

PUBLIC VERSION

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

IPR2024-00240
Patent No. 11,591,393

PETITIONER'S REPLY

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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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EX1009	Benson et al, <i>Colon Cancer, Version 3.2014: Clinical Practice Guidelines in Oncology</i> , 12(7) J. Nat’l Comprehensive Cancer Network 1028 (July 2014)	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

EX1019	Fujiwara et al, <i>Accumulated Clonal Genetic Alterations in Familial and Sporadic Colorectal Carcinomas with Widespread Instability in Microsatellite Sequences</i> , 153(4) Am. J. Pathology 1063 (1998)	X
EX1020	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014)	X
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EX1046	Taggart et al, <i>High-level Microsatellite Instability in Appendiceal Carcinomas</i> , 37(8) Am. J. Surgical Pathology 1192 (August 2013)	X
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Petitioner Merck Sharp & Dohme LLC (“Merck”) submits this Reply to the Patent Owner’s Response (“POR”) filed by The Johns Hopkins University (“JHU”).

I. INTRODUCTION

JHU’s POR arguments confirm why the Board should find unpatentable all claims of the ’393 patent. Instead of viewing the Board’s claim construction analysis at Institution objectively¹, JHU misinterprets the Board’s analysis and uses that flawed interpretation as a platform to argue against Merck’s showing that the MSI-H Study Record (“MSR”)² teaches the steps of the claimed method of treatment.³ Contrary to JHU’s straw man argument, the Board did not “disregard[]” the causal relationship between the “determining” and “treating” steps recited in the ’393 patent.⁴ The Institution Decision plainly reflects that the Board found Merck had sufficiently shown a reasonable likelihood that a causal relationship existed in the MSR between treatment of CRC patients and the

¹ Paper 10, 10-11, 15-18.

² EX1005.

³ EX1003, ¶¶50-63.

⁴ POR, 5-6.

determination of their MSI status.⁵ Even JHU's POR declarant Dr. Nils Lonberg admitted this during deposition in this proceeding.⁶

And despite agreeing in deposition that all claims of the '393 patent are directed to methods that would be practiced by a clinical oncologist⁷, which Dr. Lonberg is not, JHU continues to argue that Merck's expert declarant Dr. Alfred I. Neugut, a practicing clinical oncologist, is not qualified to provide testimony regarding the perspective of the POSA.⁸ Merck strongly disagrees with JHU. As evidenced by the accompanying rebuttal declaration of an additional practicing clinical oncologist, Paul E. Oberstein, M.D.⁹, Dr. Neugut's opinions comport with the perspective of the POSA regarding the MSR's teachings alone, and in combination with the cited prior art.¹⁰

⁵ Paper 10, 16.

⁶ EX1138, 122:5-125:14.

⁷ EX1138, 31:9-36:17.

⁸ Dr. Lonberg also agreed that the claims would not require any specialized experience researching or developing novel cancer treatments or conducting genetics research to understand the steps of the method. (EX1138, 33:18-34:8.)

⁹ EX1150, ¶¶5-17.

¹⁰ EX1150, ¶¶4, 18-19, 20-25.

The accompanying declarations of Dr. Oberstein (EX1150) and Sean D. Sheridan, Ph.D. (EX1151), an expert in intellectual property valuation, explain that the depositions of each of the six declarants JHU relies on in support of its POR¹¹ reveal stark inconsistencies between what those declarants stated in their declarations and what they actually believe. For example, Dr. Lonberg's deposition revealed that his discussion of the MSR and the prior art was not from the perspective of the POSA reading those references objectively. Instead, his conclusions were drawn from the perspective of the POSA having a "skeptical lens" or disbelief towards what is disclosed, even where none of the literature itself has expressed any such skepticism or teaching away.¹²

Based on Dr. Lonberg's deposition, it is now easy to understand why Dr. Lonberg arrives at his ultimate conclusions regarding the teachings of the MSR. He is not reading the MSR from the perspective that Federal Circuit case law instructs. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 928 (Fed. Cir. 2024) (finding analysis of prior art must utilize perspective of a POSA "capable of deducing what references fairly suggest or employing ordinary creativity"). Instead, he believes the POSA is a skeptic, questioning and ignoring

¹¹ EX2072; EX2090; EX2130; EX2137; EX2191; EX1002, 199-399.

¹² EX1138, 84:9-85:10, 85:20-21, 86:6-87:2; EX1150, ¶¶28-30.

the teachings of the prior art. It is only Merck's declarants, Dr. Neugut and Dr. Oberstein who accept the teachings of the MSR and the prior art as they would be understood by the POSA.

In a case where it is irrefutable that the treatment disclosed in the prior art MSR is the written description support for the claims, JHU devotes an inordinate amount of space in its POR, and in multiple declarations, to secondary considerations and policy arguments. But, as Drs. Oberstein and Sheridan explain in their declarations, JHU fails to meet its burden to show an actual nexus between any alleged secondary consideration and the claims of the '393 patent. And to the extent there was any invention here (there is not), as explained below, JHU cannot save its delayed filing of the '393 patent application with attorney argument before the Board.

II. ARGUMENT

A. Exemplary Testimony of JHU's Six POR Declarants Supports Unpatentability of the '393 Patent Claims

The deposition testimony provided by JHU's POR declarants conflicts with the statements they made in their declarations underscoring a lack of credibility. For example, as noted above, Dr. Lonberg, an executive at a venture capital firm and friend of named inventors Dr. Drew Pardoll and Dr. Suzanne Topalian (*see* EX1138, 165:10-11), revealed that his conclusions on anticipation and obviousness were grounded in his belief that the POSA "reads the literature skeptically,

always.” (EX1138, 84:14-16.) This is contrary to established law. *Janssen Pharms.*, 97 F.4th at 928.

Despite that lens, however, Dr. Lonberg testified that he agrees with Dr. Neugut on many of the key underlying facts. In particular, he agrees that as of July 10, 2015 (the “Critical Date”)¹³ the literature was replete with information about MSI testing, the clinical relevance of MSI-H in CRC, the correlation between mutational load and susceptibility to treatment with PD-1 inhibitors, and the prior successful treatment of cancer patients with PD-1 inhibitors. (*See, e.g.*, EX1138, 48:16-52:3, 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, ¶¶26-27.) Similarly, despite having dedicated more than 10 pages of written testimony to dispute Merck’s definition of the POSA, Dr. Lonberg revealed during deposition that he agrees that the claims describe a cancer treatment method—not a method for conducting immunology or genetic research. (EX1138, 32:2-36:17; *see also* EX2001, ¶¶79-98.)

JHU declarant Richard Goldberg, M.D., another friend of one of the named inventors (*see* EX1136, 24:20-21), admitted during deposition that before the Critical Date PD-1 inhibitors showed promise and “companies all over the world

¹³ This is the priority date alleged by JHU. (POR, 4.)

began more aggressively researching immune-oncology opportunities once the first break-through [with nivolumab] had occurred.” (EX1136, 80:13-82:13, 188:15-190:13; *see also* EX1150, ¶¶31-32.) This admission conflicts with Dr. Goldberg’s declaration testimony and his deposition revealed why: he had not actually reviewed highly relevant pieces of prior art (*e.g.*, Pernot (EX1006), Champiat (EX1032)) before rendering his opinions on the state of the art. (*See, e.g.*, EX1136, 85:20-87:22, 89:13-91:17.)

The deposition of named inventor Dr. Dung Le, revealed a lack of familiarity with the ’393 patent, the MSI-H Study (on which she was principal investigator), and her declaration. For example, Dr. Le could not recall a single Merck individual involved in the MSI-H Study, despite testifying in her declaration about her alleged “observations” of “Merck personnel involved with [the] study.” (EX1139, 66:2-5, 264:4-274:21; *see also* EX2130, ¶34; EX1150, ¶¶52-53.) Dr. Le also purportedly did not know what she meant by the phrase “initial study” used in her declaration. (*See* EX2130, ¶19.) And in fact, during deposition, changed the phrasing of the words in her declaration so that it made sense to her and reflected only her beliefs. (EX1139, 33:14-38:14, 278:17-286:14; EX1145 ¶19.) Additionally, Dr. Le admitted that Merck provided funding for the study—contrary to a number of JHU declarants’ assertions. (EX1139, 278:17-286:14; *see also* EX2072 ¶124; EX2090 ¶14.)

Likewise, named inventor Dr. Drew Pardoll revealed he was neither involved with nor knowledgeable about the MSI-H Study. (EX1140, 25:16-17, 29:3-4, 48:3-16, 71:3-5, 102:19-103:5, 124:9-125:3.) Rather confusingly, he also took positions directly contrary to representations JHU previously made to the FDA. (*Id.*, 57:7-14, 61:17-65:3.) In any event, Dr. Pardoll testified that his declaration makes no statements or comments about Merck's or the industry's beliefs, despite JHU's attempts to argue otherwise in its POR. (EX1140, 119:3-121:12, 122:7-124:2; EX1150, ¶¶54-55; *see also* POR, 73.) And while Dr. Lonberg testified that Dr. Pardoll is the one who told him that Merck did not provide any funding for the study, Dr. Pardoll testified that he "[did not] recall saying that." (EX1140, 82:11-13; EX1138, 228:19-22.)

Another JHU POR declarant, Jennifer 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.) Ms. Newberger did admit, however, that the MSR posted on ClinicalTrials.gov provided the public with a lot of information. (EX1135, 118:18-119:14, 134:19-136:11, 148:13-20, 153:19-156:12, 200:14-201:1; *id.* 124:19-125:12.)

In addition, JHU’s economic consultant, Brian Segers, stated in his declaration that he relied solely on a conversation with JHU’s declarant Dr. Goldberg to form his opinion that there was a nexus between the ’393 patent claims and the commercial success of Keytruda®. (See EX2191, ¶¶7, 27 n.35, 36-37, Appx. 5, 7, 8.) But Dr. Goldberg revealed during deposition that the alleged conversation with Mr. Segers regarding nexus never happened. Specifically, he explained that when he spoke with Mr. Segers, he did not provide Mr. Segers with “any substantive information” as that was not “the purpose of the call”—“[Mr. Segers] was interested in telling me what he was opining on, not listening to what I was opining on.” (EX1136, 193:13-195:17.)

B. Ground 1: Claims 1-2, 4-7, 11-12, 14-15, 17-20, 24-25, and 27-42 of the ’393 Patent Are Anticipated by the MSR

1. JHU Wrongly Criticizes The Board for Its Analysis Regarding the Claim Term “In Response To”

JHU’s patentability arguments for independent Claims 1 and 14 primarily hinge on erroneous characterizations of the Board’s analysis of the “in response to” limitation at Institution. (POR, 11-19; *id.* 5-9.) Specifically, JHU mischaracterizes the Board’s analysis to allege the Board “*disregards* the critical causal relationship between the ‘determining’ and ‘treating’ steps expressed by the claims” in the Institution Decision. (POR, 6 (emphasis altered).) But Dr. Lonberg admitted during deposition that the Board did not ignore a causal relationship for the “in

response to” limitation, despite previously stating in his declaration that it had.

(EX2072 ¶96; EX1138, 125:5-14.)

JHU’s POR makes plain that it is asking the Board to require not just a causal relationship, but also “administering the claimed treatment ***only as a reaction to*** the determination that the patient’s cancer is MSI-H.” (POR, 8 (emphasis altered).) In other words, JHU advocates for a construction that excludes a treatment in which pembrolizumab is administered to patients that do not have MSI-H. Such unclaimed negative limitations should not be read into claim terms. *See Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1322 (Fed. Cir. 2003) (rejecting the district court’s “additional negative limitation” because it “f[ound] no anchor in the explicit claim language”).

JHU’s attempt to insert this negative limitation is particularly improper given that the anticipatory prior art reference it seeks to avoid—the MSR—is the written description support for the claims. (EX1001, 3:19-21, 6:52-56.) Any construction that would distinguish the MSR as JHU proposes would therefore also serve to undermine the written description for the claims. *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

That the Board did not find evidence that “in response to” would be understood to exclude treatment of “other patients,” as JHU seeks to do, does not mean that the Board “disregard[ed]” the causal relationship between the

“determining” and “treating” steps. (Paper 10, 18.) As such, consistent with the usual practice, the Board resolved the Parties’ dispute to the extent necessary for its anticipation analysis and refused to import any unclaimed embodiment or negative limitation into the claim term. (Paper 10, 17-18.)

**2. JHU’s Arguments Regarding
“In Response To” Improperly Rely on a
Skeptical POSA and an Illogical View of the MSR**

JHU and Dr. Lonberg also argue the MSR does not anticipate the claims because it allegedly does not disclose testing a patient for MSI-H before administering pembrolizumab and lacks a causal relationship. (POR, 11-19; EX2072 ¶¶87-101.) This argument arises from Dr. Lonberg’s incorrect belief that the POSA would approach the prior art, including the MSR, with skepticism. (*See supra* §II.A.)

First, the MSR’s Eligibility Criteria makes plain that ***only*** patients with MSI-H CRC would be placed in Arm 1 of the study, and such patients would then be treated with 10 mg/kg pembrolizumab every 14 days—a therapeutically effective amount. (*See* EX1150, ¶¶56-70, 79-80; *see also* Pet., 21-23; EX1003, ¶¶59-63.) Dr. Lonberg’s arguments (*see* EX2072 ¶¶87-101), colored by a skeptical lens, thus assume the POSA would not understand the importance of ensuring that a patient meets all eligibility requirements prior to treatment, despite his express

agreement that the POSA proceeds logically, rationally, and without bias. (*See* EX1150, ¶¶66-70; *see also* EX1136, 82:13-84:8.)

While JHU, Dr. Lonberg, and Dr. Goldberg argue the MSR's inclusion of non-MSI-H CRC patients allows for a CRC patient to be enrolled and treated, and then later have their MSI status tested (purportedly in support of an "all-comers" study design), the existence of multiple arms only underscores the need for MSI testing before the patient is placed into the appropriate arm and treated according to the MSR (particularly considering the lack of any fourth arm to accommodate patients with non-CRC MSI negative cancers). (*See* EX1150, ¶¶65-70; *see also* EX1138, 101:8-102:5, 114:15-115:21.) Further, JHU asserts that Merck's declarant Dr. Neugut "admitted" MSI status would not need to be determined before "enrollment." (POR, 14.) This is misleading. In deposition, Dr. Neugut said that before "recruiting" patients, MSI status did not need to be determined. (EX2163, 101:21-103:1.) It is not an admission of a JHU point. Instead, it is consistent with his testimony that to carry out the MSR's study, patients must first be placed in the correct arm, which necessarily requires determining MSI status. (*See, e.g.*, EX1003, ¶¶50, 58; *see also* 2163, 102:20-103:1.)

Moreover, the MSR describes the study as "non-randomized", and therefore, would not be understood by the POSA to describe an "all-comers" study, where "patients are *randomly assigned* [to receive treatment] regardless of biomarker

status” as Dr. Lonberg alleges. (EX1150, ¶¶67; EX2072, ¶97; *see also* POR, 14-15.)

Second, nothing in the MSR tells the POSA to apply a different strategy for enrollment and treatment of CRC patients versus non-CRC patient. (EX1150, ¶¶33, 43, 61-70.) Indeed, Dr. Lonberg admitted that the POSA would understand that non-CRC patients would have their MSI status tested *prior* to enrollment and treatment with pembrolizumab. (EX1138, 101:8-102:5, 114:15-115:21.) As such, Dr. Lonberg’s arguments require the POSA to, without reason, take a *prospective* approach to identify MSI-H non-CRC patients prior to treatment but take a *retrospective* approach to identify MSI-H CRC patients after treatment. According to Dr. Lonberg, the POSA would actually confirm all inclusion criteria are met for the MSI-H non-CRC patients prior to treatment in the study, but would not do the same for the MSI-H CRC patients. (EX1138, 101:8-104:4; *id.* 97:2-101:7.) Nothing in the MSR tells the POSA to take inconsistent approaches. (EX1150, ¶¶61-70; *see also* EX1003, ¶¶53-63.)

Further demonstrating his misunderstanding of the evidence, Dr. Lonberg testified that the MSI-H Study was conducted as a retrospective study. (EX1138, 110:15-111:17.) This is incorrect as the ’393 patent itself states all patients in the study underwent MSI-H testing prior to enrollment (EX1001, 9:48-49), and the Keytruda labeling, which Dr. Lonberg reviewed, recites the study design as

prospective (EX1023, 42.). (See EX1150, ¶65 n.2.) Dr. Goldberg’s similar, incorrect understanding was based, in part, on Dr. Lonberg. (See EX1136, 67:4-69:10.)

Third, this argument also fails to account for the fact that the incidence of MSI-H in the CRC population is low. (EX1150, ¶68; *see also* EX2072, ¶50 (“[A] small percentage of cancer patients (including CRC patients) [are] MSI-H.”); EX1138, 91:4-93:14.) As Dr. Lonberg admitted, the POSA reading the MSR would understand the study anticipated enrollment of 71 patients, and the POSA would know that a small percentage of CRC patients were MSI-H. (EX1138, 108:6-109:9; *see also* EX1136, 66:16-18 (agreeing that MSI-H cancer is a relatively rare subtype of cancer); EX1150, ¶68.) An “all-comers” approach would require enrolling and treating a large sample size of CRC patients to ensure enough MSI-H CRC patients are treated given the low incidence of MSI-H in the CRC population, not the 71 total patients identified in the MSR. (EX1150, ¶¶67-70; EX1005, 4; *see also* EX2026, 3 (“[A]n all-comers trial design would require a prohibitively large sample size . . . when the marker prevalence is low (<15-20%).”).)

Fourth, during Dr. Goldberg’s deposition, he backtracked from the purported “all-comers” study design advanced by JHU in its POR, instead suggesting a hybrid model in which the study did not require testing prior to

enrollment “until such time as the MSS cohort” was filled—“[a]fter that, in order to be eligible for the study, a colorectal cancer patient had to be known to be MSI-high.” (EX1136, 67:4-68:3.) Even accepting Dr. Goldberg’s incorrect view of the study, the vast majority of MSI-H CRC patients would have been tested for MSI-H prior to enrollment and treatment, which is all that is necessary for anticipation.

3. JHU and Dr. Lonberg Ignore the Context of the MSR and What Was Known by the POSA

In addressing Dependent Claims 7, 20, 29-30, 32, 34, 36, 38, 40, and 42, JHU and Dr. Lonberg allege the MSR does not sufficiently disclose patients with metastatic or advanced disease because “measurable” and “metastatic” are not “equivalent” or “synonymous.” (POR, 19-23; EX2072 ¶¶102-107.) This is another attempt to distort, rather than address, Merck’s anticipation evidence.

As Drs. Oberstein and Neugut explain, the MSR describes a phase 2 clinical study of a cancer therapy drug that was not yet FDA-approved, and which was known to elicit a strong immune response in patients. (*See* EX1150, ¶¶77, 85; EX1003, ¶¶29-33; EX1005, 3; *see also* EX1011.) As a matter of general standard of care, an MSI-H CRC patient enrolled in a study of this type would be understood to be critically ill, with either metastatic or locally advanced cancer. (*See, e.g.*, EX1150, ¶¶75-78, 82-88, 93, 98, 103, 105, 107, 109; EX1003, ¶¶68-72, 82, 87-91, 93-94, 96, 98, 100, 102, 104; *see also* EX1009, 7.)

Likewise, as Drs. Oberstein and Neugut explain, as a matter of standard oncology practice, an MSI-H CRC patient enrolled in such a study would have already tried and failed at least two prior or different cancer therapies. (*Id.*) Moreover, the POSA would understand the MSR is directed to patients that have had at least two prior and/or different cancer therapies in view of the MSR's exclusion of patients who underwent certain prior cancer treatments. (EX1150, ¶¶76-77.)

JHU fails to address how the POSA would understand these disclosures in the context of the MSR, and as Drs. Oberstein and Neugut explain, these disclosures provide support for the POSA's understanding of the types of patients being treated in the MSI-H Study. (*See, e.g.*, EX1150, ¶¶75-78, 82-88, 93, 98, 103, 105, 107, 109; EX1003, ¶¶68-72, 82, 87-91, 93-94, 96, 98, 100, 102, 104.)

4. JHU Ignores Federal Circuit Precedent Regarding Inherent Anticipation

JHU does not point to any aspect of Merck's drug, pembrolizumab, or the claimed method itself that would serve to overcome or distinguish the principles of inherent anticipation as set out in the Federal Circuit's *Schering* and *Montgomery* decisions. (Pet., 2-3, 9-10, 15-18.) Instead, JHU and Dr. Lonberg allege dependent Claims 4 and 17 require "actually obtaining the results of the study disclosed in the [MSR]." (POR, 23-25; EX2072 ¶109.) Dr. Lonberg admitted, however, that the MSR discloses treating MSI-H CRC patients with 10 mg/kg

pembrolizumab every 14 days, and that the '393 patent's claims do not expressly recite an additional "determining" step with respect to the claimed results.

(EX1138, 58:14-18, 59:14-17, 60:11-14, 90:19-91:3; *id.* at 80:8-81:4.) Indeed, the disclosed dose was naturally and inherently effective in promoting progression-free survival in the MSI-H CRC patients in the MSI-H Study, as well as in other clinical studies. (*See, e.g.*, EX1150 ¶¶71-74, 81; *see also* EX1138, 38:11-20.)

Likewise, JHU and Dr. Lonberg argue that the MSR does not explicitly disclose the additional limitations of dependent Claims 31, 33, 35, 37, 39, and 41 because the study results were not yet obtained at the time of the MSR's posting (POR, 23; EX2072 ¶¶108-111). This argument ignores that the study results inevitably flowed from the steps of the method disclosed by the MSR. (*See, e.g.*, EX1003, ¶¶40, 60-62, 92; EX1150 ¶¶89-92, 94-97, 99-102, 104, 106, 108.) In his declaration, Dr. Lonberg acknowledge that the claimed results "correspond directly with the outcome measures obtained by the trial described in the [MSR]," given that the study described by the MSR is the written description support for the '393 patent claims. (EX2072 ¶110.)

5. JHU’s “Experimental Use” and “Policy” Arguments are Unsupported and Disregard Facts and Legal Precedent

Because JHU has not and cannot overcome Merck’s showing of anticipation by the MSR, JHU (1) advocates for new exceptions to well-established precedent regarding anticipatory references and (2) asks the Board for a change in the law that is within the purview of Congress. (POR, 29-36.) Neither facts nor law support the extraordinary results JHU seeks.

First, JHU argues the MSR should not qualify as §102 prior art, because the publication is an alleged “experimental use” akin to a “public experimental activit[y].” (POR, 29-36.) Not only does JHU’s argument conflict with the purpose of the experimental use doctrine, *Pfaff v. Wells Elecs.*, 525 U.S. 55, 64 (1998), but JHU does not point to a single case where a study record published on ClinicalTrials.gov (or any publication) was negated as §102 prior art based on experimental use.¹⁴ (See POR, 28-29.) To the contrary, the Board has found study records posted on ClinicalTrials.gov to be printed publications that can be relied upon for the purposes of determining anticipation or obviousness. See *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, No. IPR2022-00578, Paper 78 at 24-28

¹⁴ JHU’s cited case law is thus inapposite where, as here, an actual printed publication has effectively reduced any purported invention to practice. (See POR, 29-30 (citing cases).)

(P.T.A.B. Aug. 29, 2023); *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1061 (Fed. Cir. 2024) (relying on a study record posted on ClinicalTrials.gov).

Purportedly in support of this argument, JHU cites opinions from its POR declarant Ms. Newberger. (POR, 29-36; EX2137, ¶¶8-52.) JHU and Ms. Newberger's assertions regarding ClinicalTrials.gov requirements are both incorrect and irrelevant. For example, Ms. Newberger alleges JHU only submitted the information it was required to submit to ClinicalTrials.gov (*see* EX2137, ¶¶43-46), but Ms. Newberger testified that she did not even know what ClinicalTrials.gov stated or required in 2013. (EX1135, 240:9-242:15.) Moreover, the authority she cites makes plain that certain information was not *required* to be submitted in 2013, and as such, JHU did include more information in the MSR than was required, some of which Ms. Newberger did not even discuss. (EX1005, 3; EX2137, ¶33 (citing EX2149); *see also* EX1135, 127:19-128:11, 250:18-253:20.)

In any event, regardless of whether JHU was obligated to publish specific information, it indisputably did so in a printed publication in June 2013. (EX1005; *see also* EX1136, 83:11-84:2 (Dr. Goldberg confirming postings on ClinicalTrials.gov are publicly available).)

Second, JHU argues for the creation of a brand-new policy exemption, suggesting the requirements for patentability are too rigorous, and it would not be fair for JHU to be held to well-established law requiring that a patent application be filed within a year after publication by the inventors.¹⁵ (POR, 36-38.) Specifically, JHU argues that if JHU had patented the claimed methods of treatment any earlier, JHU would allegedly not have met the requirements of §101 or §112. (POR, 36-38.)

This is incorrect. It is well established that there is no requirement under §101 or §112 that evidence from human clinical trials must be provided for patentability. *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (“human trials are not required for a therapeutic invention to be patentable”); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (holding that even in situations where no art-recognized animal models exist, there is no decisional law that requires an applicant to provide data from human clinical trials.) JHU itself appeared to recognize and follow this precedent when filing its first provisional application on November 13, 2014, which, while also filed more

¹⁵ Even if JHU’s argument held any merit, which it does not, this is an improper forum for this argument.

than a year after the MSR's publication, disclosed no clinical results or data.

(EX1001, cover; EX1030, 1.)

Further, as Dr. Le admitted, positive results for patients with MSI-H CRC were being observed and recognized “early” and “within the first few patients.” (EX1139, 291:7-292:16.) Even if some clinical results were needed, JHU had such results well within the year after publication of the MSR. JHU's policy argument is nothing more than a last-ditch attempt to circumvent the publication of the MSR more than two years before the Critical Date.

C. Grounds 2-8: Claims 1-42 of the '393 Patent Are Obvious Over the MSR in View of Various References

1. JHU Does Not Challenge Obviousness as to Most Claim Limitations and Focuses Its Reasonable Expectation of Success Arguments on an Improper Scope and Time Period

JHU and its declarants present generalized arguments regarding *prima facie* obviousness for all claims based solely on the unsupported assertions that (1) there was no reasonable expectation of success for the methods of treatment claimed in the '393 patent based on the MSR, alone or in combination with the additional scientific references, and (2) that the prior art does not provide the POSA with the “in response to” part of the claims. (POR, 11-19; EX2072 ¶¶87-101.) These arguments fail, as they do not take into account the state of the prior art as of the actual Critical Date. (Pet., 7-11; EX1003 ¶¶41-49, 105-113; EX1150, ¶¶110-177.)

While JHU generically discusses obviousness as to all claims, the principal ground for unpatentability in this proceeding is anticipation based on prior publication of the MSR. (Pet., at 2-3, 12-37.) Although a claimed invention can be obvious but not anticipated, there can be no stronger evidence of obviousness than anticipation. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002). Further, while Merck has asserted unpatentability based on obviousness only as to certain dependent claims that describe trivial aspects of procedures for carrying out the methods disclosed in the MSR,¹⁶ JHU makes no argument that any such additional limitations of the claims contribute to non-obviousness. (POR, 38-57.) Rather, JHU more generally includes all claims in its assertions regarding “reasonable expectation of success.” *Id.*

As of the Critical Date, however, multiple prior art references suggested that there were expected positive results for treating MSI-H tumors with PD-1 inhibitors. (Pet., 10-11; EX1003 ¶¶41-49; EX1150, ¶¶110-177; *see also* EX1006, 3742.) Indeed, Dr. Lonberg admitted that prior to the publication of the MSR, he had “expressed enthusiasm” about doing such a study, and as of the Critical Date,

¹⁶ These include sampling body fluid (Claims 3, 13, 16, 26), or testing MSI status by immunohistochemistry (Claims 8, 21), PCR (Claims 9, 22), or next generation sequencing (Claims 10, 23). (Pet., 2-3, 38-63; Paper 10 at 4-5, 19-25.)

BMS had, in fact, pursued a study of its own PD-1 inhibitor in patients with MSI-H CRC. (EX1138, 225:15-21.) According to Dr. Lonberg, BMS's study was also a success. (*Id.*, 240:4-15.)

Dr. Lonberg also agreed that prior to the Critical Date, there were publications that discussed the treatment of CRC patients in clinical trials with PD-1 inhibitors. (EX1138, 176:14-18.) Moreover, Dr. Goldberg testified that “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.)¹⁷ Dr. Lonberg also agreed that 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, ¶¶110-177.) Notably, the positions that JHU and its declarants now take with respect to the prior art conflict with JHU's prior

¹⁷ JHU suggests it would have been unethical to conduct the MSI-H Study if it was expected that patients having MSI-H CRC would respond well to pembrolizumab. Dr. Goldberg confirmed this argument lacks merit. (EX1136, 175:17-176:8 (admitting that “[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.* at 162:3-11.)

representations to the FDA, as reflected in JHU's IND submissions. (EX1150, ¶51.)

2. JHU's Purported Evidence of Secondary Considerations Should Be Afforded Little to No Weight

The principal ground for invalidity in this proceeding is anticipation, where secondary considerations are irrelevant. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008). Nevertheless, JHU devotes a large portion of its POR to such arguments and presents testimony from four declarants purportedly directed to supporting secondary considerations, all of which apply an incorrect time-period or scope in their analysis. (EX2090; EX2130; EX2137; EX2191; *see also* EX1150, ¶¶178-187.)

JHU and its declarants fail to meet the burden of establishing nexus for any alleged secondary considerations. There can be no nexus when the 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) (“Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.”) (citation omitted).

i) JHU Has Not Shown the Claimed Method of Treatment Was Unexpected By The Critical Date

JHU's argument that the claimed method of treatment was unexpected relies on broad assertions that cancer treatment is inherently unpredictable, and that prior studies of pembrolizumab in CRC patients had allegedly "failed resoundingly." (POR, 81.) JHU's argument, however, does not account for the state of the prior art by the Critical Date, does not compare the results of the claimed method of treatment with the closest prior art, and improperly focuses on the degree of success of the study. (EX1150, ¶¶178-187.)

First, JHU utilizes the wrong time-period in its analysis of alleged unexpectedness, focusing on when the inventors purportedly first had their idea, rather than the Critical Date. (POR, 80-85.) In doing so, JHU's argument obscures the reality that, as of 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, ¶¶105-113), (3) Merck had initiated another clinical study of pembrolizumab in MSI-H CRC patients (EX1148), and (4) BMS had already begun its own study aimed at treating MSI-H CRC patients using its own PD-1 inhibitor (EX1053.) (See EX1150, ¶¶180-187.)

Second, JHU's analysis is undermined by its failure to compare the allegedly unexpected results with the closest prior art—the MSR, which described the very method of treatment claimed. *See In re Baxter Travenol Labs.*, 952 F.2d

388, 392 (Fed. Cir. 1991) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”) (citation omitted). Instead, JHU improperly compares its use of pembrolizumab for the treatment of MSI-H CRC against prior studies concerning the treatment of CRC more broadly. (POR, 80-85; *see also* EX2090, ¶¶33-45; EX1150, ¶¶184-187.)

Further, JHU incorrectly conflates the *degree* of success of the study described by the MSR with unexpectedness. *Hoffmann–La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1333-34 (Fed. Cir. 2014) (“Evidence of superior efficacy does nothing to undercut” a showing of reasonable expectation of success “even if the level of success may have turned out to be somewhat greater than would have been expected.”). The study results cited by JHU therefore do nothing to undermine the overwhelming evidence that a POSA would have expected positive results from the use of pembrolizumab to treat MSI-H CRC as of July 10, 2015. (Pet., 43-45.)

ii) JHU Has Not Shown Any Industry Skepticism at the Critical Date

JHU and its declarants also use the wrong time-period, and put forth contradictory, self-serving testimony regarding alleged actions by Merck and BMS well before the Critical Date to allege skepticism. (POR, 73-76; *see also* EX1150, ¶¶180, 183.) For example, JHU alleges that Merck did not “believe[] in the inventors’ hypothesis” and did not fund the study described by the MSR, which

JHU purports evidences skepticism by Merck. (POR, 73-76.) But Dr. Pardoll, on whom JHU relies to make this allegation, testified that he did not provide any statements or comments regarding Merck's or the industry's beliefs in the portions of his declaration cited to the Board by JHU. (*See supra* II.A; EX1140, 119:10-124:2.) Further, while Dr. Lonberg testified that the basis for his belief that "Merck declined funding the trial" came from Dr. Pardoll, Dr. Pardoll said otherwise during deposition and admitted he had never seen any documents reflecting the funding for the study. (*See supra* II.A; EX1140, 77:21-81:15.) Indeed, contrary to her declaration, Dr. Le admitted during her deposition that Merck did, in fact, provide funding for the study. (EX1139, 67:13-73:15.)

The depositions of JHU's declarants also revealed a lack of foundation for JHU's allegations. For example, Dr. Lonberg testified that he did not have any knowledge of "what was going on at Merck" when asked whether Merck was skeptical of the study. (EX1138, 228:10-16.) Similarly, Dr. Goldberg revealed he had no contact with Merck and so had "no idea what [Merck] knew." (EX1136, 112:1-4, 137:5-11.) Dr. Le could not recall a single individual at Merck involved with the study, despite alleging certain "observations" in her declaration regarding individuals at Merck. (EX1139, 268:8-278:16.) Likewise, Dr. Pardoll admitted he was not involved with the study, and did not have knowledge about whether individuals at Merck were involved in its design or conduct. (EX1140, 72:4-

73:14.) In any event, the fact is that Merck collaborated with JHU, providing its valuable, not yet FDA-approved drug free of charge, along with funding, by the Critical Date. (*See* EX1005, 1-6; EX2130, ¶34; EX1139, 67:13-73:15.)

Further, JHU's and Dr. Lonberg's allegations regarding skepticism by BMS reflect unsupported assumptions from the wrong time-frame and with no nexus to the claims. (*See* POR, 73-76; EX2072 ¶186.) Regardless, BMS began its own study of its anti-PD-1 drug in MSI-H CRC patients by February 2014—just six months after the study between Merck and JHU began and more than one year before the Critical Date. (EX1150 ¶117; EX1053.) Indeed, Dr. Lonberg testified that he, in fact, “advocat[ed] for [BMS's] involvement” in the study and “expressed enthusiasm to Drew Pardoll about doing such a clinical [study],” thereby evidencing his own personal lack of skepticism even in 2012. (EX2072 ¶186; EX1138, 225:15-228:9.)

**iii) JHU Ignores the Rapid
Development of Pembrolizumab
and PD-1 Inhibitors By the Critical Date**

While the '393 patent claims are directed to treating MSI-H CRC specifically, JHU and Dr. Goldberg rely on a generalized alleged long-felt, unmet need for treatment of advanced or metastatic CRC. (POR, 66; EX2090, ¶¶63-65; EX1136, 184:7-13.) As such, JHU's purported evidence has no nexus to the claims. *See Amerigen Pharms., Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286,

Paper 86, at 38 (P.T.A.B. Jan. 17, 2018) (requiring sufficient evidence that a “specific” long-felt need existed for the claimed method of administration); *Coalition for Affordable Drugs X, LLC v. Anacor Pharms., Inc.*, IPR2015-01780, Paper 70, at 55-56 (P.T.A.B. Feb. 23, 2017) (finding PO failed to show specific, long-felt unmet need tied to the claims). Accordingly, JHU’s and Dr. Goldberg’s discussion of therapies available in 2012 to treat metastatic CRC is not relevant to the specific method of treatment claimed here, as acknowledged by Dr. Goldberg during deposition. (POR, 76-80; EX2090, ¶¶36-39; EX1136, 178:20-179:1.)

JHU also fails to establish that the need purportedly solved by the claimed invention was unmet prior to the Critical Date. *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.’”). In particular, JHU ignores not only the publication of the MSR itself, but also the rapid development of pembrolizumab and other PD-1 inhibitors, especially following the study results published by BMS in 2010 for its PD-1 inhibitor, as acknowledged by JHU’s declarant Dr. Goldberg. (EX1136, 188:15-190:13 (“[T]here was intense interest on the part of clinical oncologists, on the part of patients, and on the part of pharmaceutical companies of testing PD-1 inhibitors as

quickly as possible to be sure that patients with cancer could realize their potential benefit.”); *id.* at 80:13-82:13, 105:2-15, 106:6-18, 107:7-110:22, 119:4-120:14; EX1003, ¶¶41-49; *see also* EX1150, ¶¶185-186.)

Further, JHU did not (because it cannot) put forth any evidence that others tried to treat MSI-H CRC 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 Critical Date treatment with an anti-PD-1 drug had led to a complete response in an MSI-H CRC patient, as reported in January 2013, and BMS had also begun treating MSI-H CRC patients with its anti-PD-1 drug, as admitted by JHU’s declarants. (EX1053; *see also* EX1136, 106:19-110:22; EX1138, 141:20-142:11.).

**iv) JHU Does Not Present Any
Evidence of Industry Praise Tied to
Novel Features of the Claimed Invention**

JHU fails to show a nexus between the ’393 patent claims and its assertions regarding industry praise. (POR, 68.) While Merck’s Keytruda is an important drug that has provided benefit to patients with many different cancers, JHU has not made any showing that this praise is linked to any purportedly novel features of

claim limitations that Merck has shown to be obvious.¹⁸ This proffered secondary consideration therefore accords little weight. *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1342 (Fed. Cir. 2020).

**v) 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." *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 Critical Date, and the prior art discloses the very aspects of the claims that JHU argues are responsible for its commercial success. (*See supra* §II.C.2.i; *see also* EX1151, ¶¶40-42.) As noted, Mr. Segers' understanding of nexus was purportedly based on a conversation with Dr.

¹⁸ 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).

Goldberg, but Dr. Goldberg testified that he did not provide Mr. Segers with “any substantive information.” (*See supra* §II.A; EX1151, ¶¶26-28.)

Moreover, JHU’s purported evidence of commercial success is severely undermined by the existence of Merck’s own patents covering Keytruda. (EX1151, ¶¶29-35.) Evidence of commercial success has been considered to be weak where market entry by others was precluded due to the existence of other patents. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (“Financial success is not significantly probative” of nonobviousness when “others were legally barred from commercially testing” the idea.). Here, Merck’s prior patents covering Keytruda through 2028 would have deterred others from developing the alleged invention, regardless of its obviousness. (EX1151, ¶¶29-35.)

JHU’s purported evidence of commercial success is also incomplete and unreliable. (EX1151, ¶¶43-72.) For example, JHU presents misleading patient and sales data, obscuring the fact that CRC patients [REDACTED], and that the growth rate of this portion of Keytruda patients has been [REDACTED]. (EX1151, ¶¶45-48, 64.) And contrary to JHU’s allegations regarding an inflection point in sales tied to the 2017 MSI-H approval, the data demonstrates that the inflection

point began in 2016, coinciding with Keytruda's 2016 approval expanding its metastatic NSCLC indication. (EX1151, ¶¶49-59.)

Moreover, there is no basis for Mr. Segers' admitted exclusion of other available MSI-H CRC treatments from his analysis (EX1137, ¶¶60, 65-68.). For those that are included, Mr. Segers relies almost entirely on an assumption extrapolating a single data point across five subsequent years. (EX1151, ¶¶61-62; EX1137, 151:8-153:1, 157:10-160:16.) While JHU and Mr. Segers claim that Keytruda [REDACTED] than it has for NSCLC, melanoma, and bladder cancers, JHU and Mr. Segers do not account for the effect of those indications' earlier launch dates, and Mr. Segers admittedly makes year-over-year comparisons of data from publications that expressly warn against making such comparisons. (EX1151, ¶¶69-70; EX1137 at 68:22-80:18.)

JHU and Mr. Segers also did not account for contributions of "other economic and commercial factors unrelated to the quality of the patented subject matter." (EX1151, ¶¶36-39); *see also In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996); *see also Ritchie v. Vast Res., Inc.*, 563 F.3d 1334, 1336-37 (Fed. Cir. 2009). For example, the success of Keytruda for prior indications likely generated positive brand recognition that then created a "halo effect" and competitive edge that is not attributable to the alleged invention. (EX1151, ¶37.) As Mr. Segers admitted in deposition, brand recognition is a factor that could increase the likelihood of a

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

III. CONCLUSION

The Board should find the challenged claims unpatentable.

Respectfully submitted,

Dated: January 31, 2025

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Counsel for Petitioner

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, 6,942 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: January 31, 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 January 31, 2025:

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