IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO, Plaintiffs, v. MERCK & CO., INC. and MERCK SHARP & DOHME CORP., Defendants.	)	C.A. No. 1:14-cv-01131-GMS
BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO, Plaintiffs, v. MERCK & CO., INC. and MERCK SHARP & DOHME CORP., Defendants.	)	C.A. No. 15-cv-00560-GMS
BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS, L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO, Plaintiffs, v. MERCK & CO., INC. and MERCK SHARP & DOHME CORP., Defendants.	)	C.A. No. 15-cv-00572-GMS

DEFENDANTS' RESPONSIVE CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

The claim constructions proposed by Defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. (collectively, "Merck") comport with the intrinsic evidence and are scientifically accurate. Plaintiffs' proposed constructions, on the other hand, fail to resolve the disputes between the parties, construe words in isolation and divorced from the specification, and are scientifically inaccurate. Accordingly, Merck's proposed constructions should be adopted.

II. DISPUTED CONSTRUCTIONS

A. "[for treatment of / of treating] a [tumor / melanoma / lung cancer / metastatic melanoma]" (all asserted '474, '999, and '994 claims)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"The act or manner of treating a [tumor, melanoma, lung cancer, or metastatic melanoma]."	**"to reduce proliferation or metastasis of cancer cells in the [tumor / melanoma / lung cancer / melanoma and melanoma metastases]"**

The heart of this dispute is whether to adopt a construction that explains what "treatment" of a type of cancer by administering an "anti-PD-1 antibody" means.[1] Plaintiffs seek to avoid providing such a construction -- their proposed construction is simply "the act or manner of treating." Plaintiffs' Opening Claim Construction Brief ("Plaintiffs' Opening Brief") at 5. But employing that circular definition in this case will create intractable problems for the jury, the parties, and the Court. That is because these asserted claims, unlike conventional pharmaceutical treatment claims, do not define any particular agents to be used in the claimed methods, either by

[1] Merck explained in its opening brief why the preambles of the asserted independent claims are limiting. *See* Defendants' Opening Claim Construction Brief ("Merck's Opening Brief") at 7-8. Plaintiffs do not assert in their opening brief that the preambles of the independent claims are not limiting. Accordingly, any such arguments in Plaintiffs' responsive brief should be disregarded. *See* L.R. 7.1.3(c)(2) ("The party filing the opening brief shall not reserve material for the reply brief which should have been included in a full and fair opening brief.").

name or by identifying properties those agents must possess to render them useful in the claimed treatment methods. Instead, the claims define these agents entirely by reference to the effect they cause in a patient -- the claimed "anti-PD-1 antibodies" are those that treat the specified manifestation of cancer in the patient (e.g., a "tumor" or a "melanoma"). Because the claims depend on the meaning of "treatment" to define the essential features of the anti-PD-1 antibodies that are used in the claimed methods, something more than a circular definition of "treatment" is required.

The Federal Circuit has recently confirmed that the courts need to construe terms the parties dispute and, in those circumstances, may not simply adopt the often nebulous "plain and ordinary meaning" of such terms. *See Eon Corp. IP Holdings LLC v. Silver Spring Networks, Inc.*, No. 2015-1237, 2016 WL 766661 (Fed. Cir. Feb. 29, 2016). There, the terms in dispute were "portable" and "mobile." The plaintiff asserted these terms should be given their plain and ordinary meaning, while the defendant asserted the terms did "not cover fixed or stationary products that are only theoretically capable of being moved." *See id.* at *2. The district court sided with plaintiff, resulting in a battle of the experts at trial over the meaning of these terms. *See id.* On appeal, the Federal Circuit held that the duty of the district courts is to "resolve a dispute about claim scope that has been raised by the parties" and "to provide the jury with a clear understanding of the disputed claim scope." *See id.* at *4.

That precise situation is presented here -- adoption of Plaintiffs' proposed construction would neither resolve the dispute between the parties, nor would it provide the jury with a clear understanding of the scope of the disputed claim term. Adoption of Plaintiffs' proposed construction would certainly result in a battle of the experts down the road when the parties

address infringement, prior art, enablement and written description because "treatment" would be undefined and therefore subject to manipulation by the parties and their experts.

Plaintiffs' construction, coupled with the absence within the claims of any other objectively defined properties or effects of the administered anti-PD-1 antibodies, creates a host of unanswerable questions for the Court and the jury. For example, (under Plaintiffs' construction) would the claims encompass administration of any antibody that binds to PD-1 or only certain antibodies that bind to PD-1? If the latter, which antibodies? Likewise, do the claims encompass administration of an antibody that binds to PD-1 and has some sort of effect on the cancer cells or the tumor or the patient? If so, what effect and how much of that effect is required? Do the claims require that the individual who administers the antibody have some sort of expectation that the antibody will have an effect on the cancer cells or the tumor or the patient? And, if so, what effect and how much of that effect is required? Likewise, do the claims require that the patient is cured? Do the claims require that the tumor disappears? Do they require that the cancer cells are no longer detectable? Or do the claims require something else?

Adoption of Plaintiffs' proposed construction would leave all of these questions unanswered and ultimately to be addressed by experts, who would supply their own understanding of what it means to "treat" in the context of these patents. There is no need for this ambiguity because the specification clearly defines what treatment means: it means that administration of anti-PD-1 antibodies causes the immune system to reduce the proliferation or metastasis of the cancer cells. *See, e.g.*, '474 Patent at col. 2:62-67 (noting that anti-PD-1 antibodies "inhibit cancer proliferation."); *see also* Merck's Opening Brief at 9-11. Accordingly, Merck respectfully submits that its construction be adopted.

Plaintiffs attack Merck's proposed construction on several grounds, none of which has merit. Relying on cases addressing different patents about different technologies with different claims, specifications and file histories, Plaintiffs assert there is a plain and ordinary meaning of the "treatment" terms in the claims and that plain and ordinary meaning does not require efficacy. Plaintiffs' Opening Brief at 6. Neither argument is relevant here.

First, as discussed above, the Federal Circuit has made clear that courts cannot adopt a nebulous "plain and ordinary meaning" when the parties dispute the scope of the claim.

Second, the Federal Circuit has made clear that "[t]he only meaning that matters in claim construction is the meaning in the context of the patent." *Trustees of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016). Here, that meaning is clear from the intrinsic evidence -- treatment is an effect that is observed on the cancer cells when the anti-PD-1 antibody is administered to the patient (i.e., the patient's immune system reduces the proliferation or metastasis of those cancer cells). There also is no prohibition against construing treatment claims in this manner. *See Gilead Sciences, Inc. v. Mylan Inc.*, 107 F. Supp. 3d 541, 560 (N.D. W. Va. 2015) (construing treatment term to mean "treatment of the symptoms or effects of an HIV infection that is therapeutically effective"). Indeed, "treatment" is the only term in the asserted claims that provides any insight into the required properties of the anti-PD-1 antibodies that are administered to the patient. Adopting Plaintiffs' construction would effectively strip that single insight away.

Plaintiffs also contend that Merck's construction demands "efficacy." It does not. Merck's construction simply identifies the functional property identified in the intrinsic evidence that anti-PD-1 antibodies possess which gives them utility in the claimed methods. Merck's construction also uses the term "reduces" in connection with "proliferation" to make clear that an

absolute therapeutic endpoint in every patient is not required. All that is required under Merck's construction is less proliferation or metastasis of the cancer cells occurs in the patient relative to what would occur if the patient were not administered the anti-PD-1 antibody, the same metric the patent disclosure relies on to contend its methods will treat various types of cancer.

Plaintiffs also argue that additional language in some of the claims demonstrates that the "treatment" terms cannot be read as requiring proof of an effect. For example, relying on *Novartis Pharms. Corp. v. Actavis, Inc.*, No. 12-366-RGA-CJB, 2013 U.S. Dist LEXIS 165317 (D. Del. Nov. 21, 2013), Plaintiffs assert that because certain claims also include "effective amount" limitations, the "treatment" limitations cannot be tied to any efficacy criteria in the patient. *See* Plaintiffs' Opening Brief at 7-8. *Novartis* does not support Plaintiffs' arguments. There, the court ruled that "treatment" limitations required something more than mere administration of the claimed compound. *Novartis*, 2013 U.S. Dist LEXIS 165317, at *38-39. By contrast here, Plaintiffs' proposed construction does not require anything other than administration of the anti-PD-1 antibody.

Plaintiffs also point to dependent claims 12 and 13 of the '474 patent and assert those claims would be superfluous if the "treatment" terms are given Merck's proposed constructions. *See* Plaintiffs Opening Brief at 8. Not so. Merck's proposed construction simply requires a *reduction* in proliferation or metastasis of the cancer cells, whereas claims 12 and 13 both require that proliferation or metastasis be *suppressed*. In other words, claims 12 and 13 require achieving a higher threshold -- that tumor proliferation or metastasis be held in check or prevented. Under Merck's construction, the independent claims plainly set a lower bar than these dependent claims. Additionally, claim 1 encompasses both tumor proliferation and metastasis.

On the other hand, claim 12 is limited to tumor proliferation and claim 13 is limited to tumor metastasis. Accordingly, Plaintiffs' claim differentiation arguments are unavailing.

Finally, Plaintiffs argue that Merck is attempting to read into the claims a specific restriction on how effectiveness is measured because, according to Plaintiffs, the specification identifies additional methods for determining effectiveness. *See* Plaintiffs' Opening Brief at 8-9. The specification does not support this argument. To the contrary, the specification equates "treatment" with the reduction or suppression of the proliferation or metastasis of the cancer cells. Indeed, the very first sentences in the disclosure of the invention make this clear:

> A problem of the present invention is to provide compositions to activate immunity by inhibiting the inhibitory signals of PD-1, PD-L1 or PD-L2 and compositions for cancer or infection treatment through this mechanism.
>
> The present inventors paid attention to PD-1, PD-L1, or PD-L2 as a new target in cancer or infection *treatment* and found that substances that inhibit the inhibitory signals of PD-1, PD-L1 or PD-L2 *inhibit cancer proliferation* through the mechanism of the recovery and activation of immune function.

'474 Patent at col. 2:58-67 (emphasis added). Example 5 of the '474 patent also expressly relates "treatment" to reduced proliferation of cancer cells. Specifically, that example concludes:

> The transplanted tumor cells *proliferation was completely inhibited* in PD-1-deficient mice to which J558 cells had been transplanted (FIG. 5(c)). These results present that inhibition of PD-L1 or PD-1 is *effective on cancer treatment*.

'474 Patent at col. 20:51-55 (emphasis added).

Plaintiffs nonetheless argue that the specification measures effectiveness in ways such as "life prolongation of an individual," suppression of "invasion" or "tumor growth and the survival rate." Plaintiffs' Opening Brief at 8-9.[2] But prolongation of life, suppression of invasion and

[2] Plaintiffs largely rely on examples 2 and 3 and corresponding figures 2 and 3. *See* Plaintiffs' Opening Brief at 8-9. Notably, however, those examples do not involve the administration of an anti PD-1 antibody. Example 2 describes experiments in which cancer cells – some of which

suppression of tumor growth are all the downstream result of reducing the proliferation or metastasis of cancer cells, not an independent means of determining whether treatment is effective. *See* Declaration of Dr. Ulrich von Andrian, Case No. 1:14-cv-01131, D.I. 83; Case No. 15-cv-00560, D.I. 50; Case No. 15-cv-00572, D.I. 50 ("UVA Dec.") at ¶ 36 ("If left unchecked, cancer cells can proliferate indefinitely, invading other tissues, impairing organ function, and ultimately causing death."); *see also* '474 Patent at col. 19:63-67 (explaining that in some test mice proliferation was suppressed and the test mice survived whereas in other test subjects proliferation was "remarkable" and the test mice died); *id.* at col. 20:20-26 (explaining that suppression of carcinoma cell growth resulted in longer survival). And, of course, the patent disclosure identifies no mechanism other than effects on proliferation and metastasis of the cancer cells as being the source of these possible therapeutic benefits.

In any event, if Plaintiffs were correct that "treatment" could be any of these things, that is a reason to construe the term, not a reason to leave it undefined. Plaintiffs should not be allowed to argue through experts at trial that the prior art is different because it does not "prolong life," while arguing that the accused method meets the claims because it reduces tumor proliferation. Plaintiffs' own arguments underscore the need for claim construction.

Accordingly, Merck respectfully requests that the Court adopt its constructions.

B. "treats the [lung cancer / metastatic melanoma]" (all asserted '999 and '994 claims)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"The act or manner of treating a [lung	**"reduces proliferation or metastasis of**

expressed PD-L1 and some of which did not -- were transplanted into mice. *See* '474 Patent at col. 19:47 – 20:3. None of the mice were administered anti-PD-1 antibodies. *See id.* Example 3 involved the administration of an anti-PD-L1 antibody, not an anti-PD-1 antibody. *See* '474 Patent at col. 20:5-26.

cancer / metastatic melanoma]."	**cancer cells in the [lung cancer] / [melanoma and melanoma metastases]"**

Plaintiffs do not separately address the "treats" limitation in the body of the claims of the '999 and '994 patents. Regardless of the meaning of the "treat" terms in the preambles of the asserted independent claims, the claims of the '999 and '994 patents contain the additional limitation that states "*wherein* the administration of the composition *treats* the lung cancer in the human" (claim 1 of the '999 patent, emphasis added) or "*wherein* the administration of the composition *treats* the metastatic melanoma in the human" (claim 1 of the '994, emphasis added). These declaratory statements are definitive and require a particular result, i.e., reduction in the proliferation or metastasis of cancer cells. These phrases would be rendered meaningless if they did not require efficacy. Plaintiffs have cited no evidence to the contrary. Accordingly, Merck respectfully requests that the Court adopt its constructions.

C. "pharmaceutically effective amount" (all asserted '474 claims) / "effective amount" (all asserted '994 claims)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"An amount sufficient to exert the pharmacological action of the drug."	**"amount sufficient to reduce proliferation or metastasis of cancer cells in the [tumor / melanoma / metastatic melanoma and melanoma metastases]"**

The underlying problem with Plaintiffs' failure to construe the "treat" terms is made even more apparent by Plaintiffs' proposed construction of the "effective amount" terms. Without a construction of the "treat" terms, Plaintiffs' proposed construction of the "effective amount" terms makes no sense because one does not know what the "pharmacological action" of the "drug" is and, accordingly, one does not know how much of that "drug" is sufficient to exert the unspecified "pharmacological action." Thus, once again, adoption of Plaintiffs' proposed

construction will result in the parties and the experts disputing the meaning of this term throughout the litigation.

Indeed, the very case law that Plaintiffs cite makes clear that a meaningless construction such as that proposed by Plaintiffs is inappropriate. Those cases adopt constructions that actually describe the pharmacological action caused by the agent being administered -- which none of the asserted claims identifies other than indirectly via the claim language specifying that the agent treats the manifestation of cancer in the patient. *See, e.g., Sanofi v. Glenmark Pharms. Inc.*, No. 14-264-RGA, 2015 U.S. Dist. LEXIS 114406, at *15 (D. Del. Aug. 28, 2015) (construing the term "effective amount" to mean "an amount effective to decrease a risk of cardiovascular hospitalization."); *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1277 (Fed. Cir. 2003) (noting that "effective amount" meant "the amount of Lewis acid inhibitor that will prevent the degradation of sevoflurane by a Lewis acid").[3]

Merck's proposed construction comports with the intrinsic evidence demonstrating that the purpose of the claimed method is to reduce proliferation or metastasis of cancer cells in a tumor ('474 patent claim 1), a melanoma ('474 patent claim 8), or a metastatic melanoma ('994 patent claim 1). Accordingly, Merck respectfully requests that the Court adopt its constructions.

[3] *Merck Sharp & Dohme Corp. v. Xellia Pharms. ApS*, No. 14-199-RGA, 2015 U.S. Dist. LEXIS 753, at *11 (D. Del. Jan. 6, 2015), where the court simply adopted the plain and ordinary meaning, is not persuasive in light of the Federal Circuit's recent decision in *Eon Corp. IP Holdings LLC v. Silver Spring Networks, Inc.*, No. 2015-1237, 2016 WL 766661 (Fed. Cir. Feb. 29, 2016).

D. "binds to . . . PD-1" (claims 2–5, 9, 12, 13 of the '474 patent)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"To form a direct interaction with PD-1."	**"interacts with . . . PD-1"**

The parties agree that "binds to" means that the antibody "interacts" with PD-1. The dispute is whether an additional label is needed to describe the nature of this interaction. The answer is no, particularly not the additional label Plaintiffs have proposed.

Plaintiffs' proposal – that binding means forming a "direct" interaction with PD-1 – has no support in the intrinsic record and is scientifically confusing.

First, the '474 patent nowhere describes antibody binding as being a "direct" interaction between an antibody and an antigen. Indeed, the word "bind" is never modified by the word "direct" in either the claims or the specification. Moreover, where the '474 patent does refer to how antibodies can vary with respect to their binding properties, it uses different terms. For example, the patent uses terms like "selectively" or "specificity" when describing different aspects of antibody binding. *See, e.g.,* '474 Patent at col. 5:12-14 ("A substance that *selectively binds* to PD-1, PD-L1 or PD-L2…") (emphasis added); *id.* at 5:18-19 ("Especially, an antibody to PD-1, PD-Ll or PD-L2 is enumerated as an excellent substance in *specificity*.") (emphasis added).

The phrase "direct interaction" also introduces confusion. For example, the meaning of the phrase "direct interaction" would not be used by scientists to describe how antibodies bind to antigens. Instead, a scientist would use terms like "specificity," "selectivity" or "affinity" to characterize the nature of antibody binding to an antigen, and "direct interaction" does not have a meaning that correlates to any of these terms. This was succinctly explained by Dr. von Andrian at his recent deposition in response to questions from Plaintiffs' counsel involving an analogous

type of protein-protein interaction that occurs when an antigen presenting cell interacts with an activated T cell:

> Q. And the specificity, selectivity and high affinity comes from the direct interaction between the T cell receptor and the MHC?
>
> MR. KUSHAN: Objection; foundation; relevance; outside the scope of the direct testimony.
>
> A. I would not agree to that statement. Many things can directly interact with other things but without any specificity or selectivity.

Deposition of Ulrich H. von Andrian, M.D., Mar. 18, 2016 ("UVA Dep."), Exhibit 1, at 102:13-21. In other words, as Dr. von Andrian explained, two molecules may "directly" interact (e.g., via "direct" contacts between the atoms in each molecule) but that interaction may be both non-specific and non-selective, terms no one would associate with the type of binding that is characteristic of an antibody. The term "direct" thus adds nothing of relevance to the term "interact."

This also explains why the two passages of the '474 patent quoted by Plaintiffs in their opening brief prove nothing. The first quote concerns agents that can include anti-PD-1 antibodies, and employs two terms – "selectively binds" and "specificity" –to describe the functional properties of those agents. *See* Plaintiffs' Opening Brief at 13. Critically, neither term is or means "direct interaction." Indeed, these are the same two terms used by Dr. von Andrian to differentiate binding that is characteristic of an antibody from non-specific and non-selective "direct interactions" that can occur between two molecules.

The second quote does not concern antibodies -- it refers to *naturally occurring* proteins that bind to PD-1 (i.e., those that "include an extracellular region which is necessary and sufficient to bind to PD-1"). *See* Plaintiffs' Opening Brief at 14. In other words, this passage is

discussing proteins such as PD-L1 and PD-L2 or fusion proteins made with portions of those proteins. And again, there is no reference in this passage to "direct" or any other type of interaction.

The label "direct" thus at best is unhelpful, and at worst is confusing, in describing the nature of the interaction between an antibody and PD-1.

In this respect, the lack of any explanation in the patent disclosure of what "direct" (as opposed to 'indirect") interactions are condemns Plaintiffs' proposed construction. For example, would non-specific interactions between an anti-PD-1 antibody and PD-1 that nonetheless involve "direct interactions" between the two molecules be enough? Likewise, would interactions between the antibody binding site and sugar residues on the PD-1 protein (as opposed to amino acid residues in that protein) qualify as a "direct" or an "indirect" interaction? *See, e.g.*, Plaintiffs' Opening Brief Exhibit B, at 102 ("Some of the most important pathogens have polysaccharide coats, and antibodies that recognize epitopes formed by the sugar subunits of these molecules are essential in providing immune protection from such pathogens."). These questions are unnecessary and arise only by adopting Plaintiffs' arbitrarily narrow definition of "interaction."

There simply is no basis for limiting the nature of binding between the claimed antibodies and PD-1 to those involving a "direct" interaction, especially where the word "direct" is scientifically imprecise and would lead to further disputes about the meaning of the construction. Accordingly, Merck respectfully requests that the Court adopt its constructions.

E. "tumor proliferation" (claim 12 of the '474 patent)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"Increase in the number of tumor cells."	**"the increase in the number of cancer cells in the tumor"**

Plaintiffs argue that "tumor proliferation" means an "increase in the number of tumor cells," pointing to several passages in the specification of the patents-in-suit. But none of the passages cited by Plaintiffs support this construction. For example, Plaintiffs point to the '474 patent and column 10, lines 27-31, which states that "*cellular* proliferation *can be evaluated* as the number of carcinoma cells per unit capacity in case of ascites tumors or blood cancers, or the size or the weight after removing in case of solid cancer." *See* Plaintiffs' Opening Brief at 15 (emphasis added). But all this passage provides is that one can evaluate whether cells have proliferated using indirect methods, such as measuring the size of the tumor. It does not mean that one of ordinary skill in the art would understand tumor proliferation to mean an increase in the number of tumor cells, as opposed to an increase in the number of *cancer* cells in the tumor. *See* UVA Dec. at ¶¶ 35-38. The other passages relied upon by Plaintiffs similarly prove nothing more than that overall tumor growth can be used as a proxy for tumor proliferation. *See* Plaintiffs Opening Brief at 15.

This is not surprising because, as Dr. Ulrich von Andrian has explained, a person of ordinary skill in the art would not understand "tumor proliferation" to mean an increase in any of the cells found in a tumor. *See* UVA Dec. at ¶¶ 34-38. As Plaintiffs concede, tumors are made up of a variety of cell types. *See* Plaintiffs' Opening Brief at 15-16. It is the cancer cells within the tumor that cause health risks. *See* UVA Dec. at ¶ 37. Thus, it is the cancer cells that treatments, such as those described in the specifications of the patents-in-suit, target.

Plaintiffs' proposed construction also cannot be reconciled with the fact that tumors also contain "good" cells. For example, tumors contain immune system cells, such as T cells, which proliferate within a tumor in order to kill cancer cells. *See* UVA Dec. at ¶ 31. A person of ordinary skill in the art would not understand such helpful activity to constitute "tumor proliferation"—and certainly would not want to suppress it, as required by claim 12—because increasing the number of T cells and other immune cells attacking the tumor is the very purpose of the alleged inventions of the patents-in-suit. *See* '474 Patent at col. 2:58-67.

There is no thus scientific basis for including proliferation of non-cancerous cells within the meaning of "tumor proliferation." Accordingly, Merck respectfully submits that its proposed construction of this term be adopted.

F. "tumor metastasis" (claim 13 of the '474 patent)

Plaintiffs' Proposed Construction	*Merck's Proposed Construction*
"The spread of cancer cells from a primary site of disease to other parts of the body."	**"the development of a tumor derived from the primary tumor at a location outside the primary tumor site"**

Plaintiffs argue that "tumor metastasis" simply means the spread of cancer cells from one site to another part of the body, without requiring the development of another tumor, but provide no intrinsic or extrinsic evidence to support that proposed construction.

Initially, none of the passages in the disclosure cited by Plaintiffs supports adoption of their scientifically flawed definition of tumor metastasis. For example, Plaintiffs point to the phrase "administration of anti-PD-1 antibody significantly suppressed metastasis of imported carcinoma cells to liver in the cancer imported animal model." Plaintiffs Opening Brief at 16-17. But that phrase fails to suggest that metastasis does not require formation of a secondary tumor; it does not explain what metastasis is, only that it is supposedly suppressed. Plaintiffs also point

to language in the specification indicating that metastasis can be determined by histological analysis of the cells. *See id.* at 17. But again, this language in no way suggests metastasis does not require formation of a secondary tumor – it just indicates that one method of analyzing whether metastasis has occurred is through histological analysis. Finally, Plaintiffs point to Example 2 of the patents-in-suit. *See* Plaintiffs Opening Brief at 17. But, as explained in Merck's opening brief, that example actually demonstrates that formation of a secondary tumor is required for metastasis. *See* Merck's Opening Brief at 17.

Merck's proposed construction of "tumor metastasis" is the scientifically accurate construction that would be recognized by a person of ordinary skill in the art. Indeed, Merck submitted a declaration from an expert in the field explaining that tumor metastasis refers to the development of a tumor at a location other than the primary tumor site. *See, e.g.,* UVA Dec. at ¶ 40; *see also* UVA Dep., Exhibit 1 at 20:3-7 (confirming term means "the spreading of cancer cells from a primary tumor to a distant part in the body where it forms a secondary tumor."); *id.* at 29:1-4 (noting that "[m]etastasis is a process whereby cells leave a site of origin, a primary tumor, and are transported away to a different part in the body where they lodge and form a secondary tumor.").[4] Accordingly, Merck respectfully requests that its proposed construction of this term be adopted.

[4] As is not unusual, definitions of this term exist that are accurate, albeit incomplete. For example, saying metastasis is the spread of cancer cells or the movement of cells from one part of the body to another or involves invasion are all accurate but incomplete definitions of metastasis. *See* U. von Andrian Dep., Exhibit 1 at 35:2-17. The Albert's textbook provides an example of this. The glossary of that textbook generically defines metastasis as the spread of cancer cells from one portion of the body to another. However, the detailed discussion in that textbook demonstrates that, in the context of cancer, metastasis requires formation of a secondary tumor. *See* UVA Dec. at ¶¶ 40, 44.

G. "expresses [PD-L1/PD-L2]" (claims 19-20, 24-27, 29-30 of the '999 patent; claims 14-15, 19-20, 25-26 of the '994 patent); "[PD-L1/PD-L2] expression" (claims 26-27, 29-30 of the '999 patent; claims 25-26 of the '994 patent)

Plaintiffs' Proposed Constructions	*Merck's Proposed Constructions*
"produces a product of the [PD-L1/PD-L2] gene" **"production of a product of the [PD-L1/PD-L2] gene"**	**"produces a detectable amount of [PD-L1/PD-L2] protein"** **"production of a detectable amount of [PD-L1/PD-L2] protein"**

The dispute here centers on whether this term refers to production by the cancer cells of the PD-L1 or PD-L2 proteins (as Merck proposes) or whether it refers expansively to production of any (or all) products of a gene. Merck also contends that the PD-L1/PD-L2 protein expression must be detectable, while Plaintiffs construction would encompass *undetectable* expression of PD-L1 or PD-L2 gene products, which will be impossible to prove or disprove. Plaintiffs' construction thus would not only improperly sweep into the claims expression of things other than the recited proteins, PD-L1 or PD-L2, it makes the claim element an effective nullity because it does not require a detectable amount of expression.

It is a bedrock principal that the claims themselves "provide substantial guidance to the meaning of particular claim terms." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (citations omitted). Here, the claims use the terms "PD-L1" and "PD-L2." "PD-L1" and "PD-L2" are proteins known as ligands. *See* '474 Patent at col. 2:13-22 ("PD-L1 . . . that is a ligand of PD-1 is expressed in so-called antigen presenting cells . . . . [] . . . PD-L1 is one of these molecules that induce the inhibitory signal by PD-1."), 2:33-37 ("Though PD-L2 . . . had been identified as a second ligand of PD-1, it has been reported that the expression and function are almost same as PD-L1"). The claims require expression of the proteins "PD-L1" or "PD-L2" and, accordingly, resolve the dispute between the parties. *See* UVA Dep., Exhibit 1 at 121:23 –

122:1 ("I think in the context of expressing PD-L1 or PD-L2 it means in the presence of the protein because that's what PD-L1 and PD-L2 are.").

Cells make proteins using genes that encode the amino acid sequence of the protein. During that process, a number of intermediary molecules are created, most notably messenger RNA sequences that encode the amino acid sequence of the PD-L1 or PD-L2 protein.[5] Messenger RNA (mRNA) molecules are not called PD-L1 or PD-L2; those terms refer to proteins. And mRNA molecules do not interact with the PD-1 receptor or cause inhibitory signaling via that receptor.

Plaintiffs point to language in the specification indicating that expression can be identified by using RT-PCR and note that RT-PCR is typically used to detect mRNA. *See* Plaintiffs' Opening Brief at 18-19. There is no dispute that scientists, on occasion, look at mRNA levels when studying expression of a gene. But Plaintiffs ignore that the term "expression" as used in the claims at issue refers to *proteins* – the claims specify the cancer cells express either PD-L1 and PD-L2. The claims do not say the cells express the PD-L1 or PD-L2 genes. Likewise, the claims refer to no product of expression of the PD-L1 or PD-L2 gene other than the PD-L1 or PD-L2 protein -- they do not, for example, refer to mRNA or any other "gene" product. Indeed, where the inventors of the patents-in-suit intended to refer to the nucleic acids

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[5] As the Federal Circuit has explained:

> In general, when a compound activates a signal transduction pathway, the cell responds by directing the production or non-production of a protein from a responsive gene in the DNA. Protein production involves two distinct processes--transcription and translation. Transcription refers to the process by which a strand of messenger RNA ("mRNA") is created by the expression of a gene. Translation refers to the process by which a corresponding protein (i.e., a sequence of amino acids) is created from the mRNA.

See, e.g., *Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1352 (Fed. Cir. 2000).

encoding the PD-L1 and PD-L2 proteins, they did so explicitly. *See* '474 Patent at cols. 2:13 ("human PD-L1 cDNA"), 2:15 ("mouse PD-L1 cDNA"), 2:33 ("human PD-L2 cDNA"), 2:35 ("mouse PD-L2 cDNA"). Similarly, where the inventors of the patents-in-suit intended to refer to mRNA corresponding to PD-L1 and PD-L2, they did so explicitly. *See* '474 Patent at col. 8:43 ("mRNA of PD-1, PD-L1, or PD-L2"). If the inventors of the patents-in-suit had intended the phrase "cancer cell expresses PD-L1/PD-L2" refer to any product of the gene that encodes PD-L1 or PD-L2, such as mRNA, they could have drafted their claims differently to recite, for example, "expresses a product of the PD-L1 gene" or "expresses mRNA encoding PD-L1." Instead, however, they wrote the claims in such a way to limit those claims to expression of the proteins "PD-L1" and "PD-L2," as reflected in Merck's proposed construction.

Plaintiffs also argue that the expressed PD-L1 or PD-L2 need not be detectable. The claims plainly require expression to be detectable. Plaintiffs' argument begs the question: if the expressed PD-L1 or PD-L2 is not detectable, how does one know whether or not the claim is infringed? Absent a requirement that there be at least a detectable amount of protein, there is no way to know. *See* UVA Dep., Exhibit 1 at 122:2-4 (noting that expression is detected by looking for the protein). Merck's proposed construction avoids this ambiguity and, therefore, Merck respectfully submits that it should be adopted.

III. CONCLUSION

Merck respectfully requests that the Court adopt its proposed constructions and find that the preambles of the asserted independent claims are limiting.

Dated: March 28, 2016

McCARTER & ENGLISH, LLP

/s/ Daniel M. Silver
Michael P. Kelly (#2295)
Daniel M. Silver (#4758)
Benjamin A. Smyth (#5528)
405 N. King St., 8th Floor
Wilmington, DE 19801
(302) 984-6300
mkelly@mccarter.com
dsilver@mccarter.com
bsmyth@mccarter.com

Counsel for Defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp.

Of Counsel:

David T. Pritikin
William H. Baumgartner, Jr.
Lisa A. Schneider
Gwen Hochman Stewart
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, IL 60603
(312) 853-7000
dpritikin@sidley.com
wbaumgartner@sidley.com
lschneider@sidley.com
gstewart@sidley.com

Jeffrey P. Kushan
Fitz B. Collings
Kirsten E. Braun
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, D.C. 20005
(202) 736-8000
jkushan@sidley.com
fcollings@sidley.com
kbraun@sidley.com

Todd L. Krause
Grace I. Chiang
SIDLEY AUSTIN LLP
787 Seventh Avenue
New York, NY 10019
(212) 839-5300
tkrause@sidley.com
gchiang@sidley.com

EXHIBIT 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELWARE
C.A. No. 14-cv-1131-GMS
C.A. No. 15-cv-560-GMS
C.A. No. 15-cv-572-GMS

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BRISTOL-MYERS SQUIBB CO., E.R. SQUIBB & SONS, LLC, ONO PHARMACEUTICAL CO., LTD, and TASUKU HONJO,

Plaintiffs,

vs.

MERCK & CO., INC. AND MERCK SHARP & DOHME CORP.,

Defendants.

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VIDEOTAPED DEPOSITION OF ULRICH H. VON ANDRIAN, M.D.

Friday, March 18, 2016, 9:04 a.m.

Sidley Austin
60 State Street
Boston, Massachusetts

------ David Arsenault, RPR, CSR ------

that have a special meaning in the art?
A. Yes.
Q. What's the special meaning of the term tumor metastasis?
A. That is the spreading of cancer cells from a primary tumor to a distant part in the body where it forms a secondary tumor.
Q. How about the term expresses PD-L1, does that have a special meaning in the art?
A. Yes.
Q. What does that mean?
A. It refers to a cell having on its surface a protein that would be defined as PD-L1.
Q. I take it the same would be true for PD-L2 expression?
A. That's correct.
Q. For the term tumor proliferation, were you asked to determine what that term meant in the context of the claims in the specification?
A. Yes.
Q. Can you identify where in your report you talk about which claims you used to determine what the meaning of tumor proliferation is?
A. I would have to go to my declaration to find that.

Metastasis is a process whereby cells leave a site of origin, a primary tumor, and are transported away to a different part in the body where they lodge and form a secondary tumor.

Q. So metastasis starts with the migration of cells from a primary tumor, right?

MR. KUSHAN: Objection; mischaracterizes his testimony.

A. So may I go back to my declaration to make sure I don't make a mistake in answering this question?

Q. Sure.

A. In Paragraph 41 I state the process of metastasis begins with cancer cell migration. Some cancer cells in a tumor possess the ability to move and detach from the surrounding cells and extra-cellular matrix. So that addresses, I believe, your question.

Q. So is it fair to say that metastasis starts with the migration of cells from a primary tumor?

A. It starts with that, yes. But that is not the entire process defining metastasis. That's just the first step in it.

Q. What is it about the cancer cells that allow them to migrate from the primary tumor?

A. I don't know one way or the other.
Q. Is it fair to say that metastasis is the spread of cancer cells from their site of origin to other sites in the body?
A. That statement is accurate but incomplete.
Q. Is it fair to say that metastasis is the movement of body cells from one part of the body to another?
A. The same. This statement describes part of the metastasis process, but it is incomplete.
Q. So there's a verb, metastasize -- right? -- that applies to the process?
A. Yes, that is being used.
Q. Is it fair to say that the verb metastasize means to invade distant structures of the body?
A. That is part of the process that is described by this term.
Q. I'm going to direct you to Tab H.
A. Yes.
Q. You recognize this, I take it?
A. Yes.
Q. This is a portion that you took out of Taber's Medical Dictionary, right?
A. That's right.
Q. So if you look at the page that you

relevance; outside the scope of his direct testimony.

A. I think I have answered your question.

Q. I'm sorry, there wasn't an answer to the last one. Is the physical interaction between the molecules you've drawn here binding?

MR. KUSHAN: Objection; foundation; relevance; outside the scope of his direct testimony.

A. This is what is implied in my sentence when I say the T cell receptor binds. The key is specificity and selectivity and high affinity.

Q. And the specificity, selectivity and high affinity comes from the direct interaction between the T cell receptor and the MHC?

MR. KUSHAN: Objection; foundation; relevance; outside the scope of the direct testimony.

A. I would not agree to that statement. Many things can directly interact with other things but without any specificity or selectivity.

Q. Okay. So the specificity, selectivity and affinity between the T cell receptor and the MHC complex that contains its cognate peptide comes from the chemical interactions between the T cell

Q. Got it. And that protein, that antigen is on the cell, right?

A. That is where it would need to be to detect PD-L1 or PD-L2.

Q. Got it. So as you say in Paragraph 53 of your declaration, which is Exhibit 4, the deposits of either the fluorescent or the colored substance shows where the antigen is in the tissue sample, right?

A. That is the usual interpretation of these types of analyses, yes.

Q. And that's what you drew in Exhibit 8.

A. Yes.

MR. KUSHAN: We'll repeat our objection to the use of that drawn exhibit as outside the scope of his direct and lacking relevance.

Q. Now, I want to stay on this issue of expression, which is what we have been talking about. You've interpreted expression as being limited only to the production of proteins, right?

MR. KUSHAN: Objection; mischaracterizes his direct testimony.

A. I didn't say that like this. I think in the context of expressing PD-L1 or PD-L2 it means the presence of the protein because that's what

PD-L1 and PD-L2 are.

Q. Can the expression of PD-L1 be detected by looking for something other than protein?

A. No. I think you need to see the protein.

Q. And would you have the same answer for PD-L2, can the expression of PD-L2 be detected by looking for something other than protein?

A. No, you have to look for the protein.

Q. Okay. If we are talking about gene expression, will you agree with me that the gene, which is part of the DNA, gets transcribed to form RNA?

A. Yes, that's correct.

Q. And the RNA is translated to form protein, right?

A. Yes, that's correct.

Q. That total process going from DNA to RNA to protein is gene expression, right?

MR. KUSHAN: Objection; foundation.

A. The relevant expression is that of the protein, not of the RNA.

Q. Okay. I understand that's your position for PD-L1 and PD-L2. My question is as a biologist will you agree with me that the transcription of DNA to form RNA and the translation to form protein as