ordinary skill in the art to treat MSI-H cancer with PD-1 inhibitors or other immunotherapy, such as pembrolizumab, and would have given them a reasonable expectation of success. Pet. 44–45. Petitioner cites, along with other references, Pernot, which states "[colorectal cancers] associated with MSI could lead to a more intense immune response, but also to specific immunoregulatory phenomena, making them good candidates for immunotherapy." (Ex. 1006,[3] 3741; *see* Pet. 43.) Petitioner also cites Champiat, which states that

[3] Pernot *et al*., Colorectal Cancer and Immunity: What We Know and Perspectives, 20(14) WORLD J. GASTROENTEROLOGY 3738 (April 2014) (Ex. 1006) ("Pernot").

> if high levels of mutational heterogeneity increase the tumor immunogenicity, it will be interesting to evaluate the clinical activity of PD-1/PD-L1 agents in DNA mismatch repair (MM)-deficient tumors, such as microsatellite instability (MSI)+ colorectal carcinoma as well as BRCA1 and 2 neoplasms (breast cancer 1 and 2, early onset), all of which display severe genomic instability.

(Ex. 1032,[4] e27817-5; *see* Pet. 43.) Petitioner argues, citing Dr. Neugut's testimony, that although these references are in the context of MSI-H colorectal cancer, one of ordinary skill in the art would have understood their teachings to apply to other MSI-H cancers because small bowel cancer is often treated similarly to colorectal cancer. Pet. 44 (citing Ex. 1003 ¶ 139).

Petitioner argues further that if Patent Owner argues the MSI-H Study Record does not expressly teach testing to determine if a patient's cancer is microsatellite instability high or DNA mismatch repair deficient, the MSI-H Study Record would have at least motivated those of ordinary skill in the art to undergo such testing to be placed in the proper study arm. Pet. 45–46 (citing Ex. 1003 ¶ 141). Petitioner also argues that testing a biological sample from a patent for MSI-H was routine in the art at the time of filing. *Id.*, 45 (citing Ex. 1003 ¶ 141).

Specifically regarding claims 6, 16, 24, 28, and 30, challenged under 35 U.S.C. § 103, Petitioner cites Benson (Ex. 1009) for its teachings of the ways in which clinical studies involving colorectal and small bowel cancer are conducted. *See* Pet. 48–51 (citing Ex. 1009, 1034.) These claims

[4] Champiat *et al*., Exomics and Immunogenics Bridging Mutational Load and Immune Checkpoints Efficacy, 3(1) OncoImmunology e27817-1(January 2014) (Ex. 1032) ("Champiat").

require treating patients who had previously been treated with a cancer therapy drug and whose cancers had progressed or who have metastatic cancer. *See* Ex. 1001, 26:11–27:17. Petitioner argues that, to the extent Patent Owner asserts the MSI-H Study Record does not disclose treating patients with these characteristics, Benson teaches that, under the standard of care, patients having tumors and measurable disease who would take part in a clinical study are generally patients who have had their cancer progress after previous drug therapies. Pet. 49 (citing Ex. 1009, 1034). Petitioner cites to other references to demonstrate that, also under the standard of care, patients with tumors and measurable disease who would take part in a clinical study are patients with metastatic, advanced, and recurrent disease. Pet. 49–50 (citing Ex. 1089,[5] 17; Ex. 1094,[6] 15; Ex. 1020,[7] 251).

Petitioner argues, citing Dr. Neugut's testimony, that patients in a clinical study such as the MSI-H Study Record describes would be patients who had already received standard of care treatment but did not respond to this treatment, and would not have been expected to respond to additional standard of care treatment. Pet. 50–51 (citing Ex. 1003 ¶ 147). Petitioner further cites to Dr. Neugut's testimony that the patient population with tumors and measurable disease who would take part in a clinical study are

[5] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Uterine Neoplasms Version 1.2014 (November 27, 2013) (Ex. 1089).
[6] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1.2014 (May 30, 2014) (Ex. 1094).
[7] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014) (Ex. 1020).

patients with metastatic, advanced, and recurrent disease. *Id.* (citing Ex. 1003 ¶ 147).

According to Petitioner, given the teachings of Benson, those of ordinary skill in the art would have been motivated to combine the teachings of the cited references and would have had a reasonable expectation of success in achieving the methods recited in dependent claims 6, 16, 24, 28, and 30. *See* Pet. 50–51.

2. Discussion

As explained above in regard to Ground 1, on this record we determine that sufficient evidence exists to institute on the basis of at least claim 1 regarding anticipation. For the same reasons, we determine the evidence is sufficient to proceed on Ground 2 on the basis of at least claim 1 regarding obviousness. "It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (citation omitted).

Furthermore, to the extent the MSI-H Study Record does not disclose improved outcomes of the claimed method, testing or treating a patient for MSI-H or MMR deficiency status, and/or specific types of cancer as recited in the dependent claims, Petitioner has directed us to sufficient evidence that it is reasonably likely it will prevail on at least one claim challenged under 35 U.S.C. § 103 based on the proposed combination of the cited references. Specifically, Petitioner has directed us to Brown, which teaches that PD-1 inhibitors are inherently more effective when treating tumors comprised of cells that are easy for immune cells to recognize (*see* Ex. 1034, 747), Duval, which teaches that MSI-H cancers have cells that are easy for immune cells to recognize (*see* Ex. 1087, 5002), and Benson, which teaches processes of conducting clinical studies (*see* Ex. 1009, 1034). Based on the record before

us and the teachings of the references in combination, Petitioner presents a reasonable likelihood that the method of at least claim 1 would have been considered obvious by one of ordinary skill in the art. *Id.*; *see also* Ex. 1003 ¶¶ 129–149.

Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

After weighing the arguments and evidence set forth in the Petition, we determine that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail in establishing that claim 1 is rendered obvious by the combination of the MSI-H Study Record, Brown, Duval, and Benson. Additionally, we have reviewed Petitioner's obvious challenges of claims 2, 4–7, 9–12, 14–17, and 19–30 and find that Petitioner has sufficiently demonstrated, on this record and as supported by the testimony of Dr. Neugut, that there is sufficient evidence to indicate a reasonable likelihood that Petitioner will prevail in establishing that the combination of the MSI-H Study Record, Brown, Duval, and Benson renders obvious each of claims 1, 2, 4–7, 9–12, 14–17, 19–30.

3. Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood that at least one of the challenged claims of the '462 patent is unpatentable. Accordingly, we institute an *inter partes* review of claims 1, 2, 4–7, 9–12, 14–17, and 19–30 of the '462 patent.

E. Grounds 3–7: Obviousness over MSI-H Study Record or MSI-H Study Record, Brown, Duval, Benson, and Koh

1. Petitioner's Contentions

In Ground 3, Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, 19–24 of the '462 patent would have been obvious over the references

discussed in Grounds 1 and 2 and further in view of Koh. Pet. 52–53. In Ground 4, Petitioner contends that claims 1, 2, 4–7, 9–12, 14–17, 19, and 25–26 would have been obvious over the references discussed in Grounds 1 and 2 and further in view of Ajani. *Id.* at 53–54. In Ground 5, Petitioner contends that claims 2, 8, 12, and 18 would have been obvious over the references discussed in Grounds 1–4 and further in view of Chapelle. *Id.* at 55–57. In Ground 6, Petitioner contends that claims 3 and 13 would have been obvious over the references discussed in Grounds 1–4 and further in view of Steinert. *Id.* at 58–59. In Ground 7, Petitioner contends that claims 7 and 17 would have been obvious over the references discussed in Grounds 1–4 and further in view of Hamid. *Id.* at 59–62.

Patent Owner at this stage does not offer any arguments addressing Petitioner's substantive showing.

We have reviewed Petitioner's contentions as to the Grounds 3–7 and are persuaded, on this record, that Petitioner's arguments and evidence are sufficient to show a reasonable likelihood that Petitioner would prevail in proving unpatentability of at least one claim in challenged in each of Grounds 3–7. *See, e.g.*, Pet. 52–61; Ex. 1003 ¶¶ 150–186.

However, the burden remains on Petitioner to prove unpatentability of each challenged claim. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of the challenged claims of the '462 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v.*

Iancu, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"); 37 C.F.R. § 42.108(a). At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *See In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response). In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board's Rules.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–30 of the '462 patent is hereby instituted on the grounds set forth in the Petition, commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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Patent 11,643,462 B2

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