IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
(Northern Division)

MERCK SHARP & DOHME LLC, Plaintiff, v. THE JOHNS HOPKINS UNIVERSITY Defendant.	Civil Action No. JRR-22-3059

PLAINTIFF MERCK SHARP & DOHME LLC'S
OPENING BRIEF REGARDING CLAIM CONSTRUCTION

JHU 2160
Merck Sharp v. Johns Hopkins
IPR2024-00649

TABLE OF EXHIBITS

Ex.	Document
A	Declaration of Preston K. Ratliff II in Support of Plaintiff Merck Sharp & Dohme LLC's Opening Brief Regarding Claim Construction
A-1	U.S. Patent No. 10,934,356
A-2	U.S. Patent No. 11,325,974
A-3	U.S. Patent No. 11,325,975
A-4	U.S. Patent No. 11,339,219
A-5	U.S. Patent No. 11,591,393
A-6	U.S. Patent No. 11,629,187
A-7	U.S. Patent No. 11,634,491
A-8	U.S. Patent No. 11,643,462
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A-10	Excerpt from the prosecution history for U.S. Patent No. 10,934,356 (February 4, 2020 Declaration)
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A-14	Excerpt from the prosecution history for U.S. Patent No. 11,629,187 (June 28, 2022 Declaration)
A-15	Excerpt from the prosecution history for U.S. Patent No. 11,634,491 (August 29, 2022 Declaration)
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A-19	Excerpt of the American Heritage Science Dictionary (2011)
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A-21	Excerpt of Merriam-Webster's Collegiate Dictionary (11th ed. 2014)
A-22	March 11, 2024 Keytruda Labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s160lbl.pdf
A-23	May 23, 2017 Keytruda Labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf
A-24	ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013) available at https://clinicaltrials.gov/study/NCT01876511?tab=history&a=1 ("MSI-H Study Record"); also available at *Merck Sharp & Dohme LLC v. The Johns Hopkins University*, 1:22-cv-03059, ECF No. 1, Compl., Ex. B (Nov. 29, 2022)
A-25	Chapelle et al, *Clinical Relevance of Microsatellite Instability in Colorectal Cancer*, 28(20) J. Clinical Oncology 3380 (2010)

A-26	National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 3.2014 (January 27, 2014)
A-27	Email from Preston K. Ratliff II to Karrie Wheatley, Ph.D., attorney of record for The Johns Hopkins University (April 22, 2024 at 08:29 AM EST) and the email from Karrie Wheatley to Preston K. Ratliff II (April 22, 2024 at 06:25 PM EST)
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I. INTRODUCTION

Claim construction often plays an important role in cases involving patents. Here, claim construction is critical because the patents at issue concern the highly-complex science of biotechnology and a jury may be empaneled to decide whether the patents at issue are invalid or infringed. The Supreme Court and the Court of Appeals for the Federal Circuit have established that the Court, and not the jury, has the duty to construe claim language as a matter of law based on what the patentee told the U.S. Patent and Trademark Office ("PTO") it invented in the "intrinsic record," also known as "intrinsic evidence" (namely, the text of the claims, the specification of the patent, and the history of the prosecution of the patents before the PTO). The Court should explain the terms for a jury to then apply. The intrinsic record is the principal tool in construing claims because it prevents a party, in this case Defendant The Johns Hopkins University ("JHU"), from arguing to a jury about the patent in a way that is different from how the claims should be interpreted as a matter of law based on the intrinsic record.

The purported inventions in this case arise from a particular September 2013 clinical research study that JHU and Plaintiff Merck Sharp & Dohme LLC ("Merck") conducted together. In this clinical study, Merck and JHU treated cancer patients with the drug pembrolizumab, also called "pembro" for short. Pembrolizumab was already a Merck drug and Merck was already developing it for cancer treatments. Merck's drug is sold under the name Keytruda®. Merck and JHU (the "Parties") entered into a written contract to collaborate on this study and worked together throughout all of its phases, sharing the study data and results. The clinical study treatment was also published in June 2013. After the study concluded, JHU unilaterally and without Merck's knowledge—contrary to the Parties' contract and even though the study was published—filed patent applications that led to the nine patents at issue here using the study data and results. Even though the Parties' collaboration contract stated that Merck

could use the data and results from the research study without the need to pay JHU, and despite the patents being invalid over the prior publication of the clinical study, JHU has demanded that Merck pay JHU hundreds of millions of dollars, tied to Merck's sales of Keytruda®.

As explained in detail below, the September 2013 joint research study treated cancer patients with pembrolizumab, after testing them for a specific biomarker, and compared the performance of pembrolizumab in the treated patients. At that time, it was already known that cancer patients both with and without that biomarker could safely receive pembrolizumab. For example, patients, including those with and without the biomarker, were treated with pembrolizumab in a Merck clinical study that began in May 2013, which is before Merck and JHU executed their contract. As such, the September 2013 joint JHU and Merck research study was focused on treating the cancer patients, collecting the data between the tested groups, and evaluating the inherent data and results.

Because the joint clinical study is the central basis in the patent specification supporting JHU's patent filings, JHU is principally asking this Court to forgo construing the disputed claim terms so that it can resist close inspection of both the actual disclosures of the patents as well as the language JHU used in describing the alleged invention and obtaining the patents. JHU's tactics are designed to either: (a) make the scope of the asserted patent claims flexible and subject to transforming into whatever undisclosed meaning JHU deems fit, or (b) avoid actual determinations of claim meanings until some indeterminate point in time. Black-letter claim construction canons and this Court's Local Rules, however, do not endorse such tactics.

Merck's proposed constructions, on the other hand, are based on the language of the claims and their context, and interpreted based on the intrinsic record. They are also consistent with extrinsic evidence (e.g., technical literature) at the time of JHU's patent filings. Further,

actual constructions as proposed by Merck are necessary in this case because the claim language is written in the highly-complex lexicon of biotechnology and involves related technical terms used in clinical research study protocols and data analysis. Thus, the terms have specialized meanings in this technical context, and require construction.

JHU's proposals, if adopted, would serve to create confusion and frustrate scrutiny of JHU's defenses to Merck's invalidity arguments and non-infringement positions. The Federal Circuit and this Court have already held that patentees should not be permitted to avoid construction of their patent claims by merely saying they have plain and ordinary meanings.[1] In particular, where there is a dispute between the parties as to the meaning of the term, that dispute should be resolved by the Court, not a jury. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech.* Co., Ltd., 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("In this case, the 'ordinary' meaning of a term does not resolve the parties' dispute, and claim construction requires the court to determine what claim scope is appropriate in the context of the patents-in-suit."). The orderly presentation of the Parties' claims and defenses by experts and trial counsel require actual construction of the disputed claim terms. The time for claim construction is now and should not be left to some indeterminate point in time.

[1] *E.g.*, *G.W. Aru, LLC v. W.R. Grace & Co.-Conn.*, No. JKB-22-2636, 2023 WL 7170356, at *8 (D. Md. Oct. 31, 2023) ("simply declaring that the claim 'needs no construction' or has the 'plain and ordinary meaning' is not enough"); *Mesh Comm, LLC v. PEPCO Energy Servs.*, No. RDB-09-2804, 2010 WL 5463934, at *8-*9 (D. Md. Dec. 29, 2010) (finding a construction of a phrase necessary after a party declared the term be given its "plain and ordinary meaning" with no additional context).

II. RELEVANT FACTUAL BACKGROUND

A. Overview of the Patents-in-Suit

Based on JHU's conduct, Merck filed this action for breach of contract and noninfringement. In response, JHU is currently asserting 144 claims from nine patents[2] (collectively, the "Patents-in-Suit"). The patents all share the same named inventors, specification,[3] and relevant priority dates. The patents are all based on the above-referenced joint clinical study (the "MSI-H Study") in which cancer patients were treated with Merck's drug, pembrolizumab, which is a PD-1 inhibitor. The cancer patients were tested for certain genetic deficiencies (specifically, having the genetic biomarker known as microsatellite instability-high, or "MSI-H"), assigned to groups, and given the drug. The effects on their cancer were measured. This study confirmed that the cancer patients who had the genetic deficiency had an improved response with Merck's drug. Patients without the genetic deficiency can also respond.[4] Indeed, both MSI-H patients and patients without this genetic biomarker were given Keytruda® in a study that began earlier than the joint clinical study.[5] In the joint clinical study, the protocol also specified comparing the data generated from treating the patients in the different groups. As will be discussed, JHU's patent claims are numerous, but they are largely focused on trying to claim the results produced by the treatment.

The prosecution history of the Patents-in-Suit, which is the complete record of the proceedings before the U.S. Patent Office, shows how JHU relied on the study's data and results.

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[2] 144 claims from the following nine patents are currently at issue in this action: U.S. Patent Nos.: 11,591,393 (the "'393 patent"); 11,649,287 (the "'287 patent"); 11,643,462 (the "'462 patent"); 11,629,187 (the "'187 patent"); 11,643,491 (the "'491 patent"); 11,325,974 (the "'974 patent"); 11,325,975 (the "'975 patent"); 11,339,219 (the "'219 patent"); and 10,934,356 (the "'356 patent").

For example, named inventor Drew Pardoll, Ph.D. provided sworn testimony to the U.S. Patent Office (the "Pardoll Declaration") that the claims were patentable because of "the ***results we disclose and claim*** in the pending application." (Ex. A-10[6] at ¶ 13 (submitted during prosecution of eight of the nine Patents-in-Suit) (emphasis added).) A similar sworn declaration from Vijay Kuchroo, Ph.D. submitted during the prosecution of JHU's first-issued patent, the '356 patent, argued that the claims were worthy of a patent because JHU "conducted . . . a ***study*** and ***validated their hypothesis***." (Ex. A-18 at ¶ 28 (emphasis added).)

Further, the entirety of the shared specification's examples, tables, and figures are devoted to the design and results of the MSI-H Study. (Ex. A-5[7] at 6:52-22:30, 3:19-21; Figs. 1-13.) Examples 1-4 (Ex. A-5 at 8:7-15:67) are the design of the MSI-H Study, and Examples 5-11 (Ex. A-5 at 16:1-18:54), Tables 1-3 (Ex. A-5 at 18:60-22:28) and Figures 1-13 report the MSI-H Study's data and results. As noted above, the treatment protocol used in the MSI-H Study ("MSI-H Study Record") was published on the U.S. Government's clinical trial website,

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[3] A patent specification is "a written description of the invention," which should provide "the manner and process of making and using [the invention]." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014). For ease of reference, Merck may at times cite the columns and lines of the specification in the '393 patent, but these cites should be understood as extending to the same substantive language in each specification in the patent family.

[4] Keytruda® is approved for over 40 indications, most of which are not related to the MSI-H genetic deficiency. (Ex. A-22.)

[5] Ex. A-23 at 41.

[6] Exs. A-10 through A-17 are substantively the same. For ease of reference, this Brief cites Ex. A10, but these cites should be understood as extending to the same substantive language in Exs. A-10 through A-17.

[7] All patents share the same specification. For ease of reference, this Brief cites the columns and lines of the specification in the '393 patent, but these cites should be understood as extending to the same substantive language in each specification in the patent family.

www.clinicaltrials.gov, on June 10, 2013, several years before JHU unilaterally first filed its patents. (Ex. A-24 at 1.)

The MSI-H Study treated cancer patients with pembrolizumab broken up into three groups: (1) patients having colorectal cancer who tested positive for the MSI-H genetic biomarker or a DNA Mismatch Repair Deficiency ("dMMR")[8] colorectal cancer; (2) patients having colorectal cancer who tested negative for that biomarker (this is called "microsatellite stable," "MSS," "mismatch repair proficient," or "MMR proficient");[9] and (3) patients having non-colorectal cancer testing positive for the biomarker. (Ex. A-24 at 4 (Arms and Interventions); Ex. A-5 at 8:9-37, 8:50-56, 13:24-30.) The MSI-H Study specified comparing the results of the treatments to show whether "MSI as a marker predict[s] treatment response." (Ex. A-24 at 5 (Outcome Measures); *see* Ex. A-5 at 13:24-27, 16:4-8, 16:29-32, 19:40-21:15, Figs. 2, 11.)

B. Disputed Terms for Claim Construction[10]

The following ten terms are disputed and thus require construction.

(1) "therapeutically effective amount of pembrolizumab" ('393 patent, Claims 1, 14; '287 patent, Claims 1, 11; '462 patent, Claims 1, 11; '187 patent, Claims 1, 11; '491 patent, Claims 1, 16);

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[8] MSI-H is thought to be caused by dMMR, which is a genetic condition. (Ex. A-5 at 1:32-34; EX1010, 1192.) MSI-H and dMMR are "biologically the same" and testing for one was considered "equivalent" to testing for the other. (Ex. A-26 at PDF p. 51; Ex. A-25 at 3380; Ex. A-5 at 10:39-64 (assessing dMMR status using MSI-H testing). Thus, reference to MSI-H should be read to mean MSI-H and dMMR, unless otherwise noted.

[9] Ex. A-26 at PDF p. 51; Ex. A-5 at 3:1-6, 6:53-62, 10:39-64.

[10] For ease of consideration, the terms reflect the order Merck believes will best assist the Court in resolving the disputes. Merck initially identified the terms for construction to JHU by simply listing them in the order they appear in the various patents and grouping the terms by concept, which was most efficient for the Parties' meet and confer and receiving JHU's positions on each term. JHU required that the Joint Claim Construction Statement (D.I. 71) generally maintain this order, and Merck agreed.

(2) "reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer"
('393 patent, Claim 14);

(3) "reducing the risk of progression of colorectal cancer in a human patient"
('287 patent, Claim 11);

(4) "reducing the risk of progression of a solid tumor"
('187 patent, Claim 11);

(5) "reducing the risk of cancer progression or increasing overall survival in a human patient"
('491 patent, Claim 16);

(6) "in response to"
('393 patent, Claims 1, 14; '287 patent, Claims 1, 11; '462 patent, Claims 1, 11; '187 patent, Claims 1, 11; '491 patent, Claims 1, 16);

(7) "objective response rate (ORR)"
('974 patent, Claim 3; '975 patent Claim 3, 10; '219 patent, Claim 2);

(8) "an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients"
('393 patent, Claims 31, 37; '287 patent, Claims 25, 31);

(9) "population of cancer patients"
'356 patent, Claims 23, 27); and

(10) "observing"
('356 patent, Claim 23).

C. Procedural Background Relating to Claim Construction[11]

On January 26, 2024, JHU communicated its initial position to Merck that no terms of the Asserted Patent Claims should be construed and that all terms of the 144 claims should be given their "plain and ordinary meaning."[12] On March 15, 2024, Merck identified the ten disputed terms at issue and provided its proposed constructions and supporting evidence.[13] On April 10, 2024, JHU provided additional positions in response to Merck's proposed claim constructions, but maintained "plain and ordinary meaning" as its primary position for all terms.[14]

On April 19, 2024, the Parties met-and-conferred, but were unable to reach agreement as to the construction of any terms. JHU was not willing to explain what it meant by "plain and ordinary meaning." (Ex. A-27.) Instead, JHU said that the Court and the person of ordinary skill in the art ("POSA") (and, presumably, the jury) would plainly understand what each of the disputed terms meant. Subsequently, on April 22, 2024, JHU dropped its "plain and ordinary meaning" constructions for two disputed terms relating to "objective response rate" and added an alternative construction for "therapeutically effective amount of pembrolizumab." To date, JHU has refused to identify how its "plain and ordinary meaning" constructions would differ, if at all, from Merck's constructions other than to state that it does not agree with Merck.

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[11] Beginning in October 2023, Merck has repeatedly requested that JHU narrow its asserted claims to streamline the case and bring better clarity to the patent issues. At present, however, JHU continues to assert an unmanageable number of patent claims—144—across nine patents, despite representing to the Court that this is "in substance a one-patent case." (D.I. 51 at PDF. p. 3.)

[12] Ex. A-28.

[13] Ex. A-29.

[14] Ex. A-30.

III. LEGAL STANDARDS

Claim construction is "a question of law." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Id.* at 1312. Claim constructions provided by the Court, "when read in light of the relevant claim language, effectively inform[] the jury of the proper way to interpret the patent claim language at issue," leaving factual disputes to be resolved by the jury. *Biedermann Techs. GmbH & Co. KG v. K2M, Inc.*, 678 F. Supp. 3d 716, 732 (E.D. Va. 2023); *see also Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996) (holding that the interpretation of claim terms "is an issue for the judge, not the jury"), aff'g, 52 F.3d 967 (Fed. Cir. 1995) (en banc). When the meaning of a claim term is disputed, "it is the court's duty to resolve it." *O2 Micro*, 521 F.3d at 1362 (vacating and remanding final judgment because the meaning and legal significance of a disputed claim term was "improperly submitted to the jury"). As the Federal Circuit explained, "competitors should be able to rest assured, if infringement litigation occurs, that a judge, trained in the law, will . . . analyze the text of the patent and its associated public record and apply the established rules of construction, and in that way arrive at the true and consistent scope of the patent owner's rights to be given legal effect." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). Courts should explain what the claim term means so that a legal question is not "improperly submitted to the jury." *Id.*

This Court's Local Rules require parties to identify "any special or uncommon meanings of words or phrases." Local Rule 805.1(b), (d). "[S]pecial or uncommon meanings" include "the broader category of meanings that would not be readily apparent to a layperson, but would be understood by 'a person of ordinary skill in the art in question at the time of the invention.'"

Durr Sys., Inc. v. EFC Sys., Inc., No. GJH-18-2597, 2022 WL 4777531, at *2 (D. Md. Sept. 30, 2022).

While the words of a claim "are generally given their ordinary and customary meaning," that is not "the meaning of the term in the abstract," but rather the "meaning to the ordinary artisan after reading the entire patent." *Phillips*, 415 F.3d at 1312, 1321; *see also Eon Corp. IP Holdings LLC v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1320 (Fed. Cir. 2016) ("A party is, therefore, not entitled to a claim construction divorced from the context of the written description and prosecution history."); *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) ("The only meaning that matters in claim construction is the meaning in the context of the patent."). The patent specification is usually "the single best guide to the meaning of the disputed term." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Further, the patent prosecution history "provides evidence of how the [Patent Office] and the inventor understood the patent," and it "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention." *Phillips*, 415 F.3d at 1312, 1317 (citations omitted).

The Court may also examine "extrinsic" evidence, which includes "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Extrinsic evidence should not be used for "the purpose of varying or contradicting the terms of the claims." *Id*. at 981. The Federal Circuit has explained that, "while extrinsic evidence can shed useful light on the relevant art, . . . it is less significant than the intrinsic record in determining the legally operative meaning of claim language." *Phillips*, 415 F.3d at 1317 (quotation marks omitted).

IV. MERCK'S PROPOSED CONSTRUCTIONS OF THE DISPUTED TERMS SHOULD BE ADOPTED

(1) "therapeutically effective amount of pembrolizumab"[15]

Representative Claim *(Claim 1 of the '393 patent)*	
A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising: testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a **therapeutically effective amount of pembrolizumab**.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"an amount of pembrolizumab that exhibits an improved response in the patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer" Alternatively: "10 mg/kg every 14 days" or indefinite	Plain and ordinary meaning, which is "therapeutically effective amount of pembrolizumab" However, if the Court finds construction of this phrase to be necessary, JHU proposes the following alternative construction: "an amount of pembrolizumab sufficient to produce the desired effect."

JHU's primary proposed construction is no construction at all. Its second proposed construction is very similar to Merck's except it uses the vague and circular phrase "desired effect," whereas Merck's construction more clearly identifies the effect based on the intrinsic record: "exhibit[ing] an improved response in the patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer." As will be shown below, Merck's construction is supported by the patent specification and prosecution history, and therefore, is the correct one. *See, e.g., Genentech, Inc. v. Iancu*, 809 F. App'x 781, 785 (Fed. Cir.

[15] '393 patent, Claims 1, 14; '287 patent, Claims 1, 11; '462 patent, Claims 1, 11; '187 patent, Claims 1, 11; '491 patent, Claims 1, 16.

2020) ("an effective amount" is "properly construed as measured relative to an untreated patient" based on the prosecution history). Alternatively, to the extent JHU cannot articulate the desired effect, then JHU should accept "effective" to be the only amount of drug actually described as having been used in the patent specification and clinical study: 10 mg/kg every 14 days. (Ex. A-5 at 8:52-53; 13:28-30.)

In particular, Merck's construction is literally drawn from JHU's own explanations to the U.S. Patent Office. *GPNE Corp. v. Apple Inc.*, 830 F.3d 1365, 1371 (Fed. Cir. 2016) (construing the term "node" as a type of "pager" based on statements in the inventor's declaration submitted as part of the prosecution history). To overcome the Patent Examiner's conclusion that the patent claims were obvious over the prior art, JHU stated in the aforementioned Pardoll Declaration that the specific dosage of pembrolizumab "allowed us to try to get at an answer to a question to which we did not know the answer—specifically whether or not ***patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated*** with [10 mg/kg of pembrolizumab every 14 days], ***compared with the more common MSS or MMR proficient colon cancers***." (Ex. A-10 at ¶ 22 (emphasis added).)[16]

Further, the shared specification supports Merck's proposed construction. The specification of the Patents-in-Suit is directed to the MSI-H Study and, specifically, an improved response in a patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer. For example, the specification makes plain that the MSI-H Study "was conducted . . . to simultaneously evaluate the efficacy of [pembrolizumab] and MSI as a treatment selection marker for anti-PD-1 therapy." (Ex. A-5 at 13:24-26.) And the specification

[16] MSS or MMR "proficient" colon cancers is just the opposite of MSI-high or MMR "deficient." (Ex. A-26 at PDF p. 51; Ex. A-5 at 3:1-6, 6:53-62, 10:39-64.)

explains that "the enhanced anti-PD-1 responsiveness of this genetically defined subset of tumors" (Ex. A-5 at 7:18-19) and that "[t]he [MSI-H Study's] data . . . supports the hypothesis that MMR-deficient tumors are more responsive to PD-1 blockade than are MMR-proficient tumors" (Ex. A-5 at 6:52-56). Thus, the specification requires that the "therapeutically effective amount of pembrolizumab" is "an amount of pembrolizumab that exhibits an improved response in the patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer."

As noted above, the prosecution history is consistent with the shared specification and Merck's proposed construction. For example, the Pardoll Declaration emphasized that the alleged invention differed from a piece of prior art because of the alleged invention's "***comparative relationship*** . . . between MSI status and efficacy of pembrolizumab." (Ex. A-10 at ¶¶ 7-9 (emphasis added).)

To the extent that "therapeutically effective amount of pembrolizumab" is not construed to mean "an amount of pembrolizumab that exhibits an improved response in the patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer," the only other guidance for its construction provided by the intrinsic record is the specific amount of "10 mg/kg every 14 days." This is the only amount of pembrolizumab that the specification discusses in any context, and was the dosing of pembrolizumab that the patients in the Parties' MSI-H Study received. (Ex. A-5 at 8:52-53; 13:28-30.) *Vitronics Corp.*, 90 F.3d at 1583 (construing "solder reflow temperature" based, in part, on ensuring that preferred embodiment in the specification meets the claims); *see also Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006). Embodiments in the specification are not necessarily limiting, but when, like here, the specification includes only a single example, and no additional

direction, the example may be limiting. *See Wang Lab'ys, Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999) (limiting claims to one of two alternatives because only one alternative was described and enabled).

JHU's proposal that the disputed claim term needs no construction because the Court and the POSA knows what it means when they see it invites legal error and jury confusion, as it does not provide sufficient guidance for assessing issues of infringement or invalidity. *E.g.*, *O2 Micro*, 521 F.3d at 1362 (explaining that simply declaring that the claim "needs no construction" or has the "plain and ordinary" meaning without more may not be enough); *Paice LLC v. Volvo Car Corp.*, No. RDB-20-3737, 2022 WL 313864, at *3-*4 (D. Md. Feb. 2, 2022) (finding certain claim terms "need construction in order to be understood by the jury"). It is also inconsistent with the specification and prosecution history and therefore should be rejected.

JHU's alternative construction ("an amount of pembrolizumab sufficient to produce the desired effect") similarly fails to provide sufficient guidance for assessing issues of infringement or invalidity because the desired effect according to JHU is completely undefined. *See Tessenderlo Kerley, Inc. v. Or-Cal, Inc.*, No. C 11-04100 WHA, 2012 WL 3276981, at *3 (N.D. Cal. Aug. 9, 2012) ("A purpose of claim construction is to remove ambiguity. Here, construing the term 'effective amount' to mean Or-Cal's broader 'desired result' would add ambiguity as to the patentee's intended, narrower meaning, which was 'the amount sufficient to enhance photosynthesis by increasing carbon dioxide uptake.'"); *see also Eli Lilly & Co. v. Apotex, Inc.*, No. 117CV02865TWPMPB, 2019 WL 7049799, at *10 (S.D. Ind. Dec. 23, 2019) (rejecting proposed constructions of "an effective amount of [compounds]" that included "capable of performing the intended result" because "the purpose or intended result" is "clearly delineated.").) That is not acceptable here where the Parties do not agree on the construction and

there is no definition in the specification of "therapeutically effective amount of pembrolizumab."

Further, JHU's construction is not appropriate where the specification is directed towards the use of a specific amount of an existing drug to obtain an improved response in patient populations exhibiting a specific biomarker as compared with patients who lack that biomarker, rather than towards establishing different effective amounts of pembrolizumab or enhancing the efficacy of pembrolizumab with a combination therapy. Indeed, Courts have often construed "therapeutically effective amount" and "effective amount" to have specific meanings.[17] JHU's proposed construction, therefore, refuses to engage with an important aspect of the meaning of this claim term, which is needed to clarify the issues for the jury. *O2 Micro*, 521 F.3d at 1362.

To the extent Merck's proposed constructions based on the intrinsic record are not adopted, the term "effective amount of pembrolizumab" should be held indefinite. "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Dow Chem. Co. v. Nova Chemicals Corp. (Canada)*, 803 F.3d 620, 634 (Fed. Cir. 2015) (quoting *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014)). Here, as discussed above, the POSA should conclude, based on the intrinsic record, that a

[17] *See Forest Lab'ys Inc. v. Cobalt Lab'ys Inc.*, No. 08-21-GMS-LPS, 2009 WL 3010837, at *4 (D. Del. Sept. 21, 2009) (construing "effective amount" as "an amount shown to cause improvement, in comparison to placebo"); *Allergan, Inc. v. Apotex, Inc.*, No. 1:10-CV-681, 2012 WL 12957378, at *3 (M.D.N.C. Aug. 2, 2012) (construing "an effective amount" as "a dose sufficient to stimulate hair growth over time with repeated applications"); *EMD Crop Bioscience v. Becker Underwood*, 2011 U.S. Dist. LEXIS 170843, at *21 (W.D. Wis. Nov. 3, 2011) (construing "effective amount of" a chemical as "an amount sufficient to achieve either enhancement of seed germination or seedling emergence or an amount sufficient to enable breaking of dormancy," and that those LCOs must "improve[] seed germination and seedling emergence in treated seeds as compared to nontreated seeds.")

"therapeutically effective amount of pembrolizumab" is "an amount of pembrolizumab that exhibits an improved response in the patient with an MSI-H or dMMR tumor, when compared to a patient with an MSS or MMR proficient cancer," or the specific amount of "10 mg/kg every 14 days," which is the only amount discussed in the specification as leading to such results in the MSI-H Study.

If neither of Merck's proposed constructions are accepted, the result is that a POSA would have no idea what other amounts or ranges the term means (because no other amount is used in the clinical study), or even what other types of parameters should be used to make such a determination (because JHU refuses to accept the comparative effect referenced in Merck's construction).

(2) "reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer"[18]

Claim Using Term *(Claim 14 of the '393 patent)*	
A method of **reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer**, the method comprising: testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"the risk of cancer progression or overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer is reduced or increased compared to a patient with an MSS or MMR proficient cancer" or indefinite	Plain and ordinary meaning, which is "reducing the risk of cancer progression or increasing overall survival in a human patient who has microsatellite instability high or DNA mismatch repair deficient colorectal cancer"

Merck's proposed construction interprets the relative word "reducing" to explain what the reduction in risk of cancer progression is being compared to. Merck's construction again tracks the language in the Pardoll Declaration—submitted during prosecution of the '393 patent—to describe the question that the MSI-H Study ultimately "answer[ed]." (Ex. A-10 at ¶ 22 (". . . ***patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated*** with [10 mg/kg of pembrolizumab every 14 days], ***compared with the more common MSS or MMR proficient colon cancers***.") (emphasis added).) JHU's construction is

[18] '393 patent, Claim 14.

not a construction at all, but rather just a circular repetition of the very words that require construction.

The patent claim term requires a comparison because it recites a "reduc[tion]" or an "increase[e]" in specific outcomes, which makes no sense unless it is compared to the same outcome in some other reference patient or group. The proper comparison is found in the intrinsic record, i.e., a comparison between a patient with an MSI-H or dMMR tumor and a patient with an MSS or MMR proficient cancer who are both being treated with pembrolizumab, as was done in the MSI-H Study. *See Genentech, Inc. v. Iancu*, 809 F. App'x 781, 785 (Fed. Cir. 2020) (construing a claim term to require a comparator based on the prosecution history). The specification is directed to the MSI-H Study and its results. (*Supra*, §§ II(A); IV(1).) Further, in arguing for issuance of its patents, JHU continually emphasized the importance of an improved response in a patient with an MSI-H or dMMR tumor compared to a patient with an MSS or MMR proficient cancer. (*Supra*, § IV(1).)

As demonstrated above, the claim language itself requires contextual support from the intrinsic record to identify the proper comparator. If, however, the only comparator found in the intrinsic record and that proposed in Merck's construction is not adopted, then Claim 14 of the '393 patent should be held to be indefinite. "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Dow Chem.*, 803 F.3d at 634. In other words, "a claim term is indefinite if it leaves the skilled artisan to consult the unpredictable vagaries of any one person's opinion." *Id.* at 635 (brackets and quotation marks omitted). Here, if Merck's construction is not adopted and the comparison is not to a patient with an MSS or MMR proficient cancer receiving the exact same treatment, as

was the case in the MSI-H Study, then it begs the question: The risk of cancer progression is being reduced compared to what? In that case, the comparison could be with anyone, such as the same patient receiving the standard of care, some other treatment, no treatment, or some other arbitrary comparator. It goes without saying that the outcome of the comparison depends on the person to whom the comparison is made.

JHU's proposal, that the disputed claim term needs no construction or should be construed as the exact same phrase because the Court and the POSA knows what it means, invites legal error and jury confusion as it does not provide sufficient guidance for assessing issues of infringement or invalidity. *E.g.*, *O2 Micro*, 521 F.3d at 1362 (explaining that simply declaring that the claim "needs no construction" or has the "plain and ordinary" meaning without more may not be enough). JHU's non-construction is problematic because the jury needs to know to whom the comparison is being made.

(3) "reducing the risk of progression of colorectal cancer in a human patient"[19]

Claim Using Term *(Claim 11 of the '287 patent)*	
A method for **reducing the risk of progression of colorectal cancer in a human patient**, the method comprising: in response to determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating a human patient having colorectal cancer that is microsatellite instability high or DNA mismatch repair deficient with a therapeutically effective amount of pembrolizumab, wherein a biological sample from the patient had previously been tested to determine whether the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"the risk of cancer progression of colorectal cancer in a human patient is reduced when compared to a patient with an MSS or MMR proficient cancer" or indefinite	Plain and ordinary meaning, which is "reducing the risk of progression of colorectal cancer in a human patient"

For the same reasons as discussed in Section IV(2), the intrinsic record makes plain that this term requires a comparison between a patient with an MSI-H or dMMR tumor and a patient with an MSS or MMR proficient cancer, both receiving the same pembrolizumab treatment, as in the MSI-H Study, or else the claim term is indefinite.

Merck's proposed construction reflects how the POSA would understand the meaning of the term when read in light of the intrinsic record (i.e., the Patents-in-Suit and their prosecution history). The language of Merck's construction here, as well, tracks the Pardoll Declaration. (Ex. A-10 at ¶ 22 (". . . ***patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated*** with [10 mg/kg of pembrolizumab every 14 days], ***compared***

[19] '287 patent, Claim 11.

with the more common MSS or MMR proficient colon cancers.") (emphasis added); *supra* § IV(2).)

JHU's proposal, that the disputed claim term needs no construction or should be construed as itself because the Court and the POSA knows what it means when they see it, invites legal error and jury confusion as it does not provide sufficient guidance for assessing issues of infringement or invalidity.

(4) "reducing the risk of progression of a solid tumor"[20]

Claim Using Term *(Claim 11 of the '187 patent)*	
A method for **reducing the risk of progression of a solid tumor** selected from the group consisting of: endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, cholangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer and oral cancer that has progressed following at least one prior treatment in a patient, the method comprising: in response to determining that the solid tumor is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab based on previous testing of a biological sample obtained from the patient that the patient's solid tumor exhibits at least one marker for high microsatellite instability or DNA mismatch repair deficiency.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"the risk of progression of a solid tumor, is reduced when compared to a solid tumor that is MSS or MMR proficient" or indefinite	Plain and ordinary meaning, which is "reducing the risk of progression of a solid tumor"

The term requires a comparison because it recites a "reduc[tion]" in a specific outcome, though a specific comparator is not explicitly stated. For the same reasons as discussed in Section IV(2), the intrinsic record makes plain that the term requires a comparison between a patient with an MSI-H or dMMR tumor and a patient with an MSS or MMR proficient cancer,

[20] '187 patent, Claim 11.

both receiving the same pembrolizumab treatment, as in the MSI-H Study, or else the claim term is indefinite.

Merck's proposed construction reflects how the POSA would understand the meaning of the term when read in light of the intrinsic record (i.e., the Patents-in-Suit and their prosecution history). The language of Merck's construction tracks the Pardoll Declaration. (Ex. A-10 at ¶ 22 (". . . ***patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated*** with [10 mg/kg of pembrolizumab every 14 days], ***compared with the more common MSS or MMR proficient colon cancers***.") (emphasis added); *supra* § IV(2).)

JHU's proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means when they see it, invites legal error and jury confusion as it does not provide sufficient guidance for assessing issues of infringement or invalidity.

(5) "reducing the risk of cancer progression or increasing overall survival in a human patient"[21]

Claim Using Term *(Claim 16 of the '491 patent)*	
A method of **reducing the risk of cancer progression or increasing overall survival** in a human patient, the method comprising: testing, or having tested, a biological sample obtained from a patient having endometrial cancer, small bowel cancer, gastric cancer, ampullary cancer, choloangiocarcinoma, pancreatic cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, ovarian cancer, uterine cancer, cervical cancer, bladder cancer, testicular cancer or oral cancer, thereby determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient; and in response to determining that the patient's cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient determined to have microsatellite instability high or mismatch repair deficient cancer with a therapeutically effective amount of pembrolizumab.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"the risk of cancer progression or overall survival in a human patient is reduced or increased when compared to a patient with an MSS or MMR proficient cancer" or indefinite	Plain and ordinary meaning, which is "reducing the risk of cancer progression or increasing overall survival in a human patient"

This term requires a comparison because it recites a "reduc[tion]" or an "increase[e]" in specific outcomes, or else the claim term is indefinite. For the same reasons as discussed in Section IV(2), the intrinsic record makes plain that the term requires a comparison between a patient with an MSI-H or dMMR tumor and a patient with an MSS or MMR proficient cancer, both receiving the same pembrolizumab treatment, as in the MSI-H Study.

Merck's proposed construction reflects how the POSA would understand the meaning of the term when read in light of the intrinsic record (i.e., the Patents-in-Suit and their prosecution history). As above, the language of Merck's construction tracks the Pardoll Declaration. (Ex. A-

[21] '491 patent, Claim 16.

10 at ¶ 22 (". . . ***patients with MSI-high or MMR deficient tumors would exhibit an improved response when treated*** with [10 mg/kg of pembrolizumab every 14 days], ***compared with the more common MSS or MMR proficient colon cancers***.") (emphasis added); *supra* § IV(2).)

JHU's proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion as it does not provide sufficient guidance for assessing issues of infringement or invalidity.

(6) "in response to"[22]

Representative Claim *(Claim 1 of the '393 patent)*	
A method of treating microsatellite instability high or DNA mismatch repair deficient colorectal cancer in a human patient, the method comprising: testing, or having tested, a biological sample obtained from a patient having colorectal cancer, thereby determining that the patient's colorectal cancer is microsatellite instability high or mismatch repair deficient; and **in response to** determining that the colorectal cancer is microsatellite instability high or DNA mismatch repair deficient, treating the patient with a therapeutically effective amount of pembrolizumab.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"as the reaction specifically to"	Plain and ordinary meaning, which is "in response to"

The claim language in context requires that "treating" occur "in response to" some form of "determining." The question for claim construction is, what does it mean, in the context of this medical treatment claim, for such treating to be in response to such determining. Scientific dictionaries are useful for understanding the meaning of "response" in this context—i.e., "a

[22] '393 patent, Claims 1, 14; '287 patent, Claims 1, 11; '462 patent, Claims 1, 11; '187 patent, Claims 1, 11; '491 patent, Claims 1, 16.

reaction, as that of an organism to any of its parts, to a ***specific*** stimulus." (Ex. A-19 at 537 (2011) (emphasis added)). In this way, the response is a reaction specifically to a stimulus.

This construction is consistent with the intrinsic record, which focuses on MSI-H as a determining marker for whether a cancer patient should be treated with pembrolizumab. For example, the specification explains that "[a]ny type of tumor that displays the MSI phenotype or a high mutational burden may be tested and/or treated according to the invention." (Ex. A-5 at 6:16-18; *see also* Ex. A-5 at 13:24-26, 7:18-19, 6:52-56, 5:45-47, 5:51-53 ("The inventors have developed a treatment for cancer patients that display the microsatellite instability phenotype or other high mutational burden"), 5:67-6:2 ("Any tumors that are MSI or otherwise high may be treated according to the invention."); Ex. A-19 at ¶¶ 19-22.)

JHU's proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion about what behavior the claims cover.

(7) "objective response rate (ORR)"[23]

Representative Claim *(Claim 4 of the '974 patent)*	
The method of claim 1, wherein the outcome that is improved is an improved **objective response rate (ORR)**, an improved progression-free survival (PFS), or an improved overall survival (OS).	
Merck's Proposed Construction	**JHU's Proposed Construction**
"the proportion of patients in a research sample who achieved best overall response of complete response or partial response"	"the proportion of patients who achieved best overall response of complete response or partial response"

The phrase "objective response rate (ORR)" is a technical term and the meaning of that term is stated expressly in the patent specification. Merck's proposed construction tracks the

[23] '974 patent, Claim 3; '975 patent Claim 3, 10; '219 patent, Claim 2.

specification's disclosures regarding the use of this term. When referring to the patients in the MSI-H Study, the specification states that "ORR (irORR) **was the proportion of patients who achieved best overall response of CR or PR (irCR or irPR)**."[24] (Ex. A-5 at 14:11-13 (emphasis added).) As the specification provides this explanation in the context of the research sample in the MSI-H Study, the context of a specific study or research sample is also an important element of the specification's disclosure, providing the necessary scope from which the proportion of patients can be measured. (Ex. A-5 at 14:11-19.) Indeed, the specification's next sentence confirms that the context of the MSI-H Study is a key to understanding the overall response rate (ORR): "Patients who were in the study long enough to have tumor response evaluations were included in the analysis for estimating response rates." (Ex. A-5 at 14:13-15.)

While JHU's proposed construction appears to align with the construction proposed by Merck, it fails to explain what the "proportion of patients" would be judged from, which makes JHU's proposed construction indefinite. "The claims, when read in light of the specification and the prosecution history, must provide objective boundaries for those of skill in the art." *Dow Chem.*, 803 F.3d at 630 (quotation marks and brackets omitted); *see also Saso Golf, Inc. v. Nike, Inc.*, 843 F. App'x 291, 296 (Fed. Cir. 2021) ("Because an artisan would not already know the bounds of the toe and heel of a golf club, and because the patent provides no guidance, we hold that claim 7 is indefinite").

For example, under JHU's construction, which does not require a research sample, or any other objective boundaries, the POSA could pick and choose patients after they were administered pembrolizumab and their outcomes were already known. If the POSA then chose

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[24] "CR" and "PR" were abbreviations used in the specification for "complete response" and "partial response," respectively. ('393 patent, at Table 2.) Additionally, the "ír" prefix is an abbreviation used in the specification for "immune-related." ('393 patent, 9:23-27.)

to consider only five patients who responded, that would result in an objective response rate of 100%, while if the POSA instead chose ten non-responders, that would result in an objective response rate of 0%. The specification, instead, like Merck's construction, contemplates choosing patients who are part of a research sample (Ex. A-5 at 14:11-15), i.e., choosing a specific set of patients whose outcomes with pembrolizumab were not known until after they were chosen, and then measuring their objective response rate. JHU's construction should be rejected.

(8) "an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients"[25]

Representative Claim *(Claim 31 of the '393 patent)*	
The method of claim 1, wherein the method results in **an objective response rate of 40% or higher for microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients**.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"a 40% or higher proportion of microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients in a research sample who achieved best overall response of complete response or partial response"	"a 40% or higher percentage of microsatellite instability high or DNA mismatch repair deficient colorectal cancer patients who achieved best overall response of complete response or partial response"

For the same reasons as discussed in Section IV(7), the explicit definition of "objective response rate" in the specification supports Merck's construction of this term, which further adds a specific percentage for the objective response rate in the specified patients.

By the plain language of the term, the objective response rate must be in a group of patients, such as a research sample. The "rate of 40% or higher" is expressly in a group of "patients." And the only guidance in the specification and claims regarding this group is that of

[25] '393 patent, Claims 31, 37; '287 patent, Claims 25, 31.

a sample of patients in a clinical study. (*Supra,* § IV(7); Ex. A-5 at 6:52-22:30, 3:19-21; Figs. 1-13.)

For the same reasons discussed in Section IV(7) above, JHU's proposed construction here fails to explain from which "proportion of patients" the response rate would be judged, which makes JHU's proposed construction indefinite. *Dow Chem.*, 803 F.3d at 630; *see also Saso Golf*, 843 F. App'x at 296.

Under JHU's proposed construction, which lacks objective boundaries, the POSA could pick and choose patients after they were administered pembrolizumab and their outcomes were already known. That *ex post facto* approach could achieve any objective response rate. For example, the POSA could choose only five responders and obtain an objective response rate of 100%, or the POSA could choose ten non-responders and obtain an objective response rate of 0%. The specification, instead, like Merck's construction, clearly contemplates choosing patients who are part of a research sample (Ex. A-5 at 14:11-15), i.e., an approach of choosing patients before knowing their outcomes with pembrolizumab and then measuring their objective response rate. JHU's construction should therefore be rejected.

(9) "population of cancer patients"[26]

Representative Claim *(Claim 23 of the '356 patent)*	
A method for treating cancer in a **population of cancer patients** in need thereof, comprising: administering an effective amount of pembrolizumab to patients in the **population of cancer patients**, which patients have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, said tumor having progressed following a prior treatment; and observing an objective response rate of about 12% to 96% in the **population of cancer patients** after administration of pembrolizumab.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"all cancer patients in the United States" Alternatively: "a group of cancer patients from which a research sample is drawn" or indefinite	Plain and ordinary meaning, which is "population of cancer patients" If the Court finds construction is necessary, "group of cancer patients"

According to this method, someone needs to treat cancer "in a population of cancer patients," where some patients in that population have a certain tumor (exhibiting MSI-H), and then an observation is made about the objective response rate percentage in the population of cancer patients itself (and not just the treated patients in the population). Of course, to do any of this math begs the question of who this population is because the result changes depending on how one defines the population. The language of both of Merck's proposed constructions derives from extrinsic evidence: a medical dictionary that provides the plain meaning of the word "population." Population is defined as "(1) All persons, plants, or animals inhabiting a specified area; (2) The group of persons from which a research sample is drawn." (Ex. A-20 at 1870.) Merck's primary proposed construction, like Taber's first definition, is all persons, i.e., cancer patients, in a specified area, i.e., the United States. Indeed, under Merck's primary proposed

[26] '356 patent, Claims 23, 27.

construction, the bounds of the claim, all cancer patients in the United States, match the fact that these are United States patents. *See* 35 U.S.C. § 271. Merck's alternative proposed construction, like Taber's second definition, is the group of persons, i.e., cancer patients, from which a research sample is drawn.

Merck's construction is consistent with the intrinsic record, including the claims themselves and the specification. ***First***, the claims themselves are broad. ('356 patent, 28:1-11, 18-20.) In Claim 23 of the '356 patent, a subset of patients drawn from "the population of cancer patients" has "a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, said tumor having progressed following a prior treatment." (*Id.*) As such, "the population of cancer patients" should, at the very least, also include some patients having tumors ***without*** an MSI-H or dMMR status.

Second, the specification supports Merck's primary and alternative constructions. When referring to Figures 4A and 4B, the '356 patent specification states that the actual patients in the colorectal cancer cohorts in the MSI-H Study had a characteristic that was "expected in a treatment refractory [colorectal cancer] ***population***." ('356 patent, 4:45-47 (emphasis added).) Based on the specification's language, "population of cancer patients" is thus either bigger than or matches the cohort of patients in the MSI-H Study. Merck's primary construction, "all cancer patients in the United States" is broader than the patients in the MSI-H Study. Merck's alternative construction, "a group of cancer patients from which a research sample is drawn," is more closely aligned with the MSI-H Study population.

Third, as discussed above, extrinsic evidence also supports Merck's primary and alternative constructions.

But if neither Merck's primary nor alternative construction is adopted, then the term should simply be ruled indefinite. *See Dow Chem.*, 803 F.3d at 634; *Teva Pharms. USA, Inc. v. Sandoz, Inc*., 789 F.3d 1335, 1344 (Fed. Cir. 2015). Without set bounds, the POSA could not ascertain with reasonable certainty the specific "population of cancer patients" from which any outcome should be measured. In particular, Claim 23 requires "observing an objective response rate of about 12% to 96% in the population of cancer patients." Thus, if the POSA could not understand who is in the population of cancer patients, the POSA would not be able to understand if any particular results met Claim 23. For example, objective responses in 12 patients would meet the "observing" limitation only if the overall population of cancer patients was between 13 and 100.

JHU's proposal, that the disputed claim term needs no construction because the Court and the POSA knows what it means, invites legal error and jury confusion. It is not proper to hand off to a jury the definition of the claim with no guidance from the Court. And JHU's proposed construction is indefinite for the same reasons the term is indefinite if neither Merck's primary nor alternative construction is adopted, as without additional parameters for the population, the POSA could not ascertain with reasonable certainty the bounds of the "group of cancer patients." For these reasons, JHU's construction should be rejected.

(10) "observing"[27]

Claim Using Term *(Claim 23 of the '356 patent)*	
A method for treating cancer in a population of cancer patients in need thereof, comprising: administering an effective amount of pembrolizumab to patients in the population of cancer patients, which patients have a tumor that exhibits a high microsatellite instability (MSI-high) or a mismatch repair (MMR) deficiency status, said tumor having progressed following a prior treatment; and **observing** an objective response rate of about 12% to 96% in the population of cancer patients after administration of pembrolizumab.	
Merck's Proposed Construction	**JHU's Proposed Construction**
"recognizing and noting a fact or occurrence"	Plain and ordinary meaning, which is "observing"

Without a proposed construction, this claim refers to an undefined entity that is "observing" a mathematical "objective response rate" of a specified percentage in a "population of cancer patients." There is nothing plain or ordinary about the meaning of the term "observing" in this context. Merck's proposed construction is drawn from a dictionary that provides meaning to "observe" in this context—"to make a scientific observation on or of" and "to come to realize or know esp. through consideration of noted facts" (Ex. A-21 at 857 (among several definitions)) and "observation" —"an act of recognizing and noting a fact or occurrence often involving measurement with instruments" (Ex. A-21 at 856-57 (among several definitions)).

This proposed construction is consistent with intrinsic evidence, including the use of "observe" in the specification. In every instance that the specification uses "observe" as a verb, the specification is recognizing or noting a fact or occurrence. (Ex. A-5 at 16:38-45 (". . . four

[27] '356 patent, Claim 23.

objective responses were ***observed*** based on immune-related response criteria . . ."), 17:16-19 (". . . no objective responses were ***observed*** . . . using RECIST criteria . . ."). Likewise, in every instance that the specification uses "observation" as a noun, the specification refers to a fact or occurrence that was recognized or noted. (*E.g.*, Ex. A-5 at 7:40-41 ("Several notable ***observations were made during the course of this study***."), 7:10-17 ("Though our estimates . . . is based only on . . . predictions . . . , this suggestion is consistent with the ***observation*** that . . .") (emphases added).) Similarly, when the specification uses "observed" as a past participle or adjective, it refers to a fact or occurrence that was noted or recognized. (Ex. A-5 at 2:9-14; 6:54-58.)

The claims of the '356 patent also support that "observing" means "recognizing and noting a factor or occurrence." For example, Claim 23 of the '356 patent requires "observing . . . an objective response rate of about 12% to 96%." ('356 patent, 28:9.) An objective response rate of "about 12% to 96%" is a statistical, quantitative range that cannot be determined without noting specific facts and occurrences. Additionally, '356 patent, Claims 1, 11, and 19 require "determining . . . a corresponding outcome that would be ***observed*** in a reference patient that has been administered pembrolizumab." ('356 patent, Claims 1, 11, 19) (emphasis added). In other words, these claims require recognizing or noting the occurrence of an outcome in a reference patient.

JHU's proposal, that the disputed claim term needs no construction, gives no help to the jury and invites legal error and jury confusion. JHU's non-construction should, therefore, be rejected.

V. CONCLUSION

Merck respectfully requests that the Court adopt its constructions or find that the terms are indefinite, which are consistent with what the law and the patents' intrinsic records require.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that a copy of the foregoing was served on all counsel of record via the Court's CM/ECF system, in accordance with the rules of electronic filing of documents on this 1st day of May, 2024.

/s/
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