

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

IPR2024-00623
Patent No. 11,325,974

PETITIONER'S REPLY

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LIST OF EXHIBITS

Ex. No.	Description	Previously Submitted
EX1001	U.S. Patent No. 11,325,974 (the “’974 patent”)	X
EX1002	File History of the ’974 patent (U.S. Patent Application No. 17/131,326)	X
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EX1006	Pernot et al, <i>Colorectal Cancer and Immunity: What We Know and Perspectives</i> , 20(14) World J. Gastroenterology 3738 (April 2014)	X
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EX1015	Kang et al, <i>Pembrolizumab KEYNOTE-001: An Adaptive Study Leading to Accelerated Approval for Two Indications and a Companion Diagnostic</i> , 28(6) Annals of Oncology 1388 (2017)	X
EX1016	ClinicalTrials.gov, NCT01848834, “Study of MK-3475 in Participants With Advanced Solid Tumors (MK-3475-012),” (October 18, 2013) available at https://classic.clinicaltrials.gov/ct2/history/NCT01848834?A=12&B=12&C=merged#StudyPageTop	X
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EX1018	Robinson et al, <i>Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) Diagnostics</i> , 99(4) J. Nat'l Cancer Inst. 291 (2007)	X
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I. INTRODUCTION

JHU's POR repeats the same irrelevant and misleading arguments it made in IPR2024-00240. This is not a case that turns on how well the claimed cancer treatment method works or whether the Parties were excited by the results of the clinical trial on which they collaborated. Instead, this case centers on the MSR's prior disclosure of JHU's claimed treatment method using the following two steps: (1) determining a patient has a tumor that is MSI-H and (2) administering an effective amount of pembrolizumab to the patient.¹

It is irrefutable that the treatment method disclosed in the MSR is the only written description support for JHU's claims and that the claimed method was disclosed *more than two years before* JHU's alleged July 2015 invention date.² JHU apparently recognizes the insurmountable hurdle the MSR poses because, just as it argued in IPR2024-00240, JHU argues here for an unprecedented change in the law in hopes of disqualifying the MSR as prior art. As explained below, no change in law is warranted.

¹ Pet., 2, 5-10; EX1003 ¶¶22-23, 34-41.

² Pet., 18; EX1003 ¶¶36, 40-41, 75.

JHU also disingenuously belittles the MSR calling it a “bare-bones clinical trial announcement posting.”³ But nothing about the MSR is bare bones. Even according to JHU’s declarant Ms. Jennifer Newberger, the MSR is full of detail and fulfilled its intended purpose of informing the public about an available treatment method for critically ill cancer patients.⁴

And, contrary to JHU’s arguments, the MSR discloses each of the claim limitations JHU argues are missing. **First**, the claim limitations reflecting the results that naturally flow from carrying out the two-step treatment method are inherent. This should be undisputed given the Federal Circuit’s *Schering* and *Montgomery* precedent.⁵ Yet, JHU continues to argue otherwise, going so far as to incorrectly call the clinical trial described in the MSR an “abstract theory.”⁶

Second, the claim limitations specifying the patient has “received a prior cancer therapy drug” and the cancer has “progressed after the patient received the

³ POR, 2.

⁴ EX1135, 118:18-121:16, 124:4-18, 134:19-136:11, 148:13-20, 153:19-156:12, 200:14-201:1; *id.* 124:19-125:12.

⁵ *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373 (Fed. Cir. 2003); *In re Montgomery*, 677 F.3d 1375 (Fed. Cir. 2012).

⁶ POR, 13-15.

prior cancer therapy drug” are disclosed in the MSR. This was explained by Merck’s declarant Dr. Alfred Neugut.⁷ To his credit, JHU’s main declarant, Dr. Nils Lonberg clarified his position on this issue in deposition and candidly admitted that the treatment method in the MSR includes patients that have received a prior cancer therapy and where the cancer progressed following a prior cancer therapy.⁸

Third, the claim limitations “metastatic cancer,” which appears in Dependent Claim 5, and “metastatic colorectal cancer,” which appears in Dependent Claim 6, are disclosed in the MSR. Dr. Neugut explained the MSR would be understood to include patients having “metastatic cancer” and “metastatic colorectal cancer.”⁹ Dr. Lonberg also clarified his position on this issue in deposition and he agrees with Dr. Neugut.¹⁰

As to obviousness, JHU offers more of the same: it focuses on how well the claimed two-step treatment method works and alleged missing limitations in the

⁷ See, e.g., EX1003 ¶¶67-72, 81-82.

⁸ EX1245, 57:5-58:2; *id.*, 40:5-14, 48:1-11, 49:2-12.

⁹ EX1003 ¶¶55-56, 68-69, 85-88. As explained below, Dr. Neugut did not retract his position during his deposition.

¹⁰ EX1245, 58:3-10; *id.*, 50:7-10, 51:4-7.

MSR.¹¹ Dr. Lonberg persists with his incorrect view that a POSA is a skeptic refusing to accept the prior art for what it teaches. Yet, when asked at his deposition whether the same prior art Merck identified in its Petition would serve as part of the rationale for conducting the trial described in the MSR, Dr. Lonberg readily agreed it would.¹² And when asked if he could identify any evidence that questioned whether the trial described in the MSR would work, he could not identify any such evidence.¹³

Finally, as in IPR2024-00240, JHU devotes an unwarranted amount of space, given the weakness of JHU's purported evidence, and multiple declarations, to secondary considerations. As Merck declarants Drs. Paul Oberstein and Sean Sheridan explain, JHU fails to meet its burden to show actual nexus between any alleged secondary considerations evidence and any novel features of the '974 patent claims. And even if JHU were credited with a presumption of nexus, the substantial weight of the evidence presented by Merck and its declarants compels a finding that, to the extent they are not anticipated, all challenged claims are unpatentable.

¹¹ POR, 24-50.

¹² EX1245, 79:5-80:16; EX1138, 141:13-19, 142:12-143:17.

¹³ EX1245, 36:5-9, 38:10-19.

II. TESTIMONY ELICITED FROM JHU'S POR DECLARANTS SUPPORTS THAT ALL JHU CLAIMS ARE UNPATENTABLE

The deposition testimony of JHU's POR declarants undermines and conflicts with their declaration. For example, Dr. Lonberg, friend of two named inventors (see EX1138, 165:10-11), revealed his conclusions were grounded in his belief that a POSA "reads the literature skeptically, always." (EX1138, 84:14-16.) But that is contrary to the perspective that the Federal Circuit instructs. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 928 (Fed. Cir. 2024) (finding analysis of prior art must utilize the perspective of a POSA "capable of deducing what references *fairly suggest or employing ordinary creativity*") (emphasis added). And as such, Dr. Lonberg strays from a fair reading of the prior art teachings. (See, e.g., EX2072 ¶71 (arguing a POSA would not understand Pernot to "even suggest[]" MSI-H patients as promising candidates for checkpoint blockade despite Pernot's discussion of MSI-H CRC as "good candidates for immunotherapy" and checkpoint blockade among the "most promising [immunotherapy] strategies" (EX1006, 3738, 3741).)

Despite that lens, Dr. Lonberg agrees with Dr. Neugut on many key facts, including that as of July 10, 2015 (the "Alleged Invention Date") the literature was replete with information about (1) MSI testing, (2) the clinical relevance of MSI-H in cancers, (3) the correlation between mutational load and susceptibility to

treatment with PD-1 inhibitors, and (4) the prior successful treatment of cancer patients with PD-1 inhibitors. (*See, e.g.*, EX1138, 48:16-52:3, 93:15-19, 95:8-13, 153:4-155:10, 162:16-163:18, 165:16-166:12, 171:13-172:19, 175:12-176:1, 180:2-183:16, 190:10-191:9, 195:21-200:4, 203:13-211:10; *see also* EX1150, ¶¶25-26; EX1243, 48:11-12, 48:22-49:1.) Dr. Lonberg also agrees that specialized experience researching or developing new treatments for cancer is not needed to practice the '974 patent claims, as those claims are not directed to methods for conducting immunology or genetics research. (EX1245, 13:20-14:1, 14:8-10, 15:16-16:11.) Accordingly, his view that a POSA must have specialized experience in these areas is unsupported. (EX2072, ¶¶86-94).

JHU declarant Dr. Richard Goldberg, another friend of a named inventor (*see* EX1136, 24:20-21), admitted that, before JHU's Alleged Invention Date, PD-1 inhibitors showed promise and "companies all over the world began more aggressively researching immune-oncology opportunities once the first breakthrough [with nivolumab] had occurred." (EX1136, 80:13-82:13, 188:15-190:13; *see also* EX1150, ¶¶29-33.) That this admission conflicts with Dr. Goldberg's testimony regarding an alleged long-felt unmet need is not surprising as he admitted he had not actually reviewed highly relevant pieces of prior art (*e.g.*, Pernot (EX1006), Champiat (EX1032)) before rendering his opinions, and was therefore unaware of critical information known by a POSA by the Alleged

Invention Date. (*See, e.g.*, EX1136, 85:20-87:22, 89:13-91:17; EX1243, 51:15-52:16, 54:17-55:1, 56:7.)

Named inventor Dr. Dung Le’s deposition revealed a lack of familiarity with the content of her declaration, undermining the credibility of her allegations regarding Merck and JHU’s purported invention. (EX1139, 11:3-17:10, 105:3-112:10, 114:21-118:18, 234:2-246:3, 290:2-292:16.) Dr. Le could not recall a single Merck individual involved in the trial described in the MSR (the “MSI-H Study”), despite earlier statements about her alleged “observations” of “Merck personnel involved with [the] study.” (EX1139, 66:2-5, 264:3-274:21; *see also* EX2130, ¶35; EX1150, ¶¶51-52.) Additionally, Dr. Le admitted Merck provided funding for the study—contrary to several JHU declarants’ assertions.¹⁴ (EX1139, 278:17-286:14; *see also* EX2072 ¶126; EX2090 ¶14.) Likewise, named inventor Dr. Drew Pardoll revealed he was neither involved with nor knowledgeable about the MSI-H Study, despite JHU’s attempt to rely on his declaration to support alleged skepticism for the MSI-H Study. (POR, 66; EX1140, 25:16-17, 29:3-4,

¹⁴ Dr. Lonberg also has no bases for his allegation that Merck did not provide any MSI-H Study funding as he revealed his understanding came from Dr. Pardoll who testified he “[did not] recall saying that” to Dr. Lonberg. (EX1140, 82:11-13; EX1138, 228:19-22; *see also* EX1138, 229:7-9.)

48:3-16, 71:3-5, 102:19-103:5, 119:3-121:12, 122:7-125:3; *see also* EX1150,

¶¶53-54.)

Another JHU declarant, Ms. Newberger, an attorney at a private law firm, testified that, despite submitting a declaration in this proceeding regarding publication of the MSR on ClinicalTrials.gov, she had “not seen the patent,” “did not ask about the patent,” and “did not see” what was actually submitted to ClinicalTrials.gov on June 10, 2013. (EX1135, 11:18-19; 36:4-7, 62:16-17; EX1242, 12:16-22, 13:12-14:11, 24:14-22.) Her testimony purportedly in support of JHU’s experimental use argument is therefore irrelevant and not reliable

III. GROUND 1: CLAIMS 1-3 AND 5-7 OF THE ’974 PATENT ARE ANTICIPATED BY THE MSR

A. ClinicalTrials.gov Study Records Are Prior Art Printed Publications and Therefore Not Subject to Experimental Use

Telling of the anticipating disclosures of the MSR, JHU argues the MSR should not qualify as prior art. (POR, 18-24.) But the Federal Circuit has found that ClinicalTrials.gov study records, like the MSR, are Section 102 prior art. *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024); *see also Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, No. IPR2022-00578, Paper 78 (P.T.A.B. Aug. 29, 2023) (relying on ClinicalTrials.gov study record for purposes of anticipation and obviousness). JHU does not cite any case law to

support its request that the Board exclude the MSR as an experimental “use.”

(POR, 26-27.) That is because there is no such case law.

Instead, JHU relies on Ms. Newberger to argue JHU submitted only required information to ClinicalTrials.gov (POR, 17-24; EX2137, ¶¶10-52), which is irrelevant and provides no justification for disqualifying a printed publication as prior art. Moreover, her assertions are unreliable. In addition to not knowing what ClinicalTrials.gov stated or required in 2013 (EX1135, 240:9-242:15), the authority she cites also makes plain that certain information in the MSR was not *required* in 2013.¹⁵ (EX2137, ¶33 (citing EX2149); EX1242, 35:6-14, 37:21-38:7; *see also* EX1135, 127:19-128:11, 250:18-253:20.)

Separately, JHU argues that had JHU patented the claimed methods of treatment any earlier, it would not have met the requirements of §101 or §112. (POR, 15-16.) It is well established, however, that there is no requirement to provide evidence from human clinical trials for claims to be patentable under §101 or §112. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir.

¹⁵ Ms. Newberger’s declarations in related proceedings provide inconsistent testimony as to allegedly required information. (*Compare* EX1281, Table 1 *with* EX1282, Table 1 *with* EX1280, Table 1; *see also* EX1242, 46:8-49:1, 50:5-54:18.)

2009); *see also Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (cited by MPEP 2107.03).

B. The Claimed Clinical Results Inherently Flow from the Treatment Method Taught to a POSA by the MSR

JHU argues the MSR “fails to inherently disclose the clinical results of JHU’s study.” (POR, 11-15.) This argument is legally incorrect and also ignores the fact that none of the claims of the ’974 patent require any specific clinical outcome other than the outcome be “improved” as compared to the outcome in a reference patient that is not MSI-H treated with pembrolizumab. (EX1001, 24:27-65.)

Even if clinical results were recited in the claims, the Federal Circuit has explained that results that *inevitably flow* from the prior art, here the MSR, constitute an inherent disclosure. (*See, e.g.*, EX1003, ¶¶40-41, 54, 73-80, 83-84; EX1150 ¶¶65-67, 71-72); *Schering*, 339 F.3d at 1378, 1380; *Montgomery*, 677 F.3d at 1381-82, 1385. Whether the *precise* results of the study described by the MSR could have been *known* before they were obtained does not undermine their inherency or that they inevitably flowed from the exact method of treatment disclosed in the MSR.

While JHU apparently recognizes the law as to inherency, it argues the study described in the MSR is an “abstract theory” and “invitation to investigate” in

hopes of aligning itself with the dissenting opinion in *Montgomery*. JHU's argument is both not based on the law and incorrect. The trial described in the MSR is a Phase 2 clinical study to treat critically ill cancer patients with a drug, which a POSA would have understood had been allowed to move forward by the FDA based on scientific rationales.¹⁶ (EX1150, ¶¶37-50.) As JHU told the FDA in its 2013 Investigational New Drug Application ("IND"), there was scientific rationale underlying that study that included the efficacy PD-1 inhibitors were showing in treatment of different cancers and the prior successful treatment of a MSI-H CRC patient with a PD-1 inhibitor. (EX1150, ¶¶37-44.)

JHU now attempts to recast teachings in the prior art as "resoundingly unsuccessful" and a "failure," but JHU omits that the single CRC responder in the BMS study that it references was known to be MSI-H prior to the publication of the MSR as reported in Lipson (Jan. 2013) and Kim (Nov. 2014). (POR, 12, 45-46; EX1150, ¶¶84, 117; EX1057, 463-64; EX1038, 7.) Moreover, despite now arguing the MSI-H Study results were "unpredictable" and "unexpected" (POR, 44-45), [REDACTED]

¹⁶ The MSR also contains extensive detail about the trial and its methods.

(EX1150, ¶¶55-78; EX1135, 118:18-121:16, 124:4-18, 134:19-136:11, 148:13-20, 153:19-156:12, 200:14-201:1; *id.* 124:19-125:12.)

[REDACTED] (EX1150, ¶38;
EX1116, 24.)

[REDACTED]
[REDACTED] (EX1246, 43:15-45:6; EX1245, 94:8-12.) [REDACTED]
[REDACTED] (EX1150, ¶¶45-47,
EX1118, 4.)

C. The MSR Teaches Treating a Cancer Patient That Has “Received a Prior Cancer Therapy Drug” and the Patient’s Cancer “Progressed After the Patient Received the Prior Cancer Therapy Drug”

JHU argues the MSR is “silent” on whether eligible patients had a prior treatment and had their cancer progress following that prior treatment. (POR, 6-9.) As Dr. Neugut explains in his declaration, a POSA reading the MSR would understand a patient to be treated in the study would have received a prior cancer therapy drug or would have had their cancer progress following a prior cancer therapy drug.¹⁷ (Pet., §§VI.B.2.c, VI.B.3; EX1003, ¶¶67-72, 81-82; *see also*

¹⁷ The cases JHU cites for the proposition that missing disclosures cannot be replaced by “Board nor attorney argument” fall flat—JHU ignores that Drs. Neugut and Oberstein provide testimony regarding a POSA’s understanding of the context provided by the MSR and relevant prior art. (POR, 6-7.)

EX1150, ¶¶58-64, 70.)¹⁸ This is further confirmed by the fact that all patients treated in the MSI-H Study did have at least one prior treatment. (EX1031, 4; EX1001, 15:59-67; EX1245, 53:9-17, 55:22-56:7.)

JHU's declarant Dr. Lonberg agrees. He candidly admitted in deposition the treatment method in the MSR applies to a patient who has received a prior cancer therapy drug and where the cancer progressed following a prior cancer therapy. (EX1245, 57:5-58:2; *id.*, 40:5-14, 48:1-11, 49:2-12.) He explained his opinion regarding the treatment method in the MSR is that it "does not require treatment of *only* patients who have received at least one prior cancer therapy." (EX1245, 57:10-14.)

Dr. Oberstein likewise agrees this type of patient is eligible and included in the treatment method in the MSR. (EX1150, ¶¶58-64, 70.) The MSR explains that patients with "measurable disease" will receive an experimental treatment in a clinical study. (EX1003 ¶¶53, 67-69; EX1005, 2 (Study Identification), 5-6

¹⁸ JHU misleadingly asserts Dr. Neugut conceded the MSR is silent on this point. (POR, 6.) In context, however, Dr. Neugut's response can only be understood as agreeing that the specific wording in counsel's question was not present. (EX2163, 96:1-99:21.) Dr. Neugut's testimony in his declaration stands. (*E.g.*, EX1003, ¶¶67-72, 81-82.)

(Eligibility); *see also id.*, 4-5 (Outcome Measures).) A physician following the standard of care would generally include a patient¹⁹ in such a clinical study if that patient had received a prior cancer therapy or had their cancer progress following the prior cancer therapy. (Pet., 23-26; EX1003 ¶¶67-72, 81-82; EX1020, PDF p.25; EX1009, 1034.)

JHU mischaracterizes Benson and the NCCN guidelines (POR, 7-8) because, while Benson encourages clinicians to include patients in clinical trials, where appropriate, clinical trials are only specified in the *standard of care* as therapy “after second progression.” (EX1009, 1034.) Had the study described by the MSR been limited to only patients who did *not* receive prior treatment, *i.e.*, “first line” patients, prior treatment would have been expressly excluded in the MSR’s exclusion criteria. (EX1150, ¶60.) It was not.

Indeed, the exclusion criteria found in the Eligibility section of the MSR expressly specify individuals who received certain prior treatments. (EX1005, 5-6 (Eligibility); EX1003, ¶70.) Contrary to JHU’s argument, a POSA would

¹⁹ In particular, with respect to claims directed to “a patient,” a POSA would understand there to be at least “a patient” whose treatment follows the standard of care. (EX1150, ¶¶64.)

understand the MSR is directed at a minimum to a patient who had at least one

different prior cancer therapy than those specifically excluded. (EX1150, ¶61.)

JHU also argues inclusion criteria added in January 2016 evidence this claim limitation is allegedly not “necessarily present to a POSA reading the original MSR.” (POR, 9.). The fact that after January 2016 *only* CRC patients who received two or more prior therapies and non-CRC patients who received one or more prior therapies could be treated in the study does nothing to undermine that, before July 10, 2015, a POSA would understand the MSR discloses—consistent with the standard of care—treating at least a patient who received a prior cancer therapy drug or had their cancer progress following treatment with a prior cancer therapy drug. (EX1150, ¶¶62-64.) Notably, all patients treated prior to January 2016 did, in fact, meet those requirements. (*Id.*; *see also* EX1001, 15:59-67; EX1031, 4-5; EX1245, 62:8-14, 64:1-14, 65:18-21, 66:16-68:16.)

Likewise, JHU’s argument that a POSA would interpret the *inclusion* of certain criteria listed in the 2014 ASCO poster as necessarily implying *exclusion* from the MSR is incorrect and illogical. (POR, 9.) The poster,²⁰ which came later, in no way relates to the sufficiency of the earlier MSR disclosures. (EX1150,

²⁰ JHU does not dispute the poster is prior art that a POSA would have knowledge of before the Alleged Invention Date. (Pet., 26n.5.)

¶63n.2.) Indeed, the poster confirms these inclusion criteria regarding prior cancer therapy were not missing from the MSR and were followed. (Pet., 26; EX1003, ¶72; EX1080 (Eligibility Criteria);.)

D. The MSR Teaches Treating a Patient with “Metastatic” Cancer

JHU argues limitations of Dependent Claims 5 and 6 limited more specifically to a patient with “metastatic” cancer are not met because allegedly “the MSR does not disclose treatment of metastatic cancer or metastatic colorectal cancer.” (POR, 17.) As Dr. Neugut explains, however, a POSA would have understood a patient having “measurable” disease in the context of the MSR refers to a patient having metastatic or advanced cancer.²¹ (EX1003, ¶¶55-56, 68, 85-88.)

²¹ JHU alleges Dr. Neugut “conced[es]” that “metastatic” and “measurable” are “total different terms,” and metastatic tumors “would not necessarily be measurable.” (POR, 18.) Dr. Neugut’s declaration, however, is entirely consistent with the MSR’s context of a phase 2 clinical study of a not yet FDA-approved cancer therapy drug known to elicit a strong immune response in patients. (*See* EX1003, ¶¶30-33; EX1150, ¶61; EX1005, 3; *see also* EX1011.).

Dr. Lonberg admitted at deposition that metastatic patients are included, clarifying the “MSR is not limited or does not require treatment of only patients who have metastatic disease.” (EX1245, 58:3-10; *see also id.* 50:7-10, 51:4-7.) Dr. Oberstein likewise agrees these types of patients are eligible and included in the treatment method of the MSR. (EX1150, ¶¶73-78.) Further, if a patient having metastatic cancer was not included, a POSA would have understood that to be highly unusual, especially because the treatment in the MSR was not directed to a local treatment, such as radiation or surgery, but rather to an immunotherapy drug. (EX1003, ¶68.)

Moreover, according to the standard of care at the time, a MSI-H cancer patient enrolled in a study of this type would be understood to be critically ill, with either metastatic or locally advanced cancer. (EX1150, ¶¶75-76; EX1003, ¶¶68-69.) Consistent with the disclosures of the MSR and the standard of care, all 41 patients treated in the study described by the MSR did have metastatic cancer.²² (EX1031, 1; EX1245, 68:18-70:16; *see also* EX1001, 8:27-28.)

²² JHU fails to address this reality, reflected in the NEJM article authored by Dr. Le. (EX1031, 1; EX1245, 68:18-70:16.)

IV. GROUNDS 2-7: ALL CLAIMS OF THE '974 PATENT ARE OBVIOUS OVER THE MSR IN VIEW OF THE PRIOR ART

A. The Prior Art Combinations Teach Treating a Cancer Patient Who Has Received a Prior Cancer Therapy Drug, Progressed After Receiving a Prior Cancer Therapy Drug, and Has Metastatic Cancer

To the extent the Board needs to reach Merck's obviousness challenges, the combinations of prior art described in Ground 2 (MSR, Pernot, and Benson)²³ and Ground 4 (MSR, Brown, Duval, and Benson) disclose the prior cancer therapy and metastatic cancer limitations to a POSA, highlighting the knowledge of a POSA and the context in which a POSA would read the MSR. (Pet., 36-45, 46-54.)

JHU's claim that Benson "allows for clinical trials as first line therapy" misses the mark.²⁴ (POR, 25-26.) That Benson may *permit* clinical trials for all cancer patients does not undermine Benson's teaching that clinical trials are only specified as *standard of care* "after second progression." (EX1009, 1034; *supra*, 14.) As such, a POSA would be motivated by Benson's disclosure to follow the standard of care for a patient, including in terms of when to place a patient in an ongoing clinical study. (Pet., 42-45, 51-54; EX1003, ¶¶104-07, 127-31; EX1150,

²³ Merck relies on three references in Ground 2, *not* 13. (POR, 41; Pet., 3, 46-45.)

²⁴ It is telling of the weakness of JHU's argument here that JHU did not dispute these limitations were obvious in IPR2024-00240.

¶¶79-89, 94-102.) Indeed, this is how the MSR's underlying clinical study was performed as reflected in the ASCO poster. (EX1080 (Eligibility Criteria); *supra*, 12-16.)

**B. The Claimed Clinical Results
Inherently Flow From the Treatment Method
Taught in the MSR and Prior Art Combinations**

As discussed above, JHU's arguments regarding specific clinical outcomes being unknown before obtaining study results (POR, 27-32) entirely ignore the Federal Circuit's precedent. Here, the claimed two-step method was disclosed in the prior art more than two years before JHU's Alleged Invention Date, and the results claimed did, in fact, naturally flow from carrying out the two method steps. (*Supra*, §III.B.)

JHU also misrepresents what a POSA would have known and understood based on the prior art. (POR, 26-31.) As discussed, contrary to JHU's current assertions, the scientific rationales provided to the FDA to conduct the MSI-H Study are consistent with the prior art cited by Merck and what was known by a POSA at the time. (*Supra*, 11; EX1150, ¶¶87-88, 97-100, 117, 125-28; *see also* EX1138, 141:13-19, 142:12-143:17; EX1243, 56:13-57:3, 57:14-58:20, 59:17-60:7, 61:5-13, 62:4-9, 62:16-63:8.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]²⁵ (EX1150, ¶¶37-44; EX1116, 2, 18-19, 39-40.) [REDACTED]

[REDACTED]
[REDACTED]. (*Id.*)

Indeed, as JHU’s own exhibit reflects, Merck “felt that [the MSI-H Study] was something worth supporting” because it “had a compelling scientific rationale” and “was based on really good science.” (EX2121, 17.)

Dr. Lonberg also admitted that even prior to the publication of the MSR, he had “expressed enthusiasm” about doing such a study, and BMS had, in fact, pursued a study of its own PD-1 inhibitor in patients with MSI-H before the Alleged Invention Date. (EX1138, 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8, 225:15-21.) According to Dr. Lonberg, BMS’s study was also a success. (*Id.*, 240:4-15.)

Instead of addressing the understanding of a POSA reading the MSR, when taken in combination with prior art discussed by JHU itself [REDACTED] JHU improperly focuses on various allegations regarding separate pieces of prior

²⁵ Dr. Lonberg agreed this information published in the prior art would have provided rationale for conducting the study described by the MSR prior to the Alleged Invention Date. (EX1245, 79:5-80:16; EX1150, ¶25.)

art. (POR, 26-31.) These arguments mischaracterize the disclosures of those references, such as alleging Pernot “says nothing about treating MSI-H patients with pembrolizumab.” (POR, 27.) As explained by Drs. Neugut and Oberstein, Pernot discusses how PD-1 inhibitors, including citing to pembrolizumab specifically, had shown promising efficacy in solid tumors such as melanoma.²⁶ (EX1150, ¶¶79-81; EX1003, ¶¶92-93, 97; EX1006, 3738, 3742.)²⁷ [REDACTED]

[REDACTED]

[REDACTED] and which a POSA would understand to provide both motivation and expectation for success for conducting the study set forth in the MSR. (EX1245, 79:5-80:16.)

Dr. Lonberg also agreed that prior to the Alleged Invention Date, there were publications that discussed treatment of CRC patients in clinical trials with PD-1 inhibitors. (EX1138, 176:14-18, 208:12-211:3.) Moreover, Dr. Goldberg testified

²⁶ While JHU appears to take some of Dr. Neugut’s testimony out of context to allege agreement that Pernot does not disclose PD-1 inhibitors or pembrolizumab (POR, 36-37), Pernot does include such disclosures, as JHU’s own declarant, Dr. Lonberg, admitted. (EX1138, 172:15-19.)

²⁷ As Dr. Oberstein explains, JHU’s approach to other references likewise mischaracterizes the art and lacks context. (EX1150, ¶¶82-87.)

“companies all over the world began more aggressively researching immune-oncology opportunities” after BMS’s results published in 2010. (EX1136, 80:13-82:13, 188:15-190:13; *id.* at 105:2-15, 106:6-18, 107:7-110:22, 119:4-120:13.) Dr. Lonberg also agreed multiple other prior art references mention additional claimed limitations. (EX1138, 172:15-174:15, 176:14-18; 183:11-16; 191:3-193:1; *see also* EX1150, ¶¶25-26.)

C. A POSA Would Have Had a Reasonable Expectation of Success in Carrying Out the Claimed Two-Step Treatment Method

As it did in IPR2024-00240, JHU misleadingly argues Merck applies the “wrong standard” for reasonable expectation of success. (POR, 31-32.) Merck applied the correct standard in its analysis, *i.e.*, that in view of the MSR and prior art teachings as of the Alleged Invention Date, a POSA would have had a reasonable expectation of success in carrying out the claimed two-step treatment method of (1) determining a patient has a tumor that is MSI-H and (2) administering an effective amount of pembrolizumab to the patient. The *Eli Lilly* case JHU cites does not apply a different standard. (POR, 31-32.)

In fact, JHU misconstrues the reasonable expectation of success standard by requiring a certain level of success and/or a certainty of success.²⁸ But “[o]bviusness does not require certainty—it requires a reasonable expectation of success.” *Vanda Pharms. Inc. v. Teva Pharms. USA, Inc.*, No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023); *see also Salix*, 98 F.4th at 1062 (finding a reasonable expectation of success where clinical trial posting on ClinicalTrials.gov and prior art reference together suggested the claimed dosage was a predictable next step, and reaffirming that absolute certainty and predictability is not required). Moreover, as the results here are inherent to carrying out the claimed method steps, there can be no question of a reasonable expectation of success in achieving the claimed results. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020).

²⁸ JHU’s assertion that it would have been unethical to conduct the MSI-H Study if it was expected that patients having MSI-H cancer would respond better to pembrolizumab lacks merit and is contradicted by Dr. Goldberg. (POR, 35; EX1136, 175:17-176:8 (Dr. Goldberg admitting “[i]t was ethical to enroll MSS patients even if the science would have suggested that MSI-high patients had a higher likelihood of response”); *see also id.*, 162:3-11.)

JHU and its declarants present generalized obviousness arguments for all claims based on the unsupported assertions that (1) there was no reasonable expectation of success for the methods of treatment claimed in the '974 patent, and (2) the prior art does not provide a POSA with the claimed results. (POR, 26-31, 32-49.) For the reasons discussed above, these arguments fail. (*Supra*, §§IV.A-C.) Additionally, as acknowledged by JHU's own declarants, multiple prior art references suggested there were expected positive results for treating MSI-H tumors with PD-1 inhibitors. (EX1245, 33:4-8, 79:5-80:16; *id.* 34:3-13, 36:5-9, 38:17-19; EX1243, 54:17-55:1, 56:7, 59:17-60:7, 61:5-13, 62:4-9, 62:16-63:8.)

D. Merck Has Shown Claims 4 and 7 Would Have Been Obvious over the Prior Art (Grounds 3, 5-7)

Section VI.D. of JHU's POR repeats in cursory form its arguments as to anticipation, without addressing the additional aspects of any of the prior art relied upon in Grounds 3, 5-7 of Merck's Petition. (POR, 49-50.) As discussed above and by Drs. Neugut and Oberstein, the combinations of the prior art relied upon in Grounds 3, 5-7 render all limitations of the '974 patent claims, as a whole, obvious. (EX1003, ¶¶108-109, 132-140; EX1150, ¶¶90-93, 103-111.) JHU's attempt to parse the prior art relied on by Merck into specific buckets of claim limitations chosen by JHU is misleading because it is inconsistent with Merck's proofs.

**V. JHU’S ALLEGED SECONDARY CONSIDERATIONS
EVIDENCE SHOULD BE AFFORDED LITTLE TO NO WEIGHT**

1. JHU Fails to Meet Its Burden to Establish Nexus

JHU alleges it is “entitled” to a presumption of nexus. (POR, 51-59.) But JHU’s cited cases make plain, a presumption of nexus exists where the purported evidence is tied to a specific product and that *product* “embodies the claimed features, and is coextensive with them.” *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023) (citation omitted); *see also WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); (POR, 51-52, 58-59.) The ’974 patent is not a product patent and JHU does not argue for a presumption of nexus to the Keytruda product generally. (POR, 52-58.)

Instead, JHU attempts to stretch the cases it cites to apply a presumption based on the Keytruda labeling and Dr. Goldberg’s unsupported allegation that the patent claims broadly cover the use of Keytruda according to certain specific indications.²⁹ (POR, 52-59; EX2090, ¶¶82-92.) That argument—even if

²⁹ Dr. Goldberg testified he never used or followed the Keytruda labeling when he treated MSI-H cancer patients, undermining his declaration testimony. (EX1243, 38:10-39:19, 40:19-41:2, 42:15-21; *see also id.* 30:11-31:7, 33:5-13, 36:22-38:9, 39:6-19, 42:22-43:8.)

supported (it is not)—is insufficient to establish co-extensiveness between the treatment method claims here and use of Keytruda. *See e.g., Teva Pharma. Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360-61 (Fed. Cir. 2021).

Moreover, Dr. Goldberg testified he does not believe the labeling instructs an oncologist to compare the outcome of a MSI-H cancer patient treated with pembrolizumab with the outcome of a MSS cancer patient, as is required by Claim 1’s limitation directed to an outcome that is improved compared to an “observed” reference patient.³⁰ (EX1243, 109:16-110:4, 111:2-13, 112:19-113:9, 138:4-16, 143:6-13, 144:20-145:9; *see also id.* 18:10-18.) As such, there is no legal or factual support to establish a presumption of nexus here based on the Keytruda labeling.

JHU also does not tie any of its purported evidence to specific claims or allegedly novel features. (POR, 59-61.) There can be no nexus when a claimed feature was “indisputably known in the prior art.” *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017); *see also In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

³⁰ Dr. Goldberg’s declaration attempts only to analyze Claim 1 and no other claims of the ’974 patent. (EX2090, ¶¶89-92.)

**2. JHU Has Not Shown the
Claimed Method of Treatment Was
Unexpected as of the Alleged Invention Date**

JHU's allegations of unexpectedness fail for the same reasons as in IPR2024-00240. (POR, 76-81.) Notably JHU argues before the Board “no one knew” pembrolizumab would be effective in MSI-H patients and the outcome was “impossible to predict” by the Alleged Invention Date. (POR, 30, 35.) But, [REDACTED]
[REDACTED]
[REDACTED].
(EX1116, 24; EX1150, ¶¶37-44; Pet., 5, 10-11, 38.)

JHU's arguments regarding unexpectedness (POR, 77, 80-81) also disregard that by July 10, 2015: (1) the MSR had published (EX1005), (2) other prior art references taught that checkpoint inhibitors would likely be successful in treating MSI-H tumors (EX1003, ¶¶42-50), (3) Merck had initiated another clinical study of pembrolizumab in MSI-H patients (EX1148), and (4) BMS had already begun its own study aimed at treating MSI-H patients using its PD-1 inhibitor (EX1053).³¹ (See EX1150, ¶¶115-119.) The overwhelming evidence in the record

³¹ JHU confusingly alleges Merck “*declined* to do a MSI-H cancer study.” (POR, 81.) It is indisputable that Merck collaborated with JHU on a MSI-H study, and

provides that a POSA would have clearly expected positive results from using pembrolizumab to treat MSI-H cancer. (Pet., 7-11, 36-46; EX1003, ¶¶42-50, 118-131; EX1150, ¶119.) JHU's focus on the specific MSI-H Study results incorrectly conflates *degree* of success with unexpectedness. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1333-34 (Fed. Cir. 2014).

3. JHU Has Not Shown Any Industry Skepticism as of the Alleged Invention Date

JHU's allegations of skepticism fail for the same reasons as in IPR2024-00240 as JHU does not evidence skepticism at or near the Alleged Invention Date. (POR, 66-69.)

More than two years before the Alleged Invention Date, Merck collaborated with JHU and provided support, including its not-yet-approved expensive drug.³²

provided its drug free of charge. (EX1005; EX1139, 73:3-6; EX2131, 10-11; EX1243, 76:6-12.) JHU fails to put forth evidence of Merck "declin[ing]" to provide funding. (POR, 67, 80-81; EX1243, 67:12-19.)

³² JHU's declarants also lack foundation for their allegations regarding Merck's views on the MSI-H Study as of the Alleged Invention Date. (See EX1138, 228:10-16; EX1136, 137:5-11; *id.*, 112:1-4; EX1243, 66:14-21; EX1140, 48:3-16; EX1139, 268:8-278:16.)

(EX1005, 3; EX1139, 66:20, 73:3-6; EX2130 ¶¶14-15, 37.) While JHU alleges “Merck admitted that the prevailing belief had been that pembrolizumab would not work even in CRC patients,” the context of the statement JHU cites makes plain that Merck was referring to a time period *prior* to the Parties’ collaboration and the relevant prior art here. (POR, 66-67; EX2121, 17.) As discussed, Merck stated it believed the study was “worth supporting” as it was “based on really good science.” (*Supra*, 19-20; EX2121, 17.) JHU’s purported support for its allegation that Merck did not “believe[] in the inventors’ hypothesis” is Dr. Pardoll. (POR, 66.) But he testified he did not provide any statements or comments regarding Merck’s or the industry’s beliefs in the portions of his declaration cited by JHU. (EX1140, 119:10-124:2.)

More than one year before the Alleged Invention Date, BMS also announced its own study of its PD-1 inhibitor to treat MSI-H cancer. (EX1053; EX1138, 217:19-218:5; EX1245, 33:4-8; EX1243, 61:5-13.) In addition, JHU’s purported industry expert “expressed enthusiasm” about doing a clinical study like that described by the MSR before the MSR even published. (EX1138, 225:15-21.) JHU’s purported evidence reflects only that BMS chose not to do the study with JHU in 2012—not skepticism of the claimed treatment method. (POR, 67-68; EX2072, ¶187; *see also* EX1138, 213:22-214:6, 217:14-218:5, 220:8-21, 223:21-225:8.)

4. JHU Ignores the Rapid Development of Pembrolizumab and PD-1 Inhibitors by the Alleged Invention Date

Any purported evidence of long-felt unmet need here is undermined by Merck's patents (EX1214; EX1215; EX1217; EX1238) covering its drug and its use broadly in the treatment of cancer. *See Acorda Theras., Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1338-42 (Fed. Cir. 2018) (discounting the weight of commercial success, failure of others, and long-felt unmet need in view of blocking patent in the record); EX1243, 64:1-4 (Dr. Goldberg: "The only way to obtain [pembrolizumab] would have been to have an agreement with Merck to provide a drug that they owned and had sole ability to provide.").)

Moreover, Dr. Goldberg, who JHU relies on for its allegations of long-felt need, revealed his view is that a long-felt need existed for an ***FDA-approved*** method of treating MSI-H cancer patients. (EX1243, 98:8-11, 104:11-16.) The '974 patent claims do not require FDA-approval and Keytruda's 2017 MSI-H approvals were not achieved on the bases of the '974 patent claims. As such, JHU's purported evidence has no nexus to the claims.³³ *See Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 86, at 38 (P.T.A.B. Jan. 17,

³³ JHU's arguments regarding Merck's statements to the FDA are not relevant here for the same reason. (POR, 72-74.)

2018); *Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.*, IPR2015-01780, Paper 70, at 55-56 (P.T.A.B. Feb. 23, 2017).

Additionally, by the Alleged Invention Date, any alleged need for the claimed method of treatment was neither unmet nor long-felt, as the MSR publicly disclosed the method of treating a MSI-H cancer patient with pembrolizumab two years prior and the development of pembrolizumab and other PD-1 inhibitors was rapid following BMS's 2010 study results for its PD-1 inhibitor. (EX1243, 102:16-103:1; EX1136, 188:15-190:13; *id.*, 80:13-82:13, 105:2-15, 106:6-18, 107:7-110:22, 119:4-120:14; *see also* EX1150, ¶¶120-124.) JHU incorrectly ignores these facts. *See Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1376 (Fed. Cir. 2022); *In re Ikeda Food Rsch. Co., Ltd.*, 758 Fed. Appx. 952, 955-56 (Fed. Cir. 2019) (nonprecedential) (A problem must be “both recognized in the prior art and there existed a failure of others to provide ‘a feasible solution to the long-standing problem.’”).

Tellingly, JHU does not (because it cannot) provide any evidence others tried to treat MSI-H patients with pembrolizumab (or any other anti-PD-1 drug) and failed. *See Adapt Pharma*, 25 F.4th at 1376 (failure of others is “particularly probative” evidence of a long-felt need) (citations omitted). Indeed, prior to the Alleged Invention Date, it was known that BMS's PD-1 inhibitor had led to a

complete response in an MSI-H CRC patient.³⁴ (EX1150, ¶¶29, 117; EX1136, 106:19-110:22; EX1138, 141:20-142:11.).

5. JHU Does Not Present Any Evidence of Industry Praise Tied to Novel Features of the Claimed Invention

JHU fails to establish nexus between purported industry praise evidence and the claimed method of treatment. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020). Specifically, JHU does not show that (1) ASCO’s selection of the abstract or Dr. Le’s presentation was due to the specific method of treatment claimed (POR, 61-62),³⁵ (2) FDA’s approval of pembrolizumab to treat MSI-H cancers or comments thereafter were due to the specific method of treatment

³⁴ JHU attempts to mislead by calling the prior BMS study “resoundingly unsuccessful” and a “failure” while omitting it was known that the complete response observed was in a MSI-H CRC patient. (*See supra*, 11; EX1057, 463; EX1038, 7.)

³⁵ Dr. Le’s testimony regarding statements made at ASCO is merely “self-referential commendation [that] fall[s] short of demonstrating true industry praise.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

claimed (POR, 63-65), or (3) Merck's comments regarding JHU's scientific work were due to the specific method of treatment claimed (POR, 65-66).

6. JHU Does Not Present Any Evidence of Commercial Success Tied to Novel Features of the Claimed Invention

JHU's commercial success argument, likewise, fails as a matter of law. It is well settled that "evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success," and when "commercial success is due to an element in the prior art, no nexus exists."³⁶ *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). JHU did not address the state of the art as of the Alleged Invention Date, and the prior art discloses the very aspects of the claims JHU argues are responsible for its commercial success. (*See supra*, §V.2; *see also* EX1151, ¶¶45-46.)

Moreover, JHU's purported evidence of commercial success is severely undermined by the existence of Merck's own patents covering Keytruda and its use broadly in the treatment of cancer. (EX1151, ¶¶31-39, EX1214; EX1215; EX1217; EX1238); *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) ("Financial success is not significantly probative" of

³⁶ No presumption of nexus is warranted here for the reasons discussed above.

(*Supra*, §V.1.)

nonobviousness when “others were legally barred from commercially testing” the idea.); *see also Acorda*, 903 F.3d at 1338-42. Mr. Segers did not consider Merck’s patents in his analysis, where Dr. Sheridan notes their existence would necessarily be an obstacle to market entry by others. (EX1151, ¶¶31-39; EX1244, 48:17-53:2.)

JHU’s purported evidence is also incomplete and unreliable. (EX1151, ¶¶48-75.) Contrary to JHU’s allegations regarding a sales inflection point tied to the 2017 MSI-H approvals, the data demonstrates the inflection point began earlier, coinciding with Keytruda’s 2016 expanded approval in metastatic NSCLC. (EX1151, ¶¶62-69.) Moreover, there is no basis for Mr. Segers’ admitted exclusion of other available MSI-H treatments from his analysis (EX1137, 64:4-67:19; EX1151, ¶58), and for two that are included, he extrapolates from a single data point across five years and ignores contrary evidence suggesting an increase in MSI-H sales by Keytruda competitors. (EX1151, ¶¶59-60; EX1137, 151:8-153:1, 157:10-160:16; EX1244, 88:15-92:4.)

JHU and Mr. Segers also do not account for contributions of “other economic and commercial factors unrelated to the quality of the patented subject matter.” (EX1151, ¶¶40-42); *see also In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996); *Ritchie v. Vast Res., Inc.*, 563 F.3d 1334, 1336-37 (Fed. Cir. 2009). As Mr. Segers admitted, brand recognition is a factor that could increase the likelihood of

a physician prescribing Keytruda over another drug—yet Mr. Segers did not account for this in his analysis. (EX1137, 110:5-114:11; *see also* EX1136, 153:16-154:19.)

VI. CONCLUSION

The Board should find the challenged claims unpatentable.

Respectfully submitted,

Dated: May 1, 2025

By: /Preston K. Ratliff II/
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply contains, as measured by the word-processing system used to prepare this paper, 6,974 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Respectfully submitted,

Dated: May 1, 2025

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CERTIFICATE OF SERVICE

I hereby certify that I caused to be served on the counsel identified below a true and correct copy of the foregoing Petitioner's Reply by electronic means on May 1, 2025:

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