Exhibit A

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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,	)	Civil Action No. 14-1131-GMS Civil Action No. 15-560-GMS Civil Action No. 15-572-GMS
v.	)	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	)	
Defendants.	)	

ORDER CONSTRUING THE TERMS OF U.S. PATENT NOs. 8,728,474, 9,067,999 & 9,073,994

After having considered the submissions of the parties and hearing oral argument on the matter, IT IS HEREBY ORDERED, ADJUDGED, and DECREED that, as used in the asserted claims of U.S. Patent Nos. 8,728,474 ("the '474 patent"), U.S. Patent No. 9,067,999 ("the '999 patent"), and U.S. Patent No. 9,073,994 ("the '994 patent"):

1. The terms "[for the treatment of/ of treating] a [tumor/ melanoma/ lung cancer/ metastatic melanoma]" and "treats the [lung cancer/ metastatic melanoma]" are construed to have their plain and ordinary meaning.[1]

[1] The court rejects the proposed constructions of "to reduce proliferation or metastasis of cancer cells in the [tumor / melanoma / lung cancer / melanoma and melanoma metastases]" and "reduces proliferation or metastasis of cancer cells in the [lung cancer] / [melanoma and melanoma metastases]" submitted by the defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. (collectively "Merck"). The parties agree that the treatment involves, as the claims state, administering an "anti-PD-1 antibody." The parties' dispute focuses primarily on whether a limitation should be incorporated in the terms that indicates the goal of the treatment. In the patents at issue, the claims explain what the method of treatment consists of, yet Merck would also have the court construe treatment to require the attempted result based upon the goal identified in the preamble: suppression of metastasis or proliferation of cancer cells. (D.I. 82 at 10.) The court declines to limit the terms in this way. While Merck claims that it is unclear

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2. The term "pharmaceutically effective amount" is construed to mean an "amount sufficient to reduce proliferation or metastasis of cancer cells in the [tumor / melanoma / metastatic melanoma and melanoma metastases]."[2]

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which kind of anti-PD-1 antibodies are claimed, the court declines to define these agents entirely based upon their intended effect on the patient. (*See* D.I. 121 at 2.)

Merck also argues that the "wherein" clauses are limiting because they require a particular effect on the disorder specified in the claim. (D.I. 82 at 11.) The plaintiffs Bristol-Myers Squibb Co., E. R. Squibb & Sons, L.L.C., Ono Pharmaceutical Co., Ltd. and Tasuku Honjo (collectively "Bristol-Myers") point out that Merck's proposed construction is redundant because claims 12 and 13 of the '474 patent are dependent claims that recite "wherein tumor proliferation is suppressed" and "wherein tumor metastasis is suppressed." (D.I. 84 at 8.) Merck responds that while claims 12 and 13 require proliferation or metastasis to be suppressed, its proposed construction simply requires a reduction in proliferation or metastasis. (D.I. 121 at 5.) In support of its construction, Merck relies on the case *Griffin v. Bertina*. 285 F.3d 1029 (Fed. Cir. 2002). In that case, the court was asked to address a patent that claimed a test to diagnose thrombosis by "assaying for the presence of a point mutation …" *Id.* at 1033. The court determined that without explaining the objective of the test, the list of steps in isolation had no meaning. While that case did feature "wherein" clauses like the patents at issue, the court is persuaded that in this case there will not be confusion about the reason for administering anti-PD-1 antibodies.

The dispute presently before the court is more like that in *Novartis Pharm. Corp. v. Actavis, Inc.*, 2013 WL 6142747 (D. Del. Nov. 21, 2013). There, the court determined that treatment means to try to cause a therapeutic improvement, without necessarily having assurance of what the outcome will be. *Id* at *11. Similarly, here the court declines to adopt a construction that conflates treatment and efficacy. According to Merck, "The claim language expressly identifies what is being treated in each of the claimed methods: a particular manifestation of cancer." (D.I. 82 at 9.) However, as Bristol-Myers points out, "The term 'effective' is used in the claims of the '474 and '994 Patents, yet the patentees chose not to use the word 'effective' to describe the 'treatment' terms, indicating a clear intent not to import an efficacy limitation." (D.I. 84 at 7-8) (citing the '474 Patent at Cls. 1, 8; '994 Patent at Cl. 1). While treatment implies the goal of achieving results, it does not require a successful outcome. *See Schering Corp. v. Mylan Pharm., Inc.*, No. 09-6383, 2011 U.S. Dist. LEXIS 63825, at *16 (D.N.J. June 15, 2011). It goes without saying that treatment is not always effective, "especially for a disease as dangerous and as complicated as cancer." (*See* D.I. 122 at 2.)

Finally, Bristol-Myers proposes a more specific construction of the ordinary meaning of the term treatment: "attempting to cause therapeutic improvement." The court finds this additional clarification unnecessary and concludes that in this case, plain and ordinary meaning suffices. *See Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012) (observing that the court construes claim terms to have their plain and ordinary meaning "unless the patentee explicitly redefines the term").

[2] The court adopts Merck's proposed construction of an "amount sufficient to reduce proliferation or metastasis of cancer cells in the [tumor / melanoma / metastatic melanoma and melanoma metastases]." Bristol-Myers' proposed construction is "An amount sufficient to exert the pharmacological action of the drug." However, as Merck asserts, "Without a construction of the 'treat' terms, one does not know what a pharmacological action is." (D.I. 121 at 8.)

The customary usage of "effective amount" is not a term of art that the court needs assistance in understanding. *See Abbott Labs. v. Baxter Pharm. Products, Inc.*, 334 F.3d 1274, 1277–78 (Fed. Cir. 2003) (holding that the customary usage of "effective amount" was an amount sufficient to achieve the claimed effect). However, here the parties dispute what the claimed effect is. Thus, reliance on 'plain and ordinary meaning' would be inadequate because it would not resolve the parties' dispute." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008). Bristol-Myers argues that "Defendants' construction not only improperly seeks to import an effectiveness limitation into the claims, it improperly seeks to impose a specific

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3. The term "binds to . . . PD-1" is construed to mean "interacts with . . . PD-1."[3]

4. The term "tumor proliferation" is construed to mean "increase in the number of tumor cells."[4]

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restriction on how effectiveness is demonstrated." (D.I. 84 at 8.) Bristol-Myers insists that there are additional ways of measuring efficacy based on the specification including "life prolongation of an individual," "suppression of proliferation, invasion and metastasis," "tumor growth and survival rate." (*Id.* at 8-9.) Merck responds that what Bristol-Myers claims are measurements of efficacy are in fact downstream benefits from reducing the proliferation or metastasis of cancer, the factor that actually determines efficacy. (D.I. 124 at 7.) Merck also argues that even if there are multiple ways of measuring efficacy, this weighs against leaving the term undefined. (*Id.*)

Bristol-Myers acknowledges that when the claim language is read in view of the specification, there can be no doubt that the effective amount is the amount sufficient to achieve "the pharmacologic action of the drug – the inhibition of the inhibitory signal of PD-1." (D.I. 122 at 6.) The claimed effect of this action is to reduce proliferation or metastasis of cancer cells. '474 Patent at col. 2:58-67, 20:51-55; (D.I. 121 at 9). The court finds that Merck's proposed construction is consistent with the claims and the specification. Adopting this construction will ensure that there is no confusion about the meaning of the claim term.

[3] The parties dispute whether "binds to . . . PD-1" requires a direct or indirect interaction with PD-1. The court finds that Merck's proposed construction, "interacts with . . . PD-1," sufficiently describes the binding action and the "direct" modifier is not necessary. Bristol-Myers asserts that " To say an antibody binds indirectly is the same as saying an antibody does not bind at all." (D.I. 184 at 14.) Chemical bonds must form directly with amino acids. (*Id.* at 9.) Merck responds that the specification uses the word "interaction" to describe the binding of "PD-1 to PD-L1" and "PD-1 to PD-L2." (D.I. 82 at 14.) "Plaintiffs' proposed construction would improperly limit the scope of the claims to one of the two types of binding interactions disclosed in the specification." (*Id.*) Bristol-Myers responds that the citations that Merck provides do not describe direct and indirect binding, but instead inhibition. (D.I. 122 at 10.) Bristol-Myers also cites to the testimony of Dr. von Andrian which describes how binding requires the molecules to be touching. (D.I. 122 at 8.) According to Bristol-Myers, direct interaction is evident from the patents' reference to selectivity and specificity.

Ultimately, the court is not persuaded that the modifier "directly" accurately captures what it means for molecules to touch. Nor is the court persuaded that "directly" conveys that an anti-PD-1 antibody will specifically recognize and selectively bind to PD-1 and not other proteins, as Bristol-Myers suggests. (*Id.*) The court is convinced by the fact that, as Merck points out, the prosecution history uses the term interaction without modifiers to describe how the claimed inhibition occurs. (D.I. 82 at 14.) Thus, the court concludes that the intrinsic evidence does not clearly support the importation of "directly" as an additional limitation.

[4] The parties dispute whether "tumor proliferation" is an "increase in the number of tumor cells" as Bristol-Myers proposes or an "increase in the number of cancer cells in the tumor" as Merck proposes. The court rejects Merck's assertion that tumor proliferation is an increase in the number of cancer cells only. Merck argues that cells in a tumor that are not cancer cells are not the target of treatment. (D.I. 82 at 16.) However, as Bristol-Myers points out, tumors are not solely made of cancer cells and depend on normal cells to grow. (D.I. 84 at 16.) "As described in the specification, tumor proliferation can be evaluated as a numerical calculation of the number of cells in the tumor or as the weight or volume of the tumor after it is removed from the body." (*Id.* at 15.) The court declines to adopt a narrow construction of the term tumor proliferation based upon the intended goal of treatment.

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5. The term "tumor metastasis" is construed to mean "the development of a tumor derived from the primary tumor at a location outside the primary tumor site."[5]

6. The term "expresses [PD-L1/PD-L2]" is construed to mean "produces a product of the [PD-L1/PD-L2] gene."[6]

Dated: June 6, 2016

UNITED STATES DISTRICT JUDGE

[5] The court rejects Bristol-Myers proposed construction of "The spread of cancer cells from a primary site of disease to other parts of the body." (D.I. 84 at 16.) Merck argues that Bristol-Myers' proposed construction conflates tumor metastasis and tumor proliferation. (D.I. 82 at 16.) Merck also objects that Bristol-Myers' proposal would eliminate the requirement that a secondary tumor form. (*Id.*) Merck points out that the lead inventor, Honjo, testified that "metastasis is the stage of cancer that [a] small number of cancer cells released from the original tumor and [sic] normally circulate the vessel or sometimes lymphatics and arrive to the other organ and settle there and starts growing and form another tumor." (D.I. 151 at 4.) In addition, Dr. von Andrian testified based on the textbook *Alberts* et al. that tumor metastasis refers to a process where cancer cells within a tumor move to different locations and create secondary tumors. (D.I. 83 at 9-12.) Bristol Myers' responds that the definition in *Alberts* does not require development of a second tumor, (D.I. 122-5 at 5), nor does the definition in *Taber's Medical Dictionary*. (D.I. 83-11 at 52.) However, the definitions that Bristol Myers' cites to refer to "metastasis" and not "tumor metastasis." The court is convinced that Merck's construction is the most scientifically accurate. Thus, the court adopts Merck's proposed construction of "the development of a tumor derived from the primary tumor at a location outside the primary tumor site." (D.I. 82 at 16.)

[6] The court rejects Merck's proposed construction of "produces a detectable amount of [PD-L1/PD-L2] protein." The parties dispute whether PD-L1/PD-L2 expression must be detectable and whether PD-L1/PD-L2 expression is only detected through PD-L1/PD-L2 proteins. According to Merck, the claim language clearly indicates that cancer cells produce a detectable amount of the PD-L1 or PD-L2 protein. (D.I. 82 at 19.) Bristol-Myers responds that "Defendants' proposed construction wrongly conflates whether a gene is expressed with the degree to which a gene is expressed – these are two fundamentally distinct concepts that are described using different terminology." (*Id.*) The court agrees with Bristol-Myers that gene expression is a "zero-sum game" and not limited by the degree that a gene is detectable. (*Id.*)

The court declines to read in the limitation that PD-L1/PD-L2 expression is a protein. According to Bristol-Myers, the products of the PD-L1 and PD-L2 genes include things other than the PD-L1 and PD-L2 proteins set forth in the claims, such as DNA and RNA. (D.I. 122 at 15-18.) Bristol-Myers argues that the patent discloses that the expression of the PD-L1/PD-L2 protein can be identified by methods that detect RNA. '474 Patent at col. 11:40-42. Additionally, according to Bristol-Myers, RT-PCR can determine the presence and amount of the relevant cytokine mRNA. The court must agree with Bristol-Myers that the proper construction is not limited to a single means of detecting PD-L1/PD-L2. The court is not persuaded that the intrinsic evidence clearly supports the importation of "protein" as a limitation. *Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1329 (Fed. Cir. 2003) ("It is axiomatic that, unless expressly compelled by the intrinsic evidence, courts must avoid the addition of a novel limitation.").

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