

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ZYDUS PHARMACEUTICALS (USA) INC., ZYDUS LIFESCIENCES
LIMITED, ZYDUS LIFESCIENCES GLOBAL FZE, AND FORMYCON AG,
Petitioner,

v.

MERCK SHARP & DOHME LLC, and
AGILENT TECHNOLOGIES, INC.,
Patent Owner.

Case No. PGR2027-00003
Patent No. 12,529,702

**PETITION FOR POST-GRANT REVIEW OF
U.S. PATENT NO. 12,529,702**

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TABLE OF ABBREVIATIONS

Abbreviation	Meaning
AIS	adjusted inflammation score
CPS	combined positive score
ER	estrogen receptor
ERPB	estrogen receptor positive breast cancer
FDA	U.S. Food & Drug Administration
FFPE	formalin-fixed and paraffin-embedded
H&E	hematoxylin and eosin
HPF	high-power field
IF	immunofluorescence
IHC	immunohistochemistry
MIC	mononuclear inflammatory cell
MIDS	mononuclear inflammatory density score
MPS	modified proportion score
NSCLC	non-small cell lung cancer
ORR	overall response rate
PD-1	programmed death-1
PD-L1	programmed death-ligand 1, also called B7-H1 or CD274
ROC	receiver operating characteristic
TIC	tumor infiltrating cell
TIIC	tumor infiltrating immune cell

Abbreviation	Meaning
TIL	tumor infiltrating lymphocyte
TIMC	tumor infiltrating mononuclear cell
TNBC	triple negative breast cancer
TPS	tumor proportion score
UC	urothelial carcinoma

I. INTRODUCTION

Zydus Pharmaceuticals (USA) Inc., Zydus Lifesciences Limited, Zydus Lifesciences Global FZE, and Formycon AG (“Petitioner” or “Zydus”) respectfully request post-grant review of claims 1-21 of US Pat. No. 12,529,702 (“*US702*”) (EX1001), assigned to Merck Sharp & Dohme LLC and Agilent Technologies, Inc. (“Merck” or “PO”).

The challenged claims are not patentable subject matter under Section 101 and should never have issued. The claims are directed to a method in which a mathematical formula is used to determine the “eligibility” of “subjects” with an unspecified “malignancy” for treatment with a prior-art class of anti-cancer agents called PD-L1 inhibitors (“anti-PD therapeutic agents” in the claims). Determining eligibility involves nothing more than the mental step of observing whether the results of the mathematical formula are above or below an arbitrary, unspecified “threshold.” Even if the formula were innovative, which it is not, a claim to a method that merely uses a mathematical formula and a mental step to assess whether a subject should receive a prior-art cancer treatment is an impermissible attempt to patent an abstract idea.

A closer inspection of the challenged claims confirms that they do not set forth any “practical application” of the abstract idea that might render the method patentable. Anti-PD therapeutic agents work by blocking the binding of the PD-1

receptor with the PD-L1 ligand. Normally, the body's immune system will detect and kill tumor cells when they arise. But the PD-L1 ligand, when expressed on the surface of tumor cells and certain immune cells known as mononuclear inflammatory cells (MIC cells), switches off this anti-tumor response. Prior-art, anti-PD therapeutic agents, such as FDA-approved Keytruda (pembrolizumab) and Opdivo (nivolumab), block the PD-L1 ligand from binding to its receptor and thereby (re)activate the immune system's anti-tumor response.

Because it was well-known that cancer patients may only benefit from anti-PD therapeutic agents if enough of their specific tumor and MIC cells actually expressed the PD-L1 ligand, it was routine in the prior art for pathologists to perform tumor biopsies, stain them to visualize which cells expressed PD-L1, and count the number of tumor and MIC cells that were PD-L1-positive (PD-L1⁺).

In the claimed method, the results of this conventional PD-L1⁺ cell count are plugged into a mathematical formula to obtain a diagnostic score, dubbed the "combined positive score" (CPS). The mental step of determining whether that CPS value meets or is below an unspecified "threshold" is then performed. If it meets the threshold, then the subject is eligible for treatment with an "anti-PD therapeutic agent."

The purported novelty of the challenged claims is the mathematical equation used to calculate the CPS, which allegedly improves on prior-art

diagnostic scores that had also been used to assess whether cancer patients would benefit from anti-PD antibody therapies. Nothing in the claims involves anything more than an abstract idea—the mathematical formula—and the mental step of comparing the results of that formula to an unspecified, arbitrary threshold. The formula itself merely embodies a natural law: the correlation between the efficacy of a therapeutic agent that works by blocking interaction of the PD-L1 ligand with its receptor and the presence on tumor and MIC cells of PD-L1 ligand to block.

None of the claims employ novel technology, such as a new therapeutic agent, a new dosing regimen, or a new use for an old therapeutic agent. Moreover, all but two claims are limited to “methods for determining eligibility” for a treatment without even reciting an administration step. In the two claims that recite administration of an “anti-PD therapeutic agent,” the claims do not specify which agent to administer, nor do they specify any particular dose or treatment. *US702* attempts to patent *all* applications of the mathematical formula, and *all* comparisons of the results of that formulation to any “threshold,” to determine eligibility for treatment with *all* anti-PD therapies. This kind of attempt to dominate an abstract idea is exactly what Section 101 was intended to prohibit.

The claims are also unpatentable for lack of enablement under Section 112(a). They are very broad, covering at least thousands of possible combinations of malignancies, CPS score thresholds, and anti-PD therapies. Yet they provide

no guidance as to which specific combinations will actually work to treat a particular malignancy with a particular anti-PD agent. The specification also does not teach any principles that would permit a skilled person to extrapolate this information. A POSA would thus have to engage in endless—and undue—trial-and-error experimentation to practice the full scope of the claims.

The claims are also unpatentable as obvious over Merck's own prior art reference, WO2014/165422 ("*WO422*", EX1010). *WO422* teaches the mathematical formula for calculating the modified proportion score (MPS) score. Like the CPS, this diagnostic score determines eligibility for anti-PD therapy by determining the relative percentage of tumor cells and MICs that are PD-L1⁺. The only difference between the scores is that the denominator of the MPS accounts for total tumor cells plus total MICs, while the CPS denominator accounts for only total tumor cells. This causes the CPS to give somewhat more weight to the presence of the PD-L1⁺ MICs when determining whether a subject will benefit from anti-PD therapy. A POSA would have been motivated to modify the MPS to remove the total number of MICs from the denominator to reduce the risk of false negatives.

While PO argued during prosecution that the CPS was novel over the prior art because it purportedly was the first score to incorporate both PD-L1⁺ tumor

cells and MICs, the very face of the MPS formula disclosed in *WO422* shows that this is not true.

Further, even if the small difference between how MICs are treated in the denominator of the MPS and CPS rendered the CPS novel, it does not render the CPS nonobvious. The prior art taught that the presence of PD-L1⁺ MICs improved prognosis. This is why the MPS factors PD-L1⁺ MICs into the numerator. However, a POSA would have understood that counting PD-L1⁻ MICs in the denominator as if they were tumor cells would create false negatives: patients would have their scores lowered simply because they had significant amounts of MIC cells in their tumors. A POSA would understand that whether PD-L1-negative or positive, the presence of MICs improved prognosis. Thus counting PD-L1⁻ MIC cells against otherwise-eligible subjects would be illogical. This would have motivated the POSA to modify the MPS to exclude the total number of MIC cells in the denominator, which would have led the skilled person directly to the CPS.

Moreover, as *WO422* and *US702* state, the underlying science here, namely the use of anti-PD therapy for treating malignancies, and the use of biomarkers for identifying patients who could benefit from such treatment, was advanced. Researchers knew for many years before the earliest possible effective filing date that the interaction of PD-L1 ligands on tumor cells and MICs in the tumor

microenvironment with PD-1 receptors on healthy killer T-cells caused those T-cells to deactivate and ignore the tumor cells. Blocking that PD-1/PD-L1 interaction could allow T-cells to reactivate and attack the cancer, and it was thus understood that, for certain cancers, subjects with PD-L1⁺ tumor cells and/or MICs were more likely to benefit from anti-PD therapy like pembrolizumab and nivolumab. Clinical trials investigating such correlations were well underway and their results published.

For these reasons, as set forth more fully below, the challenged claims should be held unpatentable on 101, 112, and 103 grounds.

A. Overview of *US702*

US702 states that “[PD-L1] expression is implicated in evasion of immune responses... including suppression of anti-tumor immune activity” and “has been shown in situ on a wide variety of solid tumors.” EX1001, 1:17-33 (citations omitted); EX1002 ¶¶127-28. According to *US702*, “therapeutic agents that target [PD-1/PD-L1] have been of significant interest,” including approved antagonists pembrolizumab (Keytruda) and nivolumab (Opdivo) and molecules under development: BMS-936559, MPDL3280A, Pidilizumab (Medivation/CureTech), MEDI4736 (AstraZeneca), and Avelumab (MSB0010718C). EX1001, 2:5-56; EX1002 ¶¶129-31. *US702* describes the use of immunohistochemical (IHC) staining to measure PD-L1 expression (EX1001, 2:61-3:7) but does not purport to

advance the field of IHC beyond what was taught in *Dako* (described below).

EX1002 ¶¶135, 257.

US702 states further that work in the field had included assessing PD-L1 expression on tumor cells and tumor-associated immune cells because “[m]ore and more clinical trials indicated that in some tumor indications PD-L1 staining on both tumor and tumor-associated immune cells is associated with clinical outcome.” EX1001, 2:58-3:7.

US702, ignoring Merck’s own earlier *WO422*, states that then-current diagnostic scores required capturing two thresholds, “one for tumor cells and one for non-tumor cells,” and purports to address the need for better scoring methods for assessing eligibility for anti-PD therapy. EX1001, 3:11-16; EX1002 ¶¶136, 160.

According to *US702*, the CPS requires “determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy; and calculating a combined positive score (CPS) for the tumor tissue sample using the formula:

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

wherein the subject is eligible for treatment with an anti-PD therapeutic agent when the CPS is above a threshold.” EX1001, 3:25-40; EX1002 ¶¶137-38, 140-41. *US702* further states that “[d]etecting PD-L1 positive cells in a tumor sample can be done in any convenient manner.” EX1001, 9:6-7. It then describes conventional techniques for counting PD-L1^{+/+} cells like flow cytometry and single cell sequencing (EX1001, 9:36-55; EX1002 ¶139); and states that staining techniques and methods for obtaining cell suspensions are known in the art (EX1001, 5:55-63, 9:67-10:9; EX1002 ¶139). *US702* also mentions that in some embodiments, “the percentage of viable PD-L1 positive and negative tumor cells and PD-L1 positive mononuclear inflammatory cells (MIC) is determined within the tumor nests and the adjacent supporting stroma,” but does not identify any benefit related thereto. *See, e.g.*, 9:15-19; EX1002 ¶140.

Missing from *US702* is any true application of CPS where a CPS score is generated and compared to an eligibility threshold for a particular subject, malignancy, and anti-PD therapy. Example 1, the only example in the patent, is prophetic. It describes a protocol for gathering data to calculate the CPS and two other scores, TPS and MIDS, in gastric carcinoma specimens when using an

unspecified anti-PD therapy. EX1001, 19:42-21:6; EX1002 ¶¶142-45. Example 1 states:

[a] cut-off is the score that differentiates diagnostically positive from diagnostically negative.

* * *

It is expected that setting the cut-off at $\geq 1\%$ for a positive result for the scores above, CPS will identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses described above.

EX1001, 20:60-21:2; EX1002 ¶146. *US702* does not identify the subject or anti-PD therapy used in Example 1, provide supporting data, or indicate whether the CPS threshold for gastric carcinoma is actually $\geq 1\%$ for any anti-PD therapy, including the unidentified therapy used in the example. Despite speculating that the CPS is “generally applicable to any cancers expressing PD-L1 in either tumor and/or immune cells” (EX1001, 21:7-8), *US702* provides no data or principles that would permit a POSA to extrapolate from the prophetic information in Example 1 to apply the claimed method to specific malignancy/anti-PD therapy combinations. EX1002 ¶¶147-48.

US702 has 21 claims. Claim 1, the only independent claim, is very broad. It does not limit the subject (which can be a human or non-human animal),

malignancy to be treated, or the CPS threshold. It also only limits the anti-PD therapeutic agent to an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof, which includes at least thousands of potential antibodies and binding fragments. EX1002 ¶¶133, 150.

Independent claim 1 is reproduced below:

1. A method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent, the method comprising:

determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy;

calculating a combined positive score (CPS) for the tumor tissue sample using the formula:

CPS =

$$\frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold,

wherein said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.

B. Prosecution History

US702 issued on January 20, 2026, listing five Agilent inventors and one Merck inventor, and listing Agilent and Merck as assignees. The underlying application, 18/098,198 (“*App198*”), filed on January 18, 2023, is a continuation of 16,804,395 (“*App395*”), filed on February 28, 2020, which is a continuation of 15/422,350 (“*App350*”), filed on February 1, 2017, which claims priority from provisional application 62/317,179 (“*App179*”, EX1009), filed on April 1, 2016. EX1001, cover page.

App179 did not list a Merck inventor or Merck as assignee. *See* EX1009, cover page. They were added with the filing of *App350*, the earliest nonprovisional application. EX1006, 96. During prosecution of *App350*, the examiner rejected the claims as anticipated by, and later obvious over, *Kowanetz* (EX1053) and *Chen* (EX1041). EX1006, 92-94, 133-141. The references were cited as disclosing methods for determining eligibility for anti-PD-1 therapy using scoring methods based on the presence of PD-L1⁺ tumor and infiltrating immune cells. *Id.* In response, PO argued that neither *Kowanetz* nor *Chen*, alone or when combined, disclosed: (a) counting the number of viable PD-L1⁺ MICs, but instead determined a percentage of tumor surface area occupied by PD-L1⁺ tumor-

infiltrating cells (semiquantitative versus qualitative); (b) using MICs specifically, but instead used MICs *and* other infiltrating cells; and/or (c) the specifics of how the CPS score is calculated. EX1006, 149-74; *see also* EX1006, 121-29.

After an advisory action and two examiner interviews, PO requested continued examination, asking that the examiner respond with more particularity. EX1006, 185. The examiner then issued a notice of allowance without providing reasons for allowance. EX1006, 215-21. The application granted as US10,613,092 (“*US092*”; EX1008).

During prosecution of continuing applications *App395* and *App198*, third-party submissions were filed identifying the same art raised during prosecution, as well as other references, including US2016/0084839 (“*Pub839*,” EX1011), the U.S. equivalent to *WO422*. EX1005, 55-78; EX1004, 48-71. In each application, the examiner issued Section 112 and double patenting rejections, but made no Section 102/103 rejections or comments on the third-party submission. *See* EX1004; EX1005. The claims of *App395* and *App198* were allowed with terminal disclaimers and issued as US11,585,817 (“*US817*”; EX1007) and *US702*, respectively.

Even though *WO422*, as well as *Pub839*, disclosed the very subject matter Merck characterized as novel, *i.e.*, quantitative measurements of the number of PD-L1⁺ cells, including the number of MIC cells specifically, Merck did not bring

that specific disclosure to the examiner's attention. As a consequence, the examiner did not use *WO422* (or *Pub839*) in any rejection.

C. Scope and Content of the Prior Art

1. Technical Background

US702 is directed to a mathematical formula for determining a subject's eligibility for treatment with an anti-PD agent. It incorporates known principles from pathology, oncology, and PD-1/PD-L1 biology. A discussion of those prior art teachings is provided below.

a) By 2016, Targeted Medicine Was a Well-Known Method for Treating Cancer

Long before the earliest possible effective filing date of *US702*, oncologists had focused their research on developing new therapeutic agents by identifying unique "biomarker" molecules present on tumor cells and then developing drugs which selectively targeted those tumor biomarkers. EX1002 ¶¶ 59-67, 95-96, 100-101. Companion diagnostic techniques were then developed to detect the biomarkers on individual patient tumors to determine whether those patients were likely to benefit from the targeted drug therapy. As discussed below, the prior art disclosed using such a strategy for the PD-1/PD-L1 biomarker, leaving little work for the named inventors of *US702*. Anti-PD therapies were already approved, and the prior art taught assays for detecting PD-L1 expression on tumor cells and MICs

and the use of such expression data to calculate scores to identify patients who might be eligible for such anti-PD therapies. EX1002 ¶¶95-101.

b) By 2016, Immunotherapy and the PD-1/PD-L1 Checkpoint Axis Had Been Extensively Studied, and It Was Known that Tumor Cells Expression of PD-L1 Could Downregulate Immune Response

Anti-PD therapies are a type of immunotherapy, *i.e.*, a cancer treatment that works with, or “boosts,” the natural anti-tumor activity of a patient’s immune system. In the immune system, specialized T-cells patrol the body to identify and destroy abnormal cells before a tumor develops. These T-cells are regulated by molecular “checkpoints,” that prevent them from attacking healthy cells. One such immune checkpoint that was well understood by 2016 was the interaction between the PD-1 receptor and the PD-L1 protein ligand that binds to PD-1. This interaction is often called the PD-1/PD-L1 axis. EX1002 ¶¶61-65.

The PD-1 receptor is expressed on activated T-cells, while PD-L1 is a protein expressed by some healthy cells. When the PD-L1 expressed on the surface of a healthy cell binds with PD-1 on an activated T-cell, it tells the T-cell not to attack the healthy cell. EX1002 ¶¶66.

Tumor cells can evade T-cell-mediated killing by upregulating the expression of PD-L1 to mimic the phenotype of a healthy cell. EX1002 ¶¶56-58, 66, 71, 75; EX1016, 16; EX1017, 563. This interaction was known long before the earliest possible effective filing date of *US702*. *Id.*; EX1002 ¶79.

By 2016, multiple studies had shown that tumor cells expressing PD-L1 could be made recognizable and killed by T-cells after the patient received anti-PD therapy. For example, *Muenst 2014* reported that in breast cancer, PD-L1 expression by tumor cells correlated with worse overall survival (EX1016, 19-20), and *Topalian* reported observing objective responses to anti-PD therapy in 36% of patients with PD-L1-expressing tumor cells, but no objective response in patients with PD-L1 negative tumor cells (EX1042, 2449-50). EX1002 ¶¶79.

c) By 2016, It Was Also Known That PD-L1 Positive and Negative MICs Were Important Aspects of Response to Anti-PD Therapy

Tumors are often “infiltrated” by MICs—including lymphocytes, monocytes, and macrophages—as part of the body’s natural anti-tumor immune response. The presence of MICs, whether PD-L1⁺ or PD-L1⁻, was known to be associated with improved prognosis in some cancers. EX1002 ¶¶86, 88-89. For example, in breast cancer patients, TILs (MICs) were more often seen in hormone receptor-negative tumors, and also linked with longer event-free survival. EX1067, e29288-1; EX1066, 989; EX1002 ¶87; *see also* EX1035, 807 (accumulation of PD-L1⁻ lymphocytes prognostic for increased survival in ovarian cancer). Such MICs may reside in the tumor nest, which is an aggregation of tumor cells without intervening stroma or non-malignant cells, and/or in the

adjacent supporting stroma, which is the connective tissue and extracellular framework surrounding the tumor. EX1060, 229; EX1002 ¶¶84.

Researchers knew that MICs¹ may express PD-L1, and that this expression can also inactivate T-cells through the PD-1/PD-L1 axis, and that such MICs may be located in the tumor nest or stroma. EX1058, 1327; EX1013, 6-7; EX1060, 229; EX1002 ¶¶81, 123. Since MICs are often located in the tumor nest or stroma, it was known that assessing the PD-1/PD-L1 axis in a given tumor required evaluating PD-L1 expression in both tumor cells and MICs. EX1013, 6, 8; EX1033, 568, 571; EX1010, [0026]-[0029], [00113]; EX1002 ¶¶84, 113, 117, 120-21.

d) By 2016, Many Anti-PD Therapies Were Being Developed, and Two, Pembrolizumab and Nivolumab, Had Received FDA Approval

When the PD-1/PD-L1 axis was elucidated and the anti-tumor efficacy of anti-PD therapy became known, many companies raced to develop such therapies. Two antibody anti-PD therapies, pembrolizumab and nivolumab, received accelerated FDA approval for unresectable or metastatic melanoma in 2014, long

¹ The term “MICs” is often used interchangeably with terms like tumor infiltrating cells (“TICs”) or tumor infiltrating lymphocytes (“TILs”). EX1002 ¶¶81-85.

before the earliest possible effective filing date of *US702*. EX1019, 1; EX1020, 1. Pembrolizumab, marketed by Merck as Keytruda, and nivolumab, marketed by Bristol-Myers Squibb as Opdivo, both block the binding of PD-1 to PD-L1. EX1019, 1; EX1020, 1. Before the earliest possible effective filing date, both were being actively developed for additional tumor types with parallel development of companion diagnostics. EX1056, 850, Table 2. In addition, MPDL3280A, a Genentech/Roche anti-PD-L1 antibody, was being developed with a PD-L1 assay and showed improved response rates in patients with PD-L1⁺ tumors and/or tumor-infiltrating immune cells. *See* EX1031, 987 (Table 1); EX1062, 63, Table 3; EX1002, ¶¶61, 76-78, 96, 114, 319.

e) By 2016, Companion Diagnostics Based on PD-L1 Expression Used Conventional Methodologies and Were Routinely Tested to Predict the Potential Efficacy of Anti-PD Therapies

By 2016, assays for biomarkers had been long used to predict biomarker-specific treatment response, and the techniques employed by *US702* to measure PD-L1 expression were quite old. A popular technique known as immunohistochemistry (IHC), in use since at least the *1940s*, detects cells that express a particular biomarker by applying enzyme-linked antibodies specific to those biomarkers. A stain that reacts with the enzyme on the bound antibodies can then be applied, which enables a pathologist to identify and count the cells

expressing the biomarker using a microscope or flow cytometry. EX1012, 13; EX1002 ¶¶97-98.

The stains used in IHC are as old as the technique itself and included dyes like hematoxylin, which stains cell nuclei blue and can provide contrast to the typical brown staining from enzyme-labeled antibodies used in IHC, and eosin, which stains cytoplasm pink. EX1012, 31, 69, 95. Before such staining, surgically-obtained tissue specimens were preserved and fixed with formalin and embedded in paraffin wax—also known as formalin-fixed and paraffin-embedded (FFPE). EX1012, 11, 31; EX1002 ¶¶99.

By the late 1970s, IHC was routinely used for cancer research and diagnosis. EX1012, 31. In 1998, an FDA approved HER2-specific IHC companion diagnostic assay was launched to identify HER2⁺ breast cancer patients that would benefit from treatment with the anti-HER2 antibody trastuzumab (Herceptin). EX1012, 13. After that, further improvements in IHC standardization had “little impact on the basics of the method.” *Id.*; EX1002 ¶¶99.

By 2004, PD-L1 expression was assayed to predict patient prognosis and/or assess likelihood of treatment success. EX1032, 17177; EX1058, 1330, 1335-336; EX1059, 464, 467; EX1002 ¶¶112. By 2016, many anti-PD therapies had been or were being developed as cancer treatments with associated companion diagnostics, with PD-L1 identified as “the favored biomarker” for predicting treatment

response. EX1031, 985; *see also* EX1013, 7. Cell lineage markers, like CD3 for T-cells and CD68 for macrophages, were also assayed to identify the specific type of cell expressing the PD-L1. EX1013, 8; EX1002 ¶¶168, 283.

Although each competing anti-PD therapy and associated companion diagnostic typically used different antibodies, staining platforms, and definitions of a “positive” predictive score, the underlying principles and techniques were conventional and essentially the same. EX1031, 987; *see also id.* at 987, Table 1; EX1062, Table 3; EX1002 ¶96. In particular, it was common to measure PD-L1 expression on both tumor cells and MICs to predict response to anti-PD therapy. EX1031, 985; EX1062, 63, Table 3; EX1002 ¶¶104-10 (citing *Muenst 2014* (EX1016), *Ali* (EX1022), *Patel* (EX1056), and *Kerr* (EX1031)).

f) By 2016, Several Methods Had Been Used To Score PD-L1 Expression, Including Scores That Incorporated Measures of PD-L1 Expression in Both Tumor Cells and MICs

By 2016, the prior art disclosed various methods for scoring PD-L1 expression in a tumor biopsy. Those scoring methods included separately scoring the percentage of PD-L1⁺ tumor cells and the density of PD-L1⁺ tumor TILs. EX1017, 10-11; EX1080, 285; EX1002 ¶¶118-19, 121.

g) The Prior Art Taught Methods for Using PD-L1 Expression Scores and Clinical Data To Determine Thresholds That Predict a Benefit From Anti-PD Therapy

Once a PD-L1 score is calculated for the tumors of a cohort of subjects, that information, together with other clinical data, can be used to generate a curve, known as a Receiver Operating Characteristic (ROC) curve, to identify a threshold that best distinguishes responders from non-responders for a particular malignancy and anti-PD therapy. The data required to generate this curve may be obtained from a clinical trial designed for this purpose, or from a retrospective analysis of such a clinical trial, provided access to such data is provided. Once the curve is generated and a threshold defined, that threshold can be used to predict whether the subject with that specific malignancy is likely to benefit from the specific anti-PD therapy. EX1002 ¶¶124-26.

2. Key Prior Art

a) WO422 (EX1010)

Merck's *WO422*, titled "Immunohistochemical Assay for Detecting Expression of Programmed Death Ligand 1 (PD-L1) in Tumor Tissue," published in 2014, more than one year before *US702*'s earliest possible effective filing date of April 1, 2016, and is therefore prior art. Post-AIA 35 U.S.C. §102(a)(1); EX1002 ¶151. Although a U.S. equivalent was listed in a third-party submission,

the examiner did not rely on *WO422* or any equivalent in any rejection. EX1004, 72-79, 85-97.

WO422 is directed to using IHC to quantify PD-L1 expression in tumor biopsy sections and identifying “PD-L1 expression levels that correlate with response of cancer patients to therapy with antagonists of Programmed Death 1 (PD-1).” EX1010, [0001]. *WO422* discloses anti-PD-L1 monoclonal antibodies and teaches that patients whose tumors express PD-L1 are more likely to respond to anti-PD therapy. EX1010, [0003]; EX1002 ¶¶152-54.

WO422, like *US702*, teaches a diagnostic score for predicting patient eligibility for anti-PD therapy based on quantifying PD-L1⁺ tumor cells *and* MICs, and a scoring process/score that “may be useful in selecting patients to receive anti-PD-1 therapy.” EX1010, [0009]; EX1002 ¶¶158-60; Sections I.A, I.C.2.a.

WO422 teaches obtaining a tissue section from a tumor stained with an antibody that binds to PD-L1 and assigning a modified proportion score (MPS):

[A]ssigning the MPS comprises estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity.

EX1010, *e.g.*, Exemplary Specific Embodiment 1 and claim 1. A POSA would have understood that the formula for calculating the MPS is the following, where

the denominator includes the total number of viable tumor cells and MICs, and the score is expressed as a percentage:

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

EX1002 ¶¶119, 156-57, 160.

WO422 further describes assigning a stroma score (“SS”) based on the presence or absence of a band of anti-membrane-stained cells in the stroma. An SS of “positive” or “negative” is assigned based on whether a stained band is detected in the stroma surrounding at least one tumor nest. EX1010, [0013]; EX1002 ¶161.

WO422, like *US702*, teaches that the following anti-PD therapeutic agents can be used with the invention: pembrolizumab, nivolumab, BMS-936559, MPDL3280A, pidilizumab, and MEDI4736. EX1010, [0072], Exemplary Specific Embodiments 25-27. Like *US702* with respect to the CPS, *WO422* discloses using the MPS for many overlapping malignancies, including melanoma, NSCLC (non-small cell lung cancer), estrogen receptor (ER) positive HER2 negative breast cancer, HER2 positive breast cancer, and triple negative breast cancer (“TNBC”). EX1010, [0017]. EX1002 ¶¶164-65.

WO422, like *US702*, teaches a broad range (>0 to 90) of potential score thresholds that may indicate eligibility for anti-PD treatment. EX1010, [0019].

WO422 also cites prior art that describes a “positive” threshold for PD-L1

expression of 1% or 5%. EX1010, [0005] (citing EX1014 and EX1042); EX1002 ¶¶155, 162-63, 166.

WO422, like US702, teaches that tumor tissue samples can be obtained by many procedures, including biopsy (EX1010, [0081], [00113]); that IHC staining may be used to identify cells that are PD-L1⁺ (*id.*, [0026]-[0029], [00113]); and that antibody 22C3 was the preferred anti-PD-L1 antibody for staining (*e.g.*, *id.*, [0022]). EX1002 ¶167.

WO422 teaches that FFPE tumor tissue sections are conventional. EX1010, [0082] (“The tissue sample may be fixed by conventional methodology... In some embodiments, the fixed tissue sample is also embedded in paraffin to prepare a formalin-fixed and paraffin-embedded (FFPE) tissue sample.”); *see id.*, Exemplary Specific Embodiment 17, Claim 13; EX1002 ¶167.

WO422 incorporates *Taube 2012* by reference, which disclosed using an IHC marker for PD-L1 expression by tumor and infiltrating immune cells along with CD3- and CD68-specific stains to interpret which cell type demonstrated expression of a given ligand. EX1010, [0006] (citing EX1013, 3-6), [0131] (incorporation by reference). EX1002 ¶¶91-94, 168.

b) *Bellmunt* (EX1023)

Bellmunt, titled “Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma,”

published in January 2015, more than one year before *US702*'s earliest possible effective filing date, and is therefore prior art. EX1002 ¶169; Post-AIA 35 U.S.C. §102(a)(1). *Bellmunt* was not of record during prosecution of *US702*. EX1004.

In *Bellmunt*, investigators evaluated PD-L1 expression in tumor cells and MICs in urothelial carcinoma (UC) to see whether PD-L1 expression was predictive of overall survival or longer survival. EX1023, 812. The extent of PD-L1⁺ tumor infiltrating immune cells ("TIICs") was assessed in proportion to the tumor on a scoring scale of 0-4, with a score of 2-4 considered positive. *Id.*, 813. A POSA would have understood that the investigators did not score PD-L1⁺ MICs by comparing them to total MICs in the tumor sample. EX1002 ¶¶170-73.

c) *Savas* (EX1060)

Savas, titled "Clinical relevance of host immunity in breast cancer: from TILs to the clinic," published in December 2015, before *US702*'s earliest possible effective filing date. EX1002 ¶¶174-75. Post-AIA 35 U.S.C. §102(a)(1). *Savas* was not of record during prosecution of *US702*. EX1004.

Savas discusses, *inter alia*, the clinical relevance of MICs in breast cancer tumors, as well as the use of immunotherapy like the anti-PD-L1 antibody MPDL3280A in patients who scored positive for PD-L1 on tumor cells and MICs. EX1060, 228, 237. With respect to MICs generally, *Savas* explains that "[t]hese infiltrates seem to reflect favourable host antitumour immune responses,

suggesting that immune activation is important for improving survival outcomes.” *Id.*, 228. With respect to PD-L1⁺ MICs specifically, *Savas* noted that in certain solid tumors, “the expression of PD-L1 on the intratumoural TILs seems to predict better responses to the anti-PD-L1 agent.” *Id.*, 238; EX1002 ¶¶176-80.

d) *Dako* (EX1012)

Dako, an IHC Guidebook titled “Immunohistochemical Staining Methods,” was authored by Dako Denmark A/S, an Agilent Technologies Company, and published in 2013, more than one year before *US702*’s the earliest possible effective filing date, and is therefore prior art. EX1002 ¶181. Post-AIA 35 U.S.C. §102(a)(1). *Dako* was not of record during prosecution of *US702*. EX1004.

Dako aims to “provide a comprehensive immunohistochemistry (IHC) resource for lab managers, lab technicians, learning pathologists, and students.” EX1012, 9. It describes the use of FFPE and hematoxylin/eosin (“H&E”) stains. EX1012, 31 (“[M]ost of the criteria for pathological diagnosis have been established by the observation of FFPE tissue sections stained by hematoxylin and eosin.”). *Dako* also teaches analyzing samples using cell suspensions and next generation sequencing. EX1012, 87, 119. EX1002 ¶¶182-85.

e) *Herbst* (EX1017)

Herbst, titled “Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients,” published in 2014, more than one year before

US702's earliest possible effective filing date, and is therefore prior art. Post-AIA 35 U.S.C. §102(a)(1). EX1002 ¶186. *Herbst* was not of record during prosecution of *US702*.

To investigate PD-L1 in human cancers, researchers used an anti-PD-L1 IHC antibody with FFPE specimens and evaluated PD-L1 expression separately on tumor cells and TIICs. *Herbst* observed PD-L1 staining in both populations, with PD-L1⁺ TIICs occurring more frequently than PD-L1⁺ tumor cells. EX1017, 4. *Herbst* used a single score for PD-L1 positivity based on the percentage of combined PD-L1⁺ TIICs in the tumor and stroma. EX1017, 6. Immunofluorescence showed that the PD-L1⁺ immune cell population included macrophages, dendritic cells, and T-cells. *Id.*, 1-2, 6. In a phase I study evaluating the anti-PD-L1 antibody MPDL3280A in patients with multiple cancer types, *Herbst* reported a statistically significant association between response and PD-L1 expression on TIICs. EX1017, 10-11, 17-18; EX1002 ¶¶187-94.

3. Level of Ordinary Skill in the Art

A POSA would have been a medical doctor and/or clinical researcher with an MD and/or Ph.D. and significant experience in one or more of the fields of histology, immunohistochemistry, and oncology. The POSA would have collaborated with others having such education and/or experience, including

scientists skilled in related fields, such as pathology, molecular biology, and immunology. EX1002 ¶¶51-54.

II. GROUNDS FOR STANDING (37 C.F.R. §42.104(A))

Petitioner certifies that *US702* is available for post-grant review under 37 C.F.R. §42.204(a) and that Petitioner is not barred or estopped from bringing this petition or challenging any claim of *US702* on the grounds identified herein.

Petitioner is not the owner or assignee of *US702*, nor has Petitioner filed a civil action challenging the validity of *US702*.

III. TIMING

US702 issued on January 20, 2026, with an earliest possible effective filing date of April 1, 2016, and is thus a post-AIA patent eligible for PGR. Pursuant to 37 CFR §42.201-202, this Petition is being filed within nine months of the issue date of *US702*.

IV. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

Pursuant to 37 C.F.R. §§42.8(a)(1) and 42.8(b), the following mandatory notices are provided as part of this Petition.

A. Real-Party-in-Interest (37 C.F.R. §42.8(b)(1))

Zydus Pharmaceuticals (USA) Inc., Zydus Lifesciences Limited, Zydus Lifesciences Global FZE, and Formycon AG are the real parties in interest.

Out of an abundance of caution, Petitioners certify that the following are also identified as real parties-in-interest, for purposes of compliance with 35 U.S.C. §312(a)(2).

Zydus Healthcare Limited
German Remedies Pharmaceuticals Private Limited
Zydus Wellness Limited
Zydus Wellness Products Limited
ZyVet Animal Health Inc.
Liva Nutritions Limited
Zydus Healthcare (USA) LLC
Sentynl Therapeutics Inc.
Zydus Animal Health and Investments Limited
Dialforhealth Unity Limited
Dialforhealth Greencross Limited
Viona Pharmaceuticals Inc.
Violio Healthcare Limited
Zynext Ventures USA LLC
Zynext Ventures PTE. LTD.
Zydus Pharmaceuticals Limited
Alidac Pharmaceuticals SA Pty. Ltd.
Biochem Pharmaceutical Private Limited
Script Management Services (Pty) Ltd.
Zydus Strategic Investments Limited
Zydus Wellness [BD] Pvt Ltd
Zydus VTEC Limited
Zydus Pharmaceuticals Mexico SA De. C.V.
LM Manufacturing India Private Limited
Zydus Pharmaceuticals Mexico Services Company SA De. C.V.
M/s. Recon Pharmaceuticals and Investments, a Partnership Firm
Zydus Worldwide DMCC
Zydus Medtech Private Limited
Zydus Wellness International DMCC
Naturell (India) Private Limited
Zydus Pharmaceuticals (Canada) Inc.

Zydus International Private Limited
Zydus Pharmaceuticals UK Limited
Zydus Lanka (Private) Limited
LM Manufacturing Limited
Zydus Nikkho Farmaceutica Ltda.
Medsolutions (Europe) Limited
Zydus Healthcare Philippines Inc.
LiqMeds Worldwide Limited
Zydus Ventures PTE. LTD.
LiqMeds Limited
Laboratorios Combix S.L.
LiqMeds Lifecare Limited
Zydus Netherlands B.V.
Naturell Inc.
Zydus France, SAS
Alidac Healthcare (Myanmar) Limited
Zydus Therapeutics Inc.
Zydus Healthcare S.A. (Pty) Ltd
Etna Biotech S.R.L.
Assertio Holdings, Inc.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is not aware of any related matters.

C. Lead and Back-Up Counsel and Service Information (37 C.F.R. §42.8(b)(3), (4))

Lead counsel is Lora M. Green (Reg. No. 43,541). Back-up counsel are:

- Robert Cerwinski (to be admitted *pro hac vice*)
- Michael Cottler (Reg. No. 79,455)
- Keith A. Zullo (Reg. No. 37,975)
- Cindy Chang (to be admitted *pro hac vice*)

D. Payment of Fees Under 37 C.F.R. §42.15(a) and §42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 604962.

V. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

A. Challenged Claims and Relief Requested

Petitioner requests institution of PGR against claims 1-21 of *US702* and cancellation of these claims as unpatentable.

B. Statutory Grounds of Challenge

Each of the following prior art references and/or combinations of references renders the challenged claims unpatentable:

Ground	35 U.S.C.	References	Claims
1	§101		1-21
2	§112		1-21
3	§103	Obvious over the combination of <i>WO422</i> (EX1010), <i>Bellmunt</i> (EX1023), and <i>Savas</i> (EX1060)	1-8, 12-14, 16-21
4	§103	Obvious over the combination of <i>WO422</i> , <i>Bellmunt</i> , <i>Savas</i> , and <i>Herbst</i> (EX1017)	9
5	§103	Obvious over the combination of <i>WO422</i> , <i>Bellmunt</i> , <i>Savas</i> , and <i>Dako</i> (EX1012)	10-11, 15

Petitioner’s full statement of the reasons for the relief requested is set forth in greater detail below, as supported by the declaration of Dr. Jonathan Braun (EX1002). Dr. Braun has decades of experience as a practicing pathologist and researcher and led the Pathology and Clinical Laboratory services of the UCLA Health System for over 20 years, where he oversaw a medical staff of over 100 pathologists and laboratory medicine clinicians who annually performed over 100,000 clinical cases involving histopathologic analysis for cancer diagnosis and treatment planning. *Id.* ¶¶6-18; EX1003.

VI. CLAIM CONSTRUCTION

Claim terms should be given the ordinary and customary meaning consistent with the specification, as a POSA would have understood them. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). Accordingly, the terms of the challenged claims should be given their plain and ordinary meaning. To avoid confusion, the plain and ordinary meaning of three claim terms are discussed below, none of which are defined in the patent. Even if the claim terms discussed below were to be given a narrower meaning, however, the claims would still be unpatentable for the grounds specified herein.

A. “Subject” Encompasses a Single Subject

Claim 1 recites a “method for determining the eligibility of a subject.” A POSA would have understood that determining the eligibility of “a subject”

encompasses determining the eligibility for administration to a single subject.

EX1002 ¶¶195-97.

Because a “subject” may be a single subject, claims 20 and 21 do not require that *every* subject whose CPS is above a threshold (claim 20), such as over 1% (claim 21), *must* be treated with an anti-PD therapeutic agent. Those claims only require that at least one subject who meets the threshold is treated with the agent.

EX1002 ¶197.

B. “Determining the Number” (Claim 1) and “Counted” (Claim 9) Include Estimating

The terms “determining the number” in claim 1 and “counted” in claim 9 should be construed to encompass not just the exact enumeration of every tumor cell and MIC, but also “estimating,” *i.e.*, an approximate numerical assessment. In other words, the claim language, read in context, requires assessment of the specified cell numbers by a POSA but does not require a precise count of every cell type mentioned in the claim. EX1002 ¶198.

First, when describing the purported invention, *US702* explains the calculation step as requiring an estimation: “To calculate the CPS, the stained area is evaluated at a higher magnification (right) *to estimate the number* of PD-L1 positive and negative tumor cells and mononuclear inflammatory cells that are PD-L1 positive.” EX1001, 17:41-44. “Because only 10% of the sample was stained, the CPS score is adjusted by multiplying the CPS of the stained area with the

percentage of the tissue that was stained (in this case, 10%).” *Id.*, 17:53-56. There is no teaching in this example of an exact enumeration of every involved tumor cell or MIC. EX1002 ¶199.

Second, Merck’s characterization of the method during prosecution as “semi-quantitative,” as opposed to “quantitative,” reinforces this reading. EX1006, 152 (“The presently claimed method is a *semi-quantitative method* which calculates the number of PD-LI positive cells in relation to the total number of tumor cells rather than the qualitative method of Kowanetz et al. [or Chen et al.] which is based on the number of tumor-infiltrating immune cells within a given area”); *see also id.* EX1006, 164, 189, 200. A semiquantitative measurement is consistent with an approximation, not an exact enumeration. EX1064, 408 (distinguishing between semiquantitative and quantitative assessments); EX1002 ¶200.

Third, the prior art is consistent with the intrinsic evidence. For example, *Taylor* explains that IHC is “difficult to run in a manner that lends itself to quantitative analysis” due to, *inter alia*, lack of standardization in pre-analytical steps and analytical steps. EX1065, 412-14. Likewise, as examples of counting, *Walker* includes “counting up to 1000 cells for reactivity to give a percentage or counting number of positive cells in 10 high-power fields (HPF).” EX1064, 407. The latter scenario, where only a portion of the cells are counted, and this count is

then used to estimate the total, is exactly the method described in the specification of *US702* above. EX1002 ¶201.

C. “Eligible for Treatment” Does Not Require Treatment

Claim 1 recites a “method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent... wherein the subject is eligible for treatment with said... agent when the CPS is above a threshold.” *US702* does not specifically define the term “eligible.” But as Dr. Braun explains, a POSA would have understood that “eligible” and “eligibility” have their common meaning of being qualified to participate in the treatment. EX1078, 3; EX1002 ¶202. Thus, the claims do not require treatment with an anti-PD therapeutic agent even if a threshold is met. *Id.*

VII. GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 1-21 are Invalid for Lack of Subject Matter Eligibility Under 35 U.S.C. §101

Claims 1-21 are not patent eligible under the two-step *Alice/Mayo* framework articulated by the Supreme Court. EX1002 ¶¶203-309, 462. The first step of this framework asks whether the claims at issue are directed to patent-ineligible subject matter such as an abstract idea, natural phenomenon, or law of nature. *Alice Corp. Pty. v. CLS Bank Int’l*, 573 U.S. 208, 217 (2014); *see also Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 78-79 (2012). Abstract ideas include mathematical equations and mental processes, such as

observations, evaluations, judgments or opinions. *Mayo*, 566 U.S. at 70-71.

Natural phenomena include naturally-occurring correlations between a patient's physical state—such as metabolite levels—and drug efficacy. *Id.* at 77.

The second step asks whether there is anything more in the claim that renders it patent eligible. It considers “the elements of each claim both individually and ‘as an ordered combination’ to determine whether the additional elements ‘transform the nature of the claim’ into a patent-eligible application.” *Alice*, 573 U.S. at 217 (“We have described step two of this analysis as a search for an ‘inventive concept’—i.e., an element or combination of elements that is ‘sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.’”). Additional elements that merely direct one to apply the natural law in a nonspecific way, or which add only well-understood, routine, or conventional steps to the natural law, generally do not transform the claim into patent-eligible subject matter. *Id.* at 225.

The USPTO's nonbinding but instructive 2019 Guidance provides a framework for analyzing Section 101 eligibility that breaks down the *Alice/Mayo* steps into the following four parts/steps:

Step 1: Is the claim directed to a statutory category, *i.e.*, a process or composition of matter? If so, proceed to Step 2A, Prong One. If not, the claim is patent ineligible.

Step 2A, Prong One: Does the claim describe an abstract idea, natural phenomenon or law of nature (*i.e.*, a “judicial exception” to Section 101? If so, proceed to Step 2A, Prong Two. If not, the claim is patent eligible.

Step 2A, Prong Two: Does the claim as a whole integrate the recited judicial exception into a “practical application” of the exception, *i.e.*, does the claim apply, rely on, or use the judicial exception “in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception.”

Step 2B: Does the claim as a whole amount to significantly more than the recited exception, *i.e.*, does any additional element, or combination of additional elements, adds an inventive concept (part of *Alice/Mayo* Step 2)? This entails determining whether the claim adds a specific limitation beyond the judicial exception that is not well-understood, routine, or conventional activity in the field, and not just a well-understood, routine, or conventional activity specified very generally. If not, the claim is patent ineligible. If so, the claim is patent eligible.

See Rizen (Suzhou) Pharm. Tech. Co. v. Alzheon, Inc., PGR2022-00051, Paper 14 at 11-12 (P.T.A.B. Jan. 13, 2023); EX1057, 51, 54-56.

In July 2024, the USPTO published Examples 47-49 to illustrate how to assess subject matter eligibility pursuant to MPEP 2106. EX1081. Claim 1 of Example 49 concerned a method of treating post-surgical fibrosis in which:

- (a) a sample collected from a glaucoma patient is genotyped;
- (b) the genotype is used to calculate a “weighted polygenic risk score” that is then used to identify whether the patient is at high risk for post-implantation inflammation (“PI”); and
- (c) an appropriate treatment is administered to the patient at high risk of PI after microstent implantation surgery.

Id., 30.

The USPTO explained that claim 1 of Example 49 is not patent eligible under the 2019 Guidance. Element (b) recites a natural law (a correlation between a patient’s genotype and their risk of PI), a mathematical calculation (a weighted polygenic risk score), and a mental step (identifying whether the patient is at high risk of PI based on the weighted polygenic risk score), which are all “judicial exceptions” to Section 101. *Id.*, 32. Although the claim requires administering a treatment, this is not a sufficient “practical application” because “it does not provide any information as to how the patient is to be treated or what the treatment is, but instead covers any possible treatment that a medical professional decides to administer to the patient.” *Id.*, 33.

Example 49 further explains that had the claim specified that the patient at risk of PI be treated with “Compound X,” which the Example describes as “a new antifibrotic drug... that effectively reduces scarring around a microstent implantation site in glaucoma patients at high risk of PI... without the undesirable side effects” of “[c]ommonly prescribed anti-fibrotic drugs.” Treatment with Compound X was essential to the claim being patent eligible. *Id.*, 34-35 (claim 2).

1. Independent Claim 1 Is Patent-Ineligible Under 35 U.S.C. §101

Claim 1, the only independent claim, is very similar to USPTO Example 49 and is not patent eligible. Claim 1 recites “a method for determining the eligibility” of an unspecified subject having an unspecified cancer malignancy for treatment with an unspecified “anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.”

The claimed method comprises the following steps:

- (1) The Determining Step:** “determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC cells in a tumor tissue sample from a subject having a malignancy.”
- (2) The Calculating Step:** “calculating a [CPS] for the tumor tissue sample using the [CPS] formula”
- (3) The Eligibility Step:** “wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold.”

a) USPTO Step 1: Claim 1 Falls Within a Statutory Category

Step 1 of the 2019 Guidance asks whether the claim falls within a statutory category. EX1057, 54; MPEP2106.03. Claim 1 is a method claim, with method steps, and therefore is within a statutory category.

b) USPTO Step 2A, Prong One (*Alice/Mayo* Step 1): Claim 1 Is Directed to a Natural Law, a Mathematical Calculation, and Mental Step

Like Example 49, Claim 1 recites a natural law: a correlation between a subject's tumor cell and MIC phenotype (whether those cells express PD-L1 or not) and whether those cells will respond to anti-PD or anti-PD-L1 antibodies. It also recites a mathematical calculation: the subject's "CPS" score is calculated via a formula that weighs the total number of tumor cells and MICs that express PD-L1 versus the total number of tumor cells. It also recites a mental step: the subject is deemed to be "eligible" for treatment with anti-PD or anti-PD-L1 antibodies if the CPS score is above some unspecified "threshold," a determination made in the mind of a doctor. Thus Claim 1 sets forth or describes three "judicial exceptions" to Section 101.

c) USPTO Step 2A, Prong One (*Alice/Mayo* Step 1): Claim 1 as a Whole Does Not Integrate the Ineligible Subject Matter into a Practical Application

Claim 1 does not integrate the judicial exceptions into a "practical application." Performing a mathematical formula is not patentable even if it is new

or yields different or better results. *See In re Bd. of Trs. of the Leland Stanford Junior Univ.*, 991 F.3d 1245, 1250-51 (Fed. Cir. 2021). Beyond employing the formula to determine eligibility for anti-PD therapy, which is not patentable, the claim does not require any specific action, such as administering an anti-PD therapy or anti-PD-L1 therapy. It also places no meaningful limitation on the eligibility determination, since it does not specify:

- the subject (human vs. non-human animal),
- the malignancy,
- the CPS threshold,
- the anti-PD or anti-PD-L1 therapeutic agent to be used in a “treatment,” and/or
- the dose/dosing regimen for that treatment.

The claim is nothing more than “a drafting effort designed to monopolize the judicial exception,” since it covers the use of the natural law, embodied in the mathematical formula, to perform the mental step of determining the eligibility of any subject having any malignancy and a CPS score above any threshold, for treatment with any anti-PD or anti-PD-L1 antibody (or fragment thereof) therapeutic agent. *See Mayo*, 566 U.S. at 77-78.

Notably, claim 1 is very different than the variant of the hypothetical claim in Example 49, which required patients identified as being at high risk of PI to then

be treated with “compound X,” a specific novel therapeutic agent with superior properties over conventional treatments. EX1002 ¶308. Claim 1 is also very different from the claims in *Vanda*, which provided “a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome.” *Rizen*, PGR2022-00051, Paper 14, 16, quoting *Vanda Pharms. Inc. v. West-Ward Pharms. Int’l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018). While *US702* alleges that the claimed eligibility determination allows skilled artisans to more accurately identify which subjects to treat (EX1001, 20:66-21:2), there is no evidence of such benefit in the specification. But even if this allegation were true, “[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.” *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379-80 (Fed. Cir. 2015) (quoting *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 591 (2013)).

Instead, claim 1 is more like the claims in *INO* that the Federal Circuit invalidated under Section 101. *INO Therapeutics LLC v. Praxair Distrib. Inc.*, 782 F. App’x 1001 (Fed. Cir. 2019). In *INO*, the natural phenomenon at issue was how a neonate patient’s body reacts to inhaled nitric oxide depending on whether “the patient has a congenital heart condition called LVD.” *Id.* at 1005. The court viewed the following claim language as merely restating a natural law: “excluding the second patient from treatment with inhaled nitric oxide, based on the

determination that the second patient has left ventricular dysfunction [LVD], so is at particular risk of increased [adverse event] upon treatment with inhaled nitric oxide.” *Id.* at 1006. The court concluded that the claim did not add anything patentable to the natural law because it was “directed to detecting the presence of LVD in a patient and then doing nothing but leaving the natural processes taking place in the body alone for the group of LVD patients.” *Id.* The *INO* claim, like *US702* claim 1, stopped “well short of an improved treatment method.” *Id.* at 1007. And unlike *Vanda*, neither the *INO* claim nor *US702* claim 1 “recite a specific method of treating the disease using an improved set of specific doses.” *Id.*

d) USPTO Step 2B (*Alice/Mayo* Step 2): The Steps in Claim 1, Whether Considered Individually or as an Ordered Combination, Do Not Transform the Nature of the Claim

USPTO Step 2B (*Alice/Mayo* Step 2) assesses whether the steps in the claimed method, when considered individually or as an ordered combination, transform the nature of the claim into a patent-eligible application (*Alice*, 573 U.S. at 217), and whether the claim adds a specific limitation beyond the judicial exception other than well-understood, routine, and conventional activities previously known to the industry, specified at a high level of generality. *Rizen*, PGR2022-00051, Paper 14, at 12; EX1057, 56. “[S]imply appending

conventional steps, specified at a high level of generality’ to the claimed law does not make it patentable.” *INO*, 782 F. App’x at 1009 (citing *Mayo*, 566 U.S. at 82).

As explained below, the Determining, Calculating, and Eligibility Steps, considered individually or as an ordered combination, do not transform the nature of the claim into patent-eligible subject matter. Rather, they add, at a high level of generality, only well-understood, routine, and conventional activities. EX1002 ¶¶203-04, 206-19, 242.

The Determining Step: the Determining Step calls for determining the number of PD-L1⁺ viable cancer cells and MICs and the number of PD-L1⁻ viable cancer cells, without limiting how to do so. As of the earliest possible effective filing date, such determinations were conventional. PD-L1 was a known biomarker for determining eligibility for anti-PD-1 and anti-PD-L1 therapy. As a result, taking biopsies, staining cells for PD-L1 expression, and counting tumor cells and MICs positive and negative for this expression were well known and routine activities. *See* EX1033, 1, 3, 9 (disclosing use of quantitative IHC); EX1002 ¶117.

The Determining Step is also framed very generally. It requires detecting and “counting” PD-L1⁺ and PD-L1⁻ cells, but does not indicate or limit how to do so. For example, consistent with the teachings in the art (*see* Section I.C.1.a.), the specification states that “[d]etecting PD-L1 positive cells in a tumor sample can be

done in any convenient manner.” EX1001, 9:6-7. The specification discloses only the same conventional technology for identifying and counting PD-L1⁺ cells that skilled artisans used prior to *US702*. See Section I.C.1.f.; EX1002 ¶¶224-28.

Thus, the Determining Step does not transform the claim.

The Calculating Step: the Calculating Step performs the abstract act of calculating the CPS. This abstract step cannot transform the claim. *RecogniCorp, LLC v. Nintendo Co.*, 855 F.3d 1322, 1327 (Fed. Cir. 2017) (“Adding one abstract idea (math) to another abstract idea... does not render the claim non-abstract.”)

The alleged advantages of the calculated CPS do not convert the formula from unpatentable to patentable subject matter. *Leland Stanford Junior Univ.*, 991 F.3d at 1251-52. “An inventive concept that transforms the abstract idea into a patent-eligible invention must be significantly more than the abstract idea itself.” *Bascom Glob. Internet Servs., Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1349 (Fed. Cir. 2016). If, as here, “a claim’s only [alleged] ‘inventive concept’ is the application of an abstract idea using conventional and well-understood techniques, the claim has not been transformed into a patent-eligible application of an abstract idea.” *BSG Tech LLC v. Buyseasons, Inc.*, 899 F.3d 1281, 1290–91 (Fed. Cir. 2018); see also *Constellation Designs, LLC v. LG Elecs.*, 174 F.4th 888, 904 (Fed. Cir. 2026).

Moreover, calculating a diagnostic score based on the presence or absence of PD-L1 in tumor cells and MICs was conventional. EX1010, claim 12 (MPS); EX1013, 8 (AIS); EX1042, 2445, 2449, 2452-53 (percentage of PD-L1⁺ tumor cells); EX1002 ¶229.

The Eligibility Step: The Eligibility Step assesses eligibility for anti-PD therapy by comparing the calculated CPS (an abstract idea) to an unspecified threshold. This is an ineligible mental step. Moreover, it is very general. Despite the fact that the patent acknowledges that the threshold depends on the anti-PD therapy (EX1001, 8:49-51), claim 1 neither identifies an anti-PD therapy nor specifies a threshold. EX1002 ¶¶230-33.

Ordered Combination: The Determining, Calculating, and Eligibility Steps, when considered as an ordered combination, do not transform the claim because they merely recite a natural law, abstract idea, and mental step. More specifically, the Determining Step merely generates input for the abstract idea represented by the CPS formula in the Calculating Step, and as explained above, the Calculating and Eligibility Step together represent the natural law that is the focus of claim 1. Accordingly, the ordered combination is just an instruction to doctors to apply a natural law and mental step before treating any patients, and does not transform the claim. EX1002 ¶¶220-23, 234-36.

* * *

For the above reasons, claim 1 of *US702* is not patent eligible and thus not patentable under Section 101. *See, e.g., Ariosa*, 788 F.3d at 1379-80.

2. Dependent Claims 2-21 Do Not Add Specific Limitations That Transform the Nature of the Claim into a Patent-Eligible Application

a) Dependent Claims 2 and 3

Claims 2 and 3 depend from claim 1 and recite “thresholds” of “from 10% to 1%” (claim 2) or “1%” (claim 3). Through dependence on claim 1, claims 2-3 incorporate the natural law, abstract idea, and mental step that make up the entirety of claim 1. Claims 2 and 3 do not add any new, practical application of these unpatentable features to the claimed process. They merely limit the threshold used in the Eligibility Step of claim 1, which does not make that step any less of a purely mental exercise. Like claim 1, claims 2 and 3 do not require any specific action, such as administering an anti-PD therapy, after assessing eligibility for anti-PD therapy. Claims 2 and 3 therefore lack an action step.

The claims also do not identify the subject (human/non-human animal), malignancy, anti-PD therapy, or effective dose/dosing regimen. They therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application, and fail to recite any otherwise unconventional method of treating. EX1002 ¶¶243-46, 248.

Notably, *US702* states that the “[t]hreshold... can thus be any applicable CPS value... **and is specific to the drug used.**” EX1001, 8:49-51. Because claims 2 and 3 do not specify any particular drug, they amount to a general directive to the skilled artisan to apply the ineligible subject matter to all possible treatments. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim into a patent-eligible application. EX1002 ¶¶205, 249.

Moreover, the concept of a diagnostic threshold for eligibility for anti-PD therapy based on PD-L1 expression is conventional. For example, *WO422* states that anti-PD therapy has been “shown to have anti-tumor activity against a variety of tumor types, with early human clinical data suggesting that patients whose tumors express PD-L1 are more likely to respond to anti-PD-I therapy.” EX1010, [0003] (citing EX1045, EX1046, EX1047, EX1048, EX1049, EX1050, EX1051 in support thereof). *WO422* further teaches that claimed thresholds of 1%, or 10% to 1%, are conventional, stating that the “cut-off” or threshold for counting a tumor tissue section as positive for PD-L1 expression was 1% or 5% of total tumor cells. EX1010, [0005]-[0006]; *see also* EX1052, [0085]; EX1002 ¶¶166, 247.

b) Dependent Claims 4-9

Claim 4 depends from claim 1 and further requires using tumor tissue from a biopsy. Claims 5-7 depend from claim 4 and require using IHC staining to detect

PD-L1 (claim 5), using an FFPE tumor tissue section (claim 6), or that the tumor tissue section is stained (claim 7). Claim 8 depends from claim 7 and requires using H&E staining. Claim 9 depends from claim 4 and further requires that the tumor cells and MICs are “counted in the tumor nests and the adjacent supporting stroma of the tumor tissue sample.” Through direct or indirect dependence on claim 1, claims 4-9 incorporate the ineligible natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶255-56, 260-61, 266-67. As explained below, claims 4-9 focus on conventional aspects of tumor sample collection and analysis, and do not transform the nature of the claim.

Like claim 1, claims 4-9 do not require any specific action, such as administering an anti-PD therapy after assessing eligibility for anti-PD therapy, and do not identify the subject, cancer to be treated, anti-PD therapy, effective dose/dosing regimen, or threshold. Claims 4-9 therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating. EX1002 ¶¶250-51, 253-54, 257-58, 262, 264-65. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim into a patent-eligible application.

Moreover, the added limitations are conventional. Using a biopsy to obtain a tumor tissue sample (claim 4) is conventional. EX1010, [0081] (“The tumor sample can be obtained by a variety of procedures including, but not limited to... biopsy”), [00113]; EX1002 ¶252. Staining tissue (claim 7) and detecting PD-L1 by IHC staining (claim 5), using an FFPE tumor tissue section (claim 6), and using H&E stain (claim 8) are conventional activities when using a biological marker to assess a tumor tissue sample. *See* EX1012, 31 (“In the majority of cases, tissue specimens for immunohistochemical (IHC) staining are routinely fixed in formalin and subsequently embedded in paraffin. Because of the long history of the use of formalin-fixed, paraffin-embedded (FFPE) tissue sections in histopathology, most of the criteria for pathological diagnosis have been established by the observation of FFPE tissue sections stained by hematoxylin and eosin.”); EX1010, [0082] (FFPE), [00113] (stained tissue samples); EX1002 ¶¶255-57, 260-61. In addition, *WO422* teaches the conventional nature of IHC staining with antibody 22C3 in FFPE tissue samples to detect PD-L1. EX1010, [0026]-[0029], [0082] (FFPE), [0113] (stained tissue samples) Fig. 3; EX1002 ¶262. *US702* also acknowledges that staining is conventional and that H&E staining is a commonly used stain in histopathology. EX1001, 10:2-19 (H&E stain “is the most commonly used light microscopy stain in histology and histopathology.”); EX1002 ¶¶257, 263.

The added limitation in Claim 9, counting tumor cells and MICs in tumor nests and adjacent supporting stroma, is also directed to conventional staining techniques. For example, claim 3 of *WO422* depends from claim 1 and recites determining the extent of staining in tumor nests (claim 1) and the surrounding stroma. EX1010, claim 3; EX1002 ¶¶266-68. *Tumeh* also discloses counting the number of PD-L1⁺ cells in the tumor parenchyma (intratumoral) and in the invasive margin (stroma). EX1033, 5 (“Slides were examined for the presence of... PD-L1 within the tumour parenchyma (tumour) and the connective tissue surrounding the tumour (invasive margin)”); EX1002 ¶¶269-70.

c) Dependent Claims 10 and 11

Claim 10 depends from claim 1 and requires that the tumor tissue sample be a cell suspension. Claim 11 depends from claim 10 and further requires that flow cytometry is used to count the number of tumor cells and MICs. Through direct or indirect dependence on claim 1, claims 10-11 incorporate the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶271-72, 276-77.

Like claim 1, claims 10-11 do not require any specific action, such as administering an anti-PD therapy, after assessing eligibility for anti-PD therapy. They also do not identify the subject, cancer to be treated, anti-PD therapy, effective dose/dosing regimen, or threshold. Claims 10-11 therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract

idea, or mental step into a practical application or convert them into an improved method of treating. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶271-72, 274-77, 279-80.

Moreover, the cell-suspension (claim 10) and flow cytometry (claim 11) steps are conventional, as taught by *Dako*: “Immunofluorescence (IF) is a common laboratory technique.... Applications include the evaluation of cells in suspension.... The degree of fluorescence can then be quantified using a flow cytometer.” EX1012, 87; EX1060, 229 (Box 1), 230; EX1002 ¶273. *US702* also acknowledges that cell suspensions are used in flow cytometry and that methods for obtaining cell suspensions “are known in the art.” EX1001, 5:55-63; EX1002 ¶¶273, 278.

d) Dependent Claims 12 and 13

Claim 12 depends from claim 1 and requires detecting one or more additional marker in the tumor tissue sample, *i.e.*, in addition to PD-L1. Claim 13 depends from claim 12 and specifies that “the marker is specific for MIC or is selected from the group consisting of CD3, CD5, CD4, CD7, CD8, and CD20.” Through direct or indirect dependence on claim 1, claims 12-13 incorporate the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶281-82.

Like claim 1, claims 12-13 do not require any specific action, such as administering an anti-PD therapy after assessing eligibility for anti-PD therapy. They also do not identify the subject, cancer to be treated, anti-PD therapy, effective dose/dosing regimen, or threshold. Claims 12-13 therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶281-82, 284-85.

Moreover, the additional marker steps are conventional. *Dako* taught the use of multi-staining IHC, wherein multiple targets are detected in a tumor sample, for example, when using sequential staining. EX1012, 83 (Chapter 6.7); EX1002 ¶283. Other references disclosed the use of IHC for PD-L1 and for one or more additional markers. For example, *Taube 2012* disclosed using an IHC marker for PD-L1 expression by tumor cells and TIICs and CD3 and CD68 immunostains to interpret which cell type demonstrated expression of a given ligand. EX1013, 8; EX1002 ¶¶168, 283.

e) Dependent Claim 14

Claim 14 depends from claim 1 and requires, “prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding

fragment thereof.” Through dependence on claim 1, claim 14 incorporates the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶286-87.

A POSA would have understood that, to determine the numbers of the cell types described in claim 1, the cells must first be contacted with an anti-PD-L1 antibody or fragment thereof so that they could be identified. This additional limitation does not materially limit claim 1. Thus, claim 14 is patent ineligible for the same reasons as claim 1.

Further, like claim 1, claim 14 does not require any specific action, such as administering an anti-PD therapy after assessing eligibility, and does not identify the subject, cancer to be treated, anti-PD therapy, effective dose/dosing regimen, or threshold. Claim 14 therefore lacks an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶286, 288-89.

Moreover, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof prior to the Determining Step is conventional. For example, *WO422* taught using the anti-PD antibody 22C3 for IHC staining to detect PD-L1 (EX1010, [0022]) and disclosed examples in which tumor tissue

samples were stained by IHC with antibody 22C3 (EX1010, [0026]-[0029], Fig. 3). A POSA would have understood that the IHC staining taught in *WO422* would entail contacting the tumor tissue sample with antibody 22C3. EX1010, [0073]; EX1012, Fig. 6.1; EX1002 ¶287.

f) Dependent Claim 15

Claim 15 depends from claim 1 and requires that single cell sequencing is used to count the number of PD-L1 and MIC cells. *US702* identifies next generation sequencing as a type of single cell sequencing. EX1001, 9:50-55. Through dependence on claim 1, claim 15 incorporates the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶290-91.

Like claim 1, claim 15 does not require any specific action, such as administering an anti-PD therapy, after assessing eligibility for anti-PD therapy, and does not identify the subject, cancer to be treated, anti-PD therapy, or effective dose/dosing regimen, or threshold. Claim 15 therefore lacks an action step and lacks the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating. Accordingly, the steps in the claimed method, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶290-91, 293-94.

Moreover, single cell sequencing was conventional. *Dako* taught that next generation sequencing was entering routine diagnostic application. EX1012, 119; *see also* EX1060, 230; EX1002 ¶292. *US702* does not improve upon the existing body of literature regarding single cell sequencing or show how to apply it for purposes of practicing the claimed method. *Id.*

g) Dependent Claims 16 and 19

Claim 16 depends from claim 1 and further requires that the malignancy is selected from a group of identified cancers, including breast cancer. Claim 19 depends from claim 16 and specifies that the breast cancer is one of five specified types of breast cancer, including estrogen receptor positive breast cancer (ERPB), HER2 positive breast cancer, and TNBC. Through direct or indirect dependence on claim 1, claims 16 and 19 incorporate the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶295-96.

Like claim 1, claims 16 and 19 do not require any specific action, such as administering an anti-PD therapy, after assessing eligibility for anti-PD therapy, and do not identify the subject, a specific cancer to be treated, anti-PD therapy, effective dose/dosing regimen, or threshold. Indeed, claim 16 identifies 20 categories of cancer (including subcategories), and claim 19 recites five types of breast cancer. Moreover, *US702* provides no teaching regarding the connection between any specific cancer type, anti-PD therapies, and applicable CPS

thresholds. Claims 16 and 19 therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating.

Accordingly, the steps in the claimed method, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶295-96, 298-99.

Moreover, using a PD-L1 score to assess eligibility of the specified cancer types for anti-PD therapy was conventional. For example, *WO422* identifies determining treatment eligibility based on PD-L1 expression for most of the cancer types listed in claim 16, including ERPB, HER2 positive breast cancer, and TNBC recited in claim 19. EX1010, [0017]; *see* EX1015, Abstract; EX1060, 237; EX1002 ¶297.

h) Dependent Claims 17 and 18

Claim 17 depends from claim 1 and requires that the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1. Claim 18 depends from claim 1 and requires that the anti-PD therapeutic agent is selected from the group consisting of Avelumab, Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736. Through dependence on claim 1, claims 17-18 incorporate the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶300-01.

Like claim 1, claims 17 and 18 do not require any specific action, such as administering an anti-PD therapy, after assessing eligibility for anti-PD therapy, and do not identify the subject, cancer to be treated, specific anti-PD therapy, and/or effective dose/dosing regimen, or threshold. More specifically, claim 17 requires that the anti-PD therapeutic agent inhibit the anti-cell death activity of PD-1/PD-L1. A POSA would have understood that any anti-PD therapy would have this effect. EX1002 ¶303. Claims 17-18 therefore lack an action step and lack the specificity required to integrate the ineligible natural law, abstract idea, or mental step into a practical application or convert them into an improved method of treating. Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claim. EX1002 ¶¶300-01, 304.

Moreover, the use of an anti-PD therapeutic agent from the group identified in claim 18 would have been conventional. For example, *WO422* discloses the use of nivolumab, pidilizumab, MPDL3280, and MEDI4736 and pembrolizumab. EX1010, Exemplary Specific Embodiment 27; EX1019, 1; EX1020, 1; EX1002 ¶302.

i) Dependent Claims 20 and 21

Claim 20 depends from claim 1 and further requires administering said anti-PD therapeutic agent to the subject when the CPS is above an unspecified

threshold. Claim 21 depends from claim 20 and further requires that the threshold is $\geq 1\%$. Through direct or indirect dependence on claim 1, claims 20-21 incorporate the natural law, abstract idea, and mental step that are the entirety of claim 1. EX1002 ¶¶305-06.

While claims 20 and 21 include an administering step, they do not provide the specificity needed to transform the nature of the claims into a patent-eligible application. For example, claims 20 and 21 do not identify the subject, cancer to be treated, specific anti-PD therapy, and/or effective dose/dosing regimen, and claim 20 also does not disclose a “threshold.” EX1002 ¶307. Claims 20-21 are therefore very different than the claims in *Vanda*. More specifically, the steps in claims 20-21 do not transform the nature of the claim because, unlike in *Vanda*, the steps in claims 20-21 do not take advantage of the body’s natural processes by providing “a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome.” *See Rizen*, PGR2022-00051, Paper 14, 16, quoting *Vanda*, 887 F.3d at 1136; EX1002 ¶308.

Claims 20 and 21 are also very different than claim 2 of Patent Office Example 49, which the example states is “eligible.” Claim 2 of Example 49 specifies the identity of the appropriate treatment (Compound X eye drops) for a specific malady (a glaucoma patient at high risk of PI after microstent implant surgery) and, according to the Patent Office, therefore “meaningfully limit[s]” the

abstract determining element in claim 1 of Example 49. EX1081, 34-35. In contrast, *US702* claims 20 and 21 do not meaningfully limit claim 1 because they do not identify an appropriate treatment for a specific cancer. They are far broader, leaving the cancer type unlimited and identifying a very broad category of therapy, an—“anti-PD therapeutic agent”—without reciting a specific anti-PD therapy, dose, or dosing regimen. Claim 20 is even broader in that it does not even limit the claimed CPS threshold. EX1002 ¶308.

Finally, the steps in claims 20-21 are conventional. Administering an anti-PD therapy after assessing PD-L1 expression and comparing it to an expression score was well-known and routine, as evidenced by at least the disclosure of such steps in *WO422*. EX1010, [0118], claim 18; EX1002 ¶307. Moreover, two anti-PD-1 therapies, Keytruda and Opdivo, were approved more than a year before the earliest possible effective filing date of *US702*, and *US702* does not change how subjects were dosed with those treatments.

In this regard, claims 20 and 21 are like the claims held invalid in *Ino*, discussed above. In *INO*, patentee argued that the claims were not directed to a natural phenomenon because they include a treatment step, the affirmative act of administering 20 ppm inhaled nitric oxide to patients without LVD. *INO*, 782 F. App’x at 1006. But the Federal Circuit held that the novelty of the claim was withholding treatment from patients with LVD. *Id.* at 1007. Treatment was

already conventional, and excluding treatment was not patent eligible. *Id.* at 1006. Similarly here, before *US702*, subjects were already receiving conventional anti-PD-1 therapy, like Keytruda and Opdivo. Under claims 20 and 21, if their CPS reached a particular threshold, they would continue to receive treatment, and the treatment would not change. If the score did not reach a threshold, treatment could be excluded. Like the claims in *INO*, the novelty is at best excluding patients from treatment, which is not patent eligible.

Accordingly, the steps in the claimed methods, considered individually or as an ordered combination, do not transform the nature of the claims into a patent-eligible application. EX1002 ¶¶305-06, 309.

B. Ground 2: Claims 1-21 Are Invalid for Lack of Enablement

The specification of *US702* does not enable the full scope of the claimed invention without undue experimentation, and all claims are therefore invalid for lack of enablement. EX1002 ¶¶310-370, 462. A claim is not enabled when a specification “discloses only a starting point for further iterative research in an unpredictable and poorly understood field.” *See Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1386 (Fed. Cir. 2013). It is also not enabled if it provides no “more than... research assignments” or “hunting license[s]” that leave scientists “forced to engage in ‘painstaking experimentation’ to see what works.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023) (citing *The Incandescent Lamp*

Patent, 159 U.S. 465, 475 (1895) and *Brenner v. Manson*, 383 U. S. 519, 536 (1966)).

These are precisely the problems a skilled artisan would face when trying to practice the claims of *US702*, given the limited guidance in its specification.

Analysis of the *Wands* factors shows that the claims of *US702* are not enabled because they would require undue experimentation to practice. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Claim 1, for example, requires assessing the eligibility of an unspecified subject (human or non-human animal) with an unspecified malignancy (there are hundreds) for an unspecified anti-PD therapy (there are at least hundreds) by determining whether the subject has a CPS that exceeds an unspecified threshold. There are at least thousands of potential combinations of these variables. Further, the threshold depends on the anti-PD therapy (and line of therapy (EX1031, 986-87)) and malignancy, and the only method provided for determining the threshold is generating a ROC curve for each therapy/malignancy combination, which requires conducting a carefully designed clinical trial. A POSA would need to undertake this research for each potential combination to determine the appropriate threshold. *US702* provides neither an experimentally determined threshold nor any teaching that would permit determination of such a threshold without extensive/undue experimentation. None of the limitations in dependent claims 2-21 remedy the deficiencies of claim 1.

1. Claim 1

As explained below, the *Wands* factors support the conclusion that undue experimentation would have been required to practice the full scope of claim 1.

a) Claim 1 Is Very Broad (Factor 1)

Claim 1 is directed to determining the eligibility of an unspecified subject with an unspecified malignancy for treatment with an unspecified anti-PD therapy based on a calculated CPS that exceeds an unspecified threshold. At least the malignancy, therapy, and threshold limitations in claim 1 are very broad:

Malignancy: The CPS threshold depends on the type of malignancy. Claim 1 does not specify the malignancy, and therefore covers the hundreds of potential malignancies, making claim 1 very broad. EX1025; EX1002 ¶¶310-11, 313, 329.

Anti-PD therapy: The CPS threshold depends on the anti-PD therapy and potentially on whether the therapy is first line or administered later in treatment. EX1031, 986-87; EX1002 ¶¶314, 331-33. Nevertheless, claim 1 does not specify the therapy or line of therapy, stating only that it can be “an anti-PD or anti-PD-L1 specific antibody or fragment thereof.” According to the specification, antibody fragments include: “fragments of antibodies which retain specific binding to antigen or target, including, but not limited to, Fab, Fv, scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, bi-specific hybrid anti-bodies, and fusion proteins comprising an antigen-binding portion of an

antibody and a non-antibody protein.” EX1001, 7:11-17; EX1002 ¶¶132, 330.

While the claims are not limited to approved therapies, it has been reported that 8 anti-PD antibodies have been approved in the U.S. and 18 have been approved worldwide (EX1075, 1; EX1073, 1), with some reports indicating that over 30 anti-PD antibodies have been approved worldwide (EX1074, 5). EX1002 ¶330. But the number of antibodies and fragments that could in theory be generated to specifically bind to the PD-1 receptor or PD-L1 ligand number in at least in the thousands. EX1002 ¶231.

Accordingly, the claim 1 anti-PD therapy limitation is very broad.

Threshold: The specification states that the threshold can be any applicable CPS value, “and is specific to the drug used” (EX1001, 8:47-51). There are hundreds of potential drugs/therapies. EX1002 ¶¶231, 329-330. Claim 1 does not specify a CPS threshold, meaning it could be any value between 0 and 100% and has to be determined before practicing the claimed method. EX1002 ¶334.

The breadth of the claims is compounded by the interrelationships between the subject, malignancy, anti-PD therapy (and line of therapy), and CPS threshold. EX1002 ¶¶322-24. The specification does not explain the relationships between these claim elements. EX1002 ¶¶325, 327-33. Indeed, the specification does not provide a single example of a threshold applicable to a specific malignancy/therapy combination. Moreover, some studies have found no significant association

between PD-L1 expression and patient outcome in some “subject” populations. EX1014, 2200; EX1002 ¶¶315-21. The lack of disclosure therefore presents scientists with a “research assignment” and at best “a starting point for further iterative research in an unpredictable and poorly understood field,” forcing the POSA “to engage in ‘painstaking experimentation’ to see what works.” *Wyeth*, 720 F.3d at 1384; *Amgen*, 598 U.S. at 614; EX1002 ¶326.

b) The Specification Provides Little Guidance (Factor 2)

The specification states that the threshold can be any applicable CPS value, and that in some embodiments, the threshold is 1%. EX1001 8:49-52. The specification provides a single prophetic example in which the malignancy is gastric carcinoma and the therapy is not identified. The example speculates that a CPS cut-off/threshold of $\geq 1\%$ is expected to “identify subjects who are responsive to anti-PD therapy that are missed by the TPS and MIDS analyses.” EX1001, 20:66-21:2. The specification theorizes that “CPS can be used to analyze triple negative breast carcinoma (TNBC) using a similar cut-off value as described above.” EX1001, 21:9-10; EX1002 ¶¶149, 335-39.

As to the threshold itself, *US702* states that “[a] cut-off is the score that differentiates diagnostically positive from diagnostically negative.” EX1001, 20:60-62. The only method identified for determining a cut-off/threshold is generating a “ROC curve for best responder/cut off (threshold) correlation”

(EX1001, 8:47-48), which as explained requires conducting a clinical trial for each malignancy/anti-PD therapy/dosing regimen combination. EX1002 ¶¶312, 340-42.

Finally, the specification provides no principles or generalized relationships between drug, malignancy, and/or drug/malignancy combination that would permit extrapolating a CPS threshold for any given combination from the specification or elsewhere. The specification's teachings regarding how to perform IHC and calculate CPS do not fill this gap. EX1002 ¶343. In view of the interrelationships between the multiple unspecified elements of the claims, undue experimentation would be required to practice the full scope of the method of claim 1.

c) The Single Example Is Not a Working Example; It Is Prophetic, Narrow, and Incomplete (Factor 3)

Example 1, *US702*'s only example, is prophetic and is thus not a working example. Example 1 describes a tumor tissue sample from a gastric carcinoma patient with no therapy identified and only an "expected" CPS threshold of $\geq 1\%$. *See* Section I.A. Example 1 includes prophetic steps up to estimating the number of PD-L1^{+/+} cells, but no TPS, MIDS, or CPS was calculated, and no population of patients was analyzed to assess responsiveness, generate an ROC curve, or identify a threshold. EX1001, 19:42-21:5. Thus, Example 1 does not convey information that would let one determine the CPS eligibility threshold for any drug/malignancy combination, let alone the at least thousands of claimed subject/drug/malignancy combinations, without undue experimentation. EX1002 ¶¶344-47.

d) The Claimed Methods Require Determining Unpredictable Clinically Meaningful Correlations Between PD-L1 Expression and Therapeutic Response (Factors 4-6)

The claimed methods require determining a CPS threshold, which is the natural correlation between PD-L1 expression and clinical response to a specific therapy. While POSAs understood that an association exists between the effectiveness of anti-PD therapy and the extent of PD-L1 expression, in view of the interrelationship between unspecified claim elements, a POSA could not have predicted the CPS threshold for the full scope of claimed drug/malignancy combinations. Indeed, in some cancers it was found that PD-L1 expression did not correlate with response to anti-PD therapy. EX1051, 6-7. In addition, the prior art did not teach any correlation or means to predict the CPS threshold for one drug/malignancy combination based on an experimentally determined CPS threshold for another drug/malignancy combination. Consequently, determining the CPS threshold requires conducting, for each drug/malignancy combination, a non-trivial clinical study. The lack of teaching in the specification therefore presents no more than a “research assignment” or “starting point for further iterative research in an unpredictable and poorly understood field,” forcing scientists “to engage in ‘painstaking experimentation’ to see what works.” *Wyeth*, 720 F.3d at 1384; *Amgen*, 598 U.S. at 614; EX1002 ¶¶348-51.

e) The Level of Skill in the Art Does Not Change the Amount of Experimentation Required (Factor 7)

As explained in Sections I.A. and VII.B.1, the claimed method requires applying an unpredictable CPS threshold that must be determined, through a clinical trial, for each drug/malignancy combination, wherein neither the specification nor prior art provide a CPS threshold for any specific drug/malignancy combination or teach how to extrapolate that threshold from available information. Accordingly, even if the level of skill in the art were high, undue experimentation would be required to practice the full scope of claim 1, particularly in view of its breadth, the unpredictable nature of the claimed method/CPS threshold, and the need to conduct a clinical trial for each drug/malignancy combination to empirically determine such threshold, if it even exists. EX1002 ¶¶352-53.

f) Extensive/Undue Experimentation Would Have Been Required To Practice the Full Scope of Claim 1 (Factor 8)

For all of the reasons above, undue experimentation would have been required to practice the full scope of claim 1. EX1002 ¶¶354-55.

* * *

For all of the above reasons, claim 1 is invalid for lack of enablement under 35 U.S.C. §112.

2. Dependent Claims 2-21 Are Invalid for Lack of Enablement

The dependent limitations in claims 2-21 do not remedy the claim 1 lack of enablement described above for the following reasons.

Claims 2 and 3 depend from claim 1 and add threshold limitations of “from 10% to 1%” (claim 2) and “1%” (claim 3). These threshold limitations do not remedy the enablement issue because the claims do not identify a subject (human or non-human animal), cancer (there are potentially over 200), anti-PD therapy/line of therapy (there are potentially hundreds), or dose/dosing regimen, all of which can impact the CPS threshold. EX1002 ¶¶133-34, 231, 329-330, 356-57. Claims 2 and 3 are therefore invalid for lack of enablement because they do not remedy the deficiencies of claim 1.

Claims 4 and 10 depend from claim 1 and require that the tumor tissue sample is a biopsy or a cell suspension, respectively. Claims 5-9 depend directly or indirectly from claim 4 and add limitations regarding how the IHC is conducted. Claims 11 and 15, which depend from claims 10 and 1, respectively, add limitations regarding how PD-L1 positivity/negativity is determined. Claims 12 and 13 depend directly or indirectly from claim 1 and require detecting a marker other than PD-L1. Claim 14 depends from claim 1 and requires a contacting step prior to the determining step. The limitations in each of claims 4-15 do not remedy the enablement issue because the claims do not identify a subject, threshold, cancer

(potentially over 200), anti-PD therapy/line of therapy (potentially hundreds), or dose/dosing regimen, all of which can impact the CPS threshold. Claims 4-15 are therefore invalid for lack of enablement because they do not remedy the deficiencies of claim 1 or the claims from which they depend. EX1002 ¶¶358-66.

Claims 16 and 19 depend directly or indirectly from claim 1 and specify selecting the malignancy from a group of at least 24 malignancies (and likely far more). The claims therefore cover many malignancies, and do not identify a subject, threshold, anti-PD therapy/line of therapy (potentially hundreds), or dose/dosing regimen, all of which can impact the CPS threshold. Claims 16 and 19 are therefore invalid for lack of enablement because they do not remedy the deficiencies of claim 1. EX1002 ¶367.

Claims 17 and 18 depend directly or indirectly from claim 1, limiting the anti-PD therapeutic agent to an agent that “inhibits the anti-cell death activity of PD-1/PD-L1” (claim 17) or an agent selected from a group of seven agents. Claim 18, the narrowest claim with respect to anti-PD therapies, remains very broad because it recites seven therapies and does not specify whether the therapy is first line or later, and does not specify a dose/dosing regimen, subject, malignancy (there are hundreds), or CPS threshold. Claims 17 and 18 are therefore invalid for lack of enablement because they do not remedy the deficiencies of claim 1. EX1002 ¶368.

Claim 20 depends from claim 1 and requires administration of an anti-PD therapeutic agent, and claim 21 depends from claim 20 and recites a threshold of $\geq 1\%$. The limitations in claims 20 and 21 do not remedy the enablement issue because the claims do not identify a subject, cancer (potentially over 200), anti-PD therapy/line of therapy (potentially hundreds), or dose/dosing regimen, all of which can impact the CPS threshold. Claims 20 and 21 are therefore invalid for lack of enablement because they do not remedy the deficiencies of claim 1. EX1002 ¶¶369-70.

C. Ground 3: Claims 1-8, 12-14, and 16-21 Are Invalid as Obvious over the Combination of *WO422*, *Bellmunt*, and *Savas*

1. Claim 1

Claim 1, which is directed to a method for determining whether a subject with a malignancy is eligible for treatment with an anti-PD therapeutic agent, would have been obvious to a POSA from the disclosures in *WO422*, *Bellmunt*, and *Savas*.

WO422 is drawn to “quantitation of PD-L1 expression in animal tissue samples by immunohistochemical (IHC) assay” for determining those subjects that may benefit from therapy with antagonists of PD-1. EX1010, [0001], [0009]. In the disclosed methods, frozen or FFPE tumor samples are stained with a primary antibody that binds to PD-L1. *Id.* [0010], [0082]; EX1002 ¶¶371-73.

WO422 notes that PD-L1 expression correlated with poor prognosis and reduced overall survival in a large set of tumors, including ovarian, renal, colorectal, pancreatic, and liver cancers and melanoma, and that anti-PD antibodies have been shown to have anti-tumor activity in a variety of tumor types, with those expressing PD-L1 most likely to respond. EX1010, [0003]; EX1002 ¶374.

According to *WO422*, one approach that had been used to quantify PD-L1 expression is the percentage of tumor cells that show staining with anti-PD-L1 antibodies over the total number of tumor cells. EX1010 [0005]. This score can be expressed as:

$$\frac{\text{PD-L1-stained viable tumor cells}}{\text{Total viable tumor cells}} \times 100\%$$

Thresholds included 1% or 5% of total tumor cells. *Id.* *WO422* discloses further that PD-L1 expression has also been quantified in infiltrating immune cells, which predominantly comprise lymphocytes. EX1010, [0006]; EX1002 ¶375-76.

WO422 teaches that quantifying PD-L1 expression using IHC analysis, “beyond a simple binary positive/negative characterization, can provide valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.” EX1010, [0009]. In embodiment 1, *WO422* teaches staining a tumor tissue section with an anti-PD-L1 antibody and examining the tissue section for staining. A subject’s MPS is determined by “estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of

the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity and assigning the resulting percentage to the tissue section as the MPS.” *Id.*, Exemplary Specific Embodiment 1. That is, MPS can be determined using the calculation:

$$\text{MPS} = \frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

The MPS thus incorporated the number of PD-L1⁺ tumor cells *and* the number of PD-L1⁺ MICs. The MPS is identical to the claimed CPS with one exception: the CPS does not include the total number of MICs in the denominator.

CPS =

$$\frac{\text{PD-L1 positive tumor cells} + \text{PD-L1 positive MIC}}{\text{PD-L1 positive tumor cells} + \text{PD-L1 negative tumor cells}} \times 100\%$$

But *WO422* is directed to the concept claimed in *US702*, *i.e.*, use of a combined score for determining eligibility for anti-PD therapy that requires counting both PD-L1⁺ tumor cells and PD-L1⁺ MICs. *See* Section I.C.2.a. The slight difference between the *US702* and *WO422* scoring methods is not sufficient to render the challenged claims nonobvious. EX1002 ¶¶376-82.

Bellmunt taught that neither the total number of MICs nor the number of PD-L1⁺ MICs carry any weight when assessing the value of PD-L1⁺ MICs for predicting whether anti-PD therapy will benefit a patient. EX1023, 812; EX1002 ¶400. A POSA would have further understood from *Savas* that the expression of

PD-L1 on MICs leads to a better responses to anti-PD therapies for certain breast cancers and that the presence of MICs generally, regardless of PD-L1 expression, is also associated with better outcomes. EX1060, 228, 231, 238; EX1002 ¶¶177, 179.

Given that PD-L1⁺ MICs were known to be beneficial to patients receiving anti-PD therapy, and that PD-L1⁻ MICs were not viewed as weighing against anti-PD treatment but indeed were also thought to lead to better outcomes, a POSA would have known that counting total MICs in the denominator of the MPS would have penalized a subject's potential eligibility. This could render some subjects ineligible for treatment simply because their tumors contained a significant percentage of PD-L1⁻ MICs, which were regarded as beneficial. Accordingly, it would have been obvious to remove the total number of MICs from the denominator to arrive at the CPS equation with a reasonable expectation of success of determining eligibility for treatment with an anti-PD1 therapeutic agent. EX1002 ¶ 382.

a) “A method for determining the eligibility of a subject having a malignancy for treatment with an anti-PD therapeutic agent, the method comprising:”

As discussed above, *WO422* is drawn to “quantitation of PD-L1 expression in animal tissue samples by immunohistochemical (IHC) assay” for determining those subjects that may benefit from therapy with antagonists of PD-1. EX1010,

[0001], [0009]. *WO422* thus teaches the preamble of claim 1, to the extent the preamble is limiting. EX1002 ¶383.

- b) **“determining the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive mononuclear inflammatory cells (MIC) in a tumor tissue sample from a subject having a malignancy:”**

WO422 teaches a method in which a tumor tissue section is stained with an anti-PD-L1 antibody. An MPS is determined by “estimating, across all of the viable tumor cells and mononuclear inflammatory cells in all of the examined tumor nests, the percentage of cells that have at least partial membrane staining of any intensity, and assigning the resulting percentage to the tissue section.”

EX1010, *e.g.*, Exemplary Specific Embodiment 1, claim 10; *see also id.*, [0112] (“Medium and high power is typically used to examine individual tumor nests to estimate the number and intensity of viable tumor and mononuclear inflammatory cells that exhibit at least partial membrane staining”). As discussed in Section VI.B., the Determining Step encompasses both the exact enumeration of every cell, as well as an approximate numerical assessment. *WO422* thus discloses this step of claim 1. EX1002 ¶¶384-87.

- c) “calculating a combined positive score (CPS) for the tumor tissue sample using the [CPS] formula:”

$$CPS = \frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ negative tumor cells}} \times 100\%$$

The MPS can be determined using the calculation:

$$MPS = \frac{PD-L1 \text{ positive tumor cells} + PD-L1 \text{ positive MIC}}{\text{Total number of viable tumor cells} + \text{Total number of MIC}} \times 100\%$$

Thus, as explained above, the MPS differs from the CPS only in that in the CPS the total number of MICs are not added into the denominator. As explained below, a POSA would have been motivated to modify the MPS to remove the total number of MICs from the denominator, at least for assessing eligibility for treatment of certain tumors responsive to anti-PD therapy. EX1002 ¶¶388-89, 416.

A POSA would have understood that the numerator of a “score,” like the MPS, is intended to include the elements of the score that are expected to have predictive value. This is why the numerator of the MPS, for example, includes PD-L1⁺ tumor cells and PD-L1⁺ infiltrating cells. EX1002 ¶¶390-91. A POSA would have understood that a subject would benefit from anti-PD therapy in part because that therapy would prevent PD-L1⁺ infiltrating cells, including MICs, from disrupting the body’s immune response against the tumor. EX1002 ¶392. This is consistent with the understanding that, as discussed above, PD-L1 expression by MICs inhibits T-cell function by binding to PD-1 on T-cells. *E.g.*, EX1016, 22 If

there are many PD-L1⁺ MICs relative to tumor cells, then there is a greater likelihood that blocking the PD-1/PD-L1 interaction with anti-PD therapy will increase the immune system's ability to attack tumor cells.

But whether there are a lot of negative MICs will not matter. Unlike PD-L1⁻ tumor cells, the presence of PD-L1⁻ MICs will not alter the efficacy of anti-PD therapy because PD-L1⁻ MICs do not inhibit T-cell immune response through the PD-L1/PD-1 axis. EX1002 ¶393.

Indeed, it was thought that the presence of such PD-L1⁻ MICs could lead to *better* outcomes. As is clear from references like *Savas*, MICs, whether PD-L1⁺ or not, may be potentially helpful for tumors like breast cancer that respond to anti-PD therapy. EX1060, 231-232, 237. *Savas*, like *WO422*, discusses the use of PD-L1 staining of tumor cells and MICs for predicting whether patients with breast cancer, including TNBC, will benefit from anti-PD therapy. *Savas* explains that generally, “[t]hese infiltrates seem to reflect favourable host antitumour immune responses, suggesting that immune activation is important for improving survival outcomes.” EX1060, 228; *see* Section I.C.2.c.

Thus, a POSA would have been motivated to remove the MICs from the denominator of the MPS, where the presence of PD-L1⁻ MICs will weigh against eligibility, potentially rendering some subjects ineligible for treatment despite the fact that PD-L1⁻ MICs are at worst a neutral factor and at best a positive one.

To understand how including PD-L1⁻ MICs in the denominator can lower the score and increase the risk of false negatives, consider a hypothetical subject with 100 tumor cells and 20 MICs, 13 PD-L1⁺ cells (tumor and MIC), and a hypothetical MPS eligibility threshold of 10%. This subject would have an MPS of 10.8 and would be eligible for treatment. Increasing total MICs from 20 to 50 in the denominator, however, reduces the MPS from 10.8 to 8.7—even if all 30 additional MICs were PD-L1⁻, rendering the subject ineligible for treatment despite the fact that such PD-L1⁻ MICs do not affect anti-PD therapy and in fact could be beneficial. EX1002 ¶¶394-99.

Further, a diagnostic score that included PD-L1⁺ MICs and not the total number of MICs was not novel. *Bellmunt*, which evaluated the predictive value of PD-L1⁺ MICs, scored PD-L1 expression by evaluating “the extent of PD-L1-positive [MICs]” in the tumor. EX1023, 813; *see* Section I.C.2.b. *Bellmunt* thus confirms that POSAs understood that PD-L1⁻ MICs do not negatively impact anti-PD therapy and should not weigh against treatment in a diagnostic score. This understanding would have motivated a POSA to modify the MPS in *WO422* to include only PD-L1⁺ MICs in the score, as in *Bellmunt*, by removing the total MICs from the denominator. EX1002 ¶¶400-02, 404-06.

A POSA also would have had a reasonable expectation that removing the total MICs from the denominator of the MPS would lead to success in determining

the eligibility of patients for anti-PD therapy. EX1002, ¶¶407-414. *WO422* itself disclosed the value of the MPS for determining eligibility, stating that the MPS “provide[s] valuable predictive information to identify patients who are more likely to respond to treatment with anti-PD-1 therapy.... A PD-L1 expression score produced by performing this scoring process may be useful in selecting patients to receive anti-PD-1 therapy.” EX1010, [0009]; EX1002 ¶¶408-10. Further, the POSA would have understood that removing total MICs from the denominator would reduce the possibility of false negatives without otherwise altering the effectiveness of the MPS as a determinant of eligibility. EX1002 ¶¶394-400.

- d) **“wherein the subject is eligible for treatment with said anti-PD therapeutic agent when the CPS is above a threshold, wherein said anti-PD therapeutic agent comprises an anti-PD or anti-PD-L1 specific antibody or binding fragment thereof.”**

WO422 teaches treating a subject with a PD-L1 antagonist if the MPS exceeds a threshold. EX1010, [0019], [00118], Exemplary Specific Embodiments 23-24, Claims 18-19. EX1002 ¶415.

Thus, the combination of *WO422*, *Bellmunt*, and *Savas* renders independent claim 1 obvious for the reasons set forth above. EX1002 ¶416.

2. Claims 2 and 3

(Claim 2) “wherein the threshold is from 10% to 1%”

(Claim 3) “wherein the threshold is 1%”

Claims 2 and 3 each depend from claim 1 and add CPS thresholds. *WO422* discloses that a patient is treated with a PD-1 antagonist if the MPS is above a specified threshold, which is greater than zero. EX1010, [0019]. Claim 1 requires only that the CPS be used to determine eligibility for treatment with an anti-PD therapeutic agent. A POSA would have understood that an MPS threshold of equal to or greater than 1 indicates that PD-L1⁺ tumor cells and/or MICs exist. A POSA would likewise have understood that a subject with an MPS score between 1 and 10 would have PD-L1⁺ tumor cells that would likely respond to an anti-PD-1 therapeutic agent. EX1002 ¶¶417-19.

For these reasons and the reasons discussed above with respect to claim 1, claims 2 and 3 are would have been obvious to a POSA over the combination of *WO422*, *Bellmunt*, and *Savas*. EX1002 ¶420.

3. Claims 4-7

(Claim 4) “wherein the tumor tissue sample is a tissue section of a tumor biopsy”

(Claim 5) “wherein PD-L1 is detected by immunohistochemistry (IHC) staining”

(Claim 6) “wherein the tumor tissue section is a formalin fixed and embedded in paraffin wax (FFPE) tumor tissue section”

(Claim 7) “wherein the tissue section is stained”

Claim 4, which depends from claim 1, and claims 5-7, which depend from claim 4, are all directed to routine and conventional methods for staining for PD-L1. These limitations are taught by *WO422*, which teaches obtaining a tumor tissue sample from a biopsy ([0081] and [00113]), IHC staining to detect PD-L1 ([0026]-[0029], [00113]), an FFPE tumor tissue section ([0021], [0082], Exemplary Specific Embodiment 17, Claim 13), and staining a tissue section ([0010], [0017], [0024]-[0029], [0066], [0080], [00113], [00122], [00129], Exemplary Specific Embodiments 1, 12, Claims 1, 10, 23). For these reasons and the reasons discussed above with respect to claim 1, claims 4-7 are rendered obvious by the combination of *WO422*, *Bellmont*, and *Savas*. EX1002 ¶¶421-24.

4. Claim 8: “wherein the stain is a hematoxylin and eosin (H&E) stain”

Claim 8 depends from claim 7 and adds the limitation that the stain is an H&E stain. It would have been obvious at the time of invention to use H&E stain

because its use was well-known and routine. *WO422* teaches that the “IHC assay may be performed using an automated pathology system, which may include automated staining (conventional stains, histochemical techniques, immunostainers.)” EX1010 [0097]. As discussed in Sections I.C.1.e. and VII.A.2.b., the routine use of H&E stains was known in the prior art. EX1060, 229 (“TILs are commonly detected in haematoxylin and eosin (H&E) stained histological slides via light microscopy); *see also* EX1023, 813; *US702*, 10:2-19 (disclosing H&E stain as the most commonly used light microscopy stain in histology and histopathology); EX1002 ¶425.

For these reasons and the reasons discussed above with respect to claims 1 and 7, claim 8 would have been obvious to a POSA over the combination of *WO422*, *Bellmunt*, and *Savas*. EX1002 ¶426.

5. Claims 12 and 13

(Claim 12) “wherein one or more additional marker is detected in the tumor tissue sample”

(Claim 13) “wherein the marker is specific for MIC or is selected from the group consisting of: CD3, CD5, CD4, CD7, CD8, and CD20”

Claim 12 depends from claim 1 and recites that an additional marker is detected, and claim 13 depends from claim 12 and limits the marker to one of CD3, CD5, CD4, CD7, CD8, and CD20.

Savas discloses that the immune microenvironment of the tumor is also shaped by competing co-stimulatory and co-inhibitory signals. EX1060, 236. *Savas* notes that “the presence of activated CD8⁺ T-cells in the tumour microenvironment is associated with favourable outcomes,” although they may also induce counter-immune mechanisms. *Id.* Thus, it would have been obvious to a POSA to detect another marker, such as CD8, given that CD8 was associated with favorable outcomes. EX1002 ¶¶402, 427-29.

For these reasons and the reasons discussed above with respect to claim 1, claims 12 and 13 would have been obvious to a POSA over the combination of *WO422*, *Bellmunt*, and *Savas*. EX1002 ¶429.

6. Claim 14: “wherein the method further comprises, prior to the determining step, contacting the tumor tissue sample with an anti-PD-L1 antibody or binding fragment thereof”

Claim 14 depends from claim 1 and requires contacting the tumor tissue sample with an anti-PD-L1 antibody. As discussed above, it was routine and conventional to use an anti-PD-L1 antibody to detect PD-L1⁺ cells. *See* Section I.C.1.e. Moreover, *WO422* explicitly teaches the use of anti-PD-L1 antibodies for detecting PD-L1⁺ cells. EX1010, [00101]. For these reasons and the reasons discussed above with respect to claim 1, claim 14 is rendered obvious by the combination of *WO422*, *Bellmunt*, and *Savas*. EX1002 ¶¶430-32.

7. **Claims 16 and 19**

(Claim 16) “wherein the malignancy is selected from the group consisting of: [listing of 20 cancer-type categories]”

(Claim 19) “wherein the breast cancer is triple negative breast cancer, hormone receptor positive breast cancer, estrogen receptor positive breast cancer, progesterone receptor positive breast cancer, or Her2 positive breast cancer”

Claim 16 depends from claim 1, and claim 19 depends from claim 16. Both claims add long lists of malignancy limitations that include TNBC, estrogen positive HER2 negative breast cancer, or HER2 positive breast cancer. *WO422* discloses that the tumor is selected from a group of 20 listed categories of cancers that include TNBC, estrogen positive HER2 negative breast cancer, or HER2 positive breast cancer. EX1010, [0017]. Moreover, *Savas* also discloses that the “presence of high levels of lymphocytic infiltration has been consistently associated with a more favourable prognosis in patients with early stage triple-negative and HER-2 positive breast cancer.” EX1060, 228. For these reasons and the reasons discussed above with respect to claim 1, it would have been obvious to a POSA to treat breast cancer, such as triple-negative and HER2 positive breast cancer as required by claims 16 and 19. Claims 16 and 19 are therefore rendered obvious by the combination of *WO422*, *Bellmont*, and *Savas* for the reasons set forth above and as to claim 1. EX1002 ¶¶433-35.

8. Claims 17 and 18

(Claim 17) “wherein the anti-PD therapeutic agent inhibits the anti-cell death activity of PD-1/PD-L1”

(Claim 18) “wherein the anti-PD therapeutic agent is selected from the group consisting of: Avelumab (MSB0010178C), Nivolumab, Pembrolizumab, BMS-936559, MPDL3280A, Pidilizumab, and MEDI4736”

Claims 17 and 18 depend from claim 1 and further define the anti-PD therapeutic agent. *WO422* discloses that the PD-L1 antagonist can be, *inter alia*, nivolumab, MPDL3280A, BMS-936559, MEDI4736, or pembrolizumab. EX1010, [0072], Exemplary Specific Embodiments 25-27, Claims 20-21. Each of these compounds was in the prior art and known to be an “anti-PD therapeutic agent [that] inhibits the anti-cell death activity of PD-1/PD-L1,” as recited in claim 17. EX1002 ¶¶437-38; EX1001, 2:13-56 (identifying, *inter alia*, the following “[e]xamples of anti-PD therapeutics”: nivolumab, BMS-936559, and MPDL3280A). For these reasons and the reasons discussed above with respect to claim 1, it would have been obvious to a POSA to use an anti-PD therapeutic agent to inhibit the anti-cell death activity of PD-1/PD-L1, such as those taught by *WO422* and listed in claim 18. Thus, claims 17 and 18 are rendered obvious by the combination of *WO422*, *Bellmunt*, and *Savas*. EX1002 ¶¶436-40.

9. Claims 20 and 21

(Claim 20) “further comprising administering said anti-PD therapeutic agent to the subject when the CPS is above the threshold”

(Claim 21) “wherein the threshold is greater than or equal to 1%”

Claim 20 depends from claim 1 and further adds a step of administering an anti-PD therapeutic agent. Claim 21 depends from claim 20 and adds that the threshold is greater than or equal to 1. *WO422* discloses treating a patient with a PD-1 antagonist when the score is above a threshold. EX1010, [0019], [00118], Exemplary Specific Embodiment 23, Claim 18. Moreover, as discussed with respect to claims 2-3, *WO422* teaches thresholds from above zero to 90%, including 1%. Sections I.C.1.g, VII.C.2. For these reasons and the reasons discussed above with respect to claims 1-3, it would have been obvious to a POSA to administer an anti-PD therapeutic agent when the CPS is above a threshold, such as a threshold of 1%, because the patient is PD-L1+. Thus, claims 20 and 21 would have been rendered obvious by the combination of *WO422*, *Bellmunt*, and *Savas* for the reasons discussed above. EX1002 ¶¶441-44.

D. Ground 4: Claim 9 Is Invalid as Obvious over the Combination of *WO422*, *Bellmunt*, *Savas*, and *Herbst*

(Claim 9) “wherein the viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC are counted in the tumor nests and the adjacent supporting stroma of the tumor tissue sample”

Claim 9 depends from claim 4 (which depends from claim 1), and adds the limitation that the PD-L1 positive MICs are also counted in the stroma. By 2015, a POSA would have been motivated to count PD-L1⁺ cells in tumor nests and adjacent supporting stroma together to obtain a single measure of their overall abundance for the following reasons. First, *Savas* discloses that stromal TILs are associated with a better prognosis and teaches looking at the stromal-compartment TILs, noting that the fibrous stroma is part of the malignant tumor, and thus stromal immune cells are considered to be true tumor-infiltrating cells. EX1060, 229. Second, *WO422* recognized the need to assess MIC PD-L1 positivity in both tumor nests and stroma for purposes of predicting whether a patient will benefit from anti-PD therapy. EX1010, [0012]–[0017]. Third, pooling the PD-L1⁺ MICs from both sources would simplify that assessment, as reflected in the prior art. For example, in clinical trials of Roche’s anti-PD therapy, MPDL3280A, a single score for PD-L1 positivity in MICs was calculated, as opposed to separate scores for the intra-nest and adjacent stromal areas. EX1017, 2; EX1002 ¶448; *see also* Section I.C.2.e. *Bellmunt* also provides a single score for MICs in the tumor nest and

stroma. EX1023, 813. It would have thus been obvious at the time of invention to count the PD-L1⁺ MICs in the tumor nests and the adjacent supporting stroma of the tumor tissue sample for these reasons and the reasons discussed above with respect to claims 1 and 4. Claim 9 would have thus been obvious to a POSA over the combination of *WO422*, *Bellmunt*, *Savas*, and *Herbst*. EX1002 ¶¶445-51.

E. Ground 5: Claims 10, 11, and 15 Are Invalid as Obvious over the Combination of *WO422*, *Bellmunt*, *Savas*, and *Dako*

1. Claim 10: “wherein the tumor tissue sample is a cell suspension”

Claim 10 depends from claim 1 and adds that the tumor tissue sample is a cell suspension. As discussed in Section I.C.2.d, as of the earliest possible effective filing date, it was routine and conventional to prepare a tumor tissue sample as a cell suspension. *See* EX1012, 87 (“Immunofluorescence (IF) is a common laboratory technique used in almost all aspects of biology....

Applications include the evaluation of cells in suspension, cultured cells, frozen tissue, FFPE tissue, beads, and microarrays for the detection of specific proteins.”)

In addition, *Savas* describes the use of flow cytometry (EX1060, 229 (Box 1), 230), which a POSA would have understood entailed analysis of a cell suspension.

EX1002 ¶452. For these reasons and the reasons discussed above with respect to claim 1, it would have been obvious to a POSA to use a cell suspension as the tumor sample, as the use of cell suspensions was routine. Claim 10 would have

thus been obvious to a POSA over the combination of *WO422*, *Bellmunt*, *Savas*, and *Dako*. EX1002 ¶¶452-55.

2. Claim 11: “wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determining [sic] by flow cytometry”

Claim 11 depends from claim 10, and adds the limitation that the number of PD-L1 positive and negative tumor cells and PD-L1 positive MICs are determined by flow cytometry. *Savas* notes that flow cytometry is the “analysis of single cells using a variety of cell surface and intracellular fluorescent markers.” EX1060, 229 (Box 1). *Savas* further notes that both IHC and flow cytometry may be used to assess markers on a cell, and that flow cytometry is a more comprehensive technique. *Id.*, 230; *see also* EX1012, 87. It would have thus been obvious to a POSA to use flow cytometry to determine the number of PD-L1 positive and negative tumor cells and PD-L1 positive MICs. For these reasons and the reasons discussed as to claims 1 and 10, it would have been obvious to a POSA to use flow cytometry to determine the number of viable PD-L1⁺ and PD-L1⁻ tumor cells, and the number of viable PD-L1⁺ MICs in the tumor tissue sample because the use of such methods was routine. Claim 11 would have thus been obvious based on the combination of *WO422*, *Bellmunt*, *Savas*, and *Dako*. EX1002 ¶¶456-57.

3. Claim 15: “wherein the number of viable PD-L1 positive tumor cells, the number of viable PD-L1 negative tumor cells, and the number of viable PD-L1 positive MIC in the tumor tissue sample are determined by single cell sequencing”

Claim 15 depends from claim 1 and adds determining the number of cells using single cell sequencing. *Savas* teaches that gene expression analysis/single cell sequencing may be used to provide information about relevant lymphocyte subpopulations. EX1060, 230. And as discussed above (Section VII.A.2.f.), as of the earliest possible effective filing date, it was routine and conventional to count cells using single cell sequencing. *See* EX1012, 119 (“New, non-slide-based tests, e.g. next generation sequencing, are in the process of entering routine diagnostic application providing new important information for cancer diagnostics.”). For these reasons and the reasons discussed above with respect to claim 1, it would have been obvious to a POSA to use single cell sequencing to determine the number of viable PD-L1⁺ tumor cells, the number of viable PD-L1⁻ tumor cells, and the number of viable PD-L1⁺ MICs in the tumor tissue sample because the use of such methods was routine. Claim 15 would have thus been obvious to a POSA over the combination of *WO422*, *Bellmunt*, *Savas*, and *Dako*. EX1002 ¶¶458-59.

F. Objective Indicia of Nonobviousness

Petitioner is not aware of any relevant objective indicia of nonobviousness that have a nexus to, or are commensurate in scope with, any of the challenged

claims. EX1002 ¶¶460-61. Petitioner reserves the right to respond to any allegations that objective indicia support the validity of the challenged claims.

VIII. CONCLUSION

For the reasons set forth above, claims 1-21 of *US702* are unpatentable. Petitioner requests that post-grant review of these claims be instituted and that the claims be cancelled.

Respectfully submitted,

Dated: October 20, 2026

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

IX. APPENDIX – LIST OF EXHIBITS CITED

Exhibit No.	Description
1001	U.S. Patent No. 12,529,702 to Kulangara et al. (Jan. 20, 2026) (“US702”)
1002	Declaration of Jonathan Braun, M.D., Ph.D. in Support of PGR Petition
1003	Jonathan Braun, M.D., Ph.D. <i>curriculum vitae</i>
1004	Excerpts from prosecution history of U.S. Application No. 18/098,198, now U.S. Patent No. 12,529,702
1005	Excerpts from prosecution history of U.S. Application No. 16/804,395, now U.S. Patent No. 11,585,817
1006	Excerpts from prosecution history of U.S. Application No. 15/422,350, now U.S. Patent No. 10,613,092
1007	U.S. Patent No. 11,585,817 to Kulangara et al. (Feb. 21, 2023) (“US817”)
1008	U.S. Patent No. 10,613,092 to Kulangara et al. (Apr. 7, 2020) (“US092”)
1009	U.S. Provisional Patent Application No. 62/317,179 to Kulangara et al. (filed Apr. 1, 2016) (“App179”)
1010	International Publication WO 2014/165422 A1 to Dolled-Filhart et al. (Oct. 9, 2014) (“WO422”)
1011	U.S. Patent Publication 2016/0084839 to Dolled-Filhart et al. (Mar. 24, 2016) (“Pub839”)
1012	Taylor, C.R. & Rudbeck, L. (eds.), <i>IHC Guidebook, Immunohistochemical Staining Methods</i> , 6th ed., Dako Denmark A/S (Nov. 7, 2013) (“Dako”)
1013	Taube, J.M., et al., <i>Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape</i> , 4 SCIENCE TRANSLATIONAL MEDICINE 127:127RA37, 1-10 & Supplementary Materials (Mar. 28, 2012) (“Taube 2012”)
1014	Gadiot, J., et al., <i>Overall survival and PD-L1 expression in metastasized malignant melanoma</i> , 117 CANCER 10, 2192-201 (Epub Nov. 29, 2010) (“Gadiot”)

Exhibit No.	Description
1015	Muenst, S., et al., <i>The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer</i> , 139 BREAST CANCER RESEARCH AND TREATMENT 3, 667-76 (Epub June 12, 2013) (“Muenst 2013”)
1016	Muenst, S., et al., <i>Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer</i> , 146 BREAST CANCER RESEARCH AND TREATMENT 1, 15-24 (Epub May 20, 2014) (“Muenst 2014”)
1017	Herbst, R.S., et al. <i>Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients</i> , 515 NATURE 7528, 563-67 & Extended Data (Nov. 27, 2014) (“Herbst”)
1018	U.S. National Library of Medicine, ClinicalTrials.gov, NCT01295827, <i>Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/ MK-3475-001/ KEYNOTE-001) (KEYNOTE-001)</i> , (Version 56, Jan. 30, 2015), available at https://clinicaltrials.gov/study/NCT01295827 (“NCT827-V56”)
1019	KEYTRUDA® (pembrolizumab) for injection, for intravenous use, FOOD AND DRUG ADMINISTRATION (Sept. 2014) available at https://www.accessdata.fda.gov/Drugsatfda_docs/Label/2014/125514lbl.Pdf (“Keytruda 2014PF”)
1020	OPDIVO® (nivolumab) injection, for intravenous use, FOOD AND DRUG ADMINISTRATION (Dec. 2014) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000LBL.pdf (“Opdivo 2014PF”)
1021	Bristol-Myers Squibb, <i>Bristol-Myers Squibb Receives Accelerated Approval of Opdivo (nivolumab) from the U.S. Food and Drug Administration</i> (Dec. 22, 2014), available at https://news.bms.com/news/details/2014/Bristol-Myers-Squibb-Receives-Accelerated-Approval-of-Opdivo-nivolumab-from-the-US-Food-and-Drug-Administration/default.aspx (“BMS-PR2014”)
1022	Ali, H.R., et al., <i>PD-L1 protein expression in breast cancer is rare, enriched in basal-like tumours and associated with infiltrating lymphocytes</i> , 26 ANNALS OF ONCOLOGY 7, 1488-93 & Supplemental Data (Epub Apr. 20, 2015) (“Ali”)

Exhibit No.	Description
1023	Bellmunt, J., et al., <i>Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma</i> , 26 ANNALS OF ONCOLOGY 4, 812-17 & Supplementary Data (excluding unavailable Supplementary Fig. S3, Table S4, and Table S5) (Epub Jan. 18, 2015) (“ <i>Bellmunt</i> ”)
1024	U.S. National Library of Medicine, ClinicalTrials.gov, NCT01295827, <i>Study of Pembrolizumab (MK-3475) in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-small Cell Lung Carcinoma (P07990/ MK-3475-001/ KEYNOTE-001) (KEYNOTE-001)</i> , (Version 1, Feb. 14, 2011), available at https://clinicaltrials.gov/study/NCT01295827 (“ <i>NCT827-VI</i> ”)
1025	Cancer Research UK, <i>Types of cancer</i> (last reviewed Oct. 9, 2023), available at https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancer-start-grow-spread/types-of-cancer (“ <i>Cancer Research UK</i> ”)
1026	Irwin, K. & McConnel, K., University of California, Los Angeles (UCLA), <i>FDA Approves New Breast Cancer Drug Herceptin</i> , (Sept. 29, 1998) available at https://www.newswise.com/articles/fda-approves-new-breast-cancer-drug-herceptin (“ <i>UCLA-PR1998</i> ”)
1027	Taube, J.M., et al., <i>Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy</i> , 20 CLINICAL CANCER RESEARCH 19, 5064-74 & Supplementary Materials (Apr. 8, 2014) (“ <i>Taube 2014</i> ”)
1028	Detjen, K.M., et al, <i>Molecular mechanism of interferon alfa-mediated growth inhibition in human neuroendocrine tumor cells</i> , 118 GASTROENTEROLOGY 4, 735-48 (Apr. 2000) (“ <i>Detjen</i> ”)
1029	--Intentionally Left Blank--
1030	Raedler, L.A., <i>Keytruda (Pembrolizumab): First PD-1 Inhibitor Approved for Previously Treated Unresectable or Metastatic Melanoma</i> , 8 AMERICAN HEALTH & DRUG BENEFITS (SPEC FEATURE), 96-100 (Mar. 2015) (“ <i>Raedler</i> ”)
1031	Kerr, K.M., et al., <i>Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art?</i> 10 JOURNAL OF THORACIC ONCOLOGY: OFFICIAL PUBLICATION OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER 7, 985-89 (Jul. 2015) (“ <i>Kerr</i> ”)

Exhibit No.	Description
1032	Thompson, R.H., et al., <i>Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target</i> , 101 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 49, 17174-179 (Epub Nov. 29, 2004) (“Thompson”)
1033	Tumeh, P.C., et al., <i>PD-1 blockade induces responses by inhibiting adaptive immune resistance</i> , 515 NATURE 7528, 568-71 & Extended Data (Nov. 27, 2014) (“Tumeh”)
1034	Lu, B., et al., <i>T-cell-mediated tumor immune surveillance and expression of B7 co-inhibitory molecules in cancers of the upper gastrointestinal tract</i> , 50 IMMUNOLOGIC RESEARCH, 269-75 (Jun. 30, 2011) (“Lu”)
1035	Santoemma, P.P., et al., <i>Tumor infiltrating lymphocytes in ovarian cancer</i> , 16 CANCER BIOLOGY & THERAPY 6, 807-20 (Epub Apr. 20, 2015) (“Santoemma”)
1036	Kan, G. & Dong, W., <i>The expression of PD-L1 APE1 and P53 in hepatocellular carcinoma and its relationship to clinical pathology</i> , 19 EUROPEAN REVIEW FOR MEDICAL AND PHARMACOLOGICAL SCIENCES 16, 3063-71 (Aug. 4, 2015) (“Kan”)
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1038	U.S. Food & Drug Admin., <i>In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff</i> (Aug. 6, 2014) (“FDA Companion Diagnostic Guidance”)
1039	Kandoth, C., et al., <i>Mutational landscape and significance across 12 major cancer types</i> , 502 NATURE, 333-39 (excluding Supplementary Data) (Oct. 17, 2013) (“Kandoth”)
1040	Nomi, T., et al., <i>Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer</i> , 13 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 7, 2151-157 (Apr. 1, 2007) (“Nomi”)
1041	U.S. Publication No. 2016/0222118 to Chen et al. (Aug. 4, 2016) (“Chen”)
1042	Topalian, S.L., et al., <i>Safety, activity, and immune correlates of anti-PD-1 antibody in cancer</i> , 366 THE NEW ENGLAND JOURNAL OF MEDICINE 26, 2443-54 & Appendix (excluding trial protocol and disclosure forms) (Jun. 28, 2012) (“Topalian”)

Exhibit No.	Description
1043	--Intentionally Left Blank--
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1045	Iwai, Y., et al., <i>Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade</i> , 99 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 19, 12293-297 (Epub Sep. 6, 2002) (“Iwai”)
1046	Ohigashi, Y., et al., <i>Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer</i> , 11 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 8, 2947-53 (Apr. 15, 2005) (“Ohigashi”)
1047	Ghebeh, H., et al., <i>The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: correlation with important high-risk prognostic factors</i> , 8 NEOPLASIA 3, 190-98 (Mar. 2006) (“Ghebeh”)
1048	Hamanishi, J., et al., <i>Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer</i> , 104 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 9, 3360-65 & Supplementary Material (Epub Feb. 21, 2007) (“Hamanishi”)
1049	Yang, W., et al., <i>PD-L1: PD-1 interaction contributes to the functional suppression of T-cell responses to human uveal melanoma cells in vitro</i> , 49 INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 6, 2518-25 (Epub Feb. 22, 2008) (“Yang”)
1050	Gao, Q., et al., <i>Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma</i> , 15 CLINICAL CANCER RESEARCH: AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 3, 971-79 & Supplementary Data (Feb. 1, 2009) (“Gao”)
1051	Brahmer, J.R., et al., <i>Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates</i> 28 JOURNAL OF CLINICAL ONCOLOGY: OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY 19, 3167-75 & Appendix (Epub Jun. 1, 2010) (“Brahmer”)

Exhibit No.	Description
1052	International Publication WO 2015/026634 A1 to Strack et al. (Feb. 26, 2015) (“WO634”)
1053	U.S. Patent Publication No. 2016/0009805 to Kowanetz et al. (Jan. 14, 2016) (“Kowanetz”)
1054	--Intentionally Left Blank--
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1056	Patel, S.P. & Kurzrock, R., <i>PD-L1 expression as a predictive biomarker in cancer immunotherapy</i> , 14 MOLECULAR CANCER THERAPEUTICS 4, 847-56 (Apr. 2015) (“Patel”)
1057	2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50 (Jan. 7, 2019) (“Revised Guidance”)
1058	Kuang, D., et al., <i>Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1</i> , 206 JOURNAL OF EXPERIMENTAL MEDICINE 6, 1327-37 & Supplementary Material (Epub May 18, 2009) (“Kuang”)
1059	Lipson, E.J., et al., <i>Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody</i> , 19 CLINICAL CANCER RESEARCH 2, 462-68 (Epub Nov. 20, 2012) (“Lipson”)
1060	Savas, P., et al., <i>Clinical relevance of host immunity in breast cancer: from TILs to the clinic</i> , 13 NATURE REVIEWS CLINICAL ONCOLOGY 4, 228-41 (Epub Dec. 15, 2015) (“Savas”)
1061	U.S. Patent Application Publication 2013/0309250 A1 to Cogswell et al. (Nov. 21, 2013) (“Pub250”)
1062	González-Cao, M., et al., <i>Targeting PD-1/PD-L1 in lung cancer: current perspectives</i> , 2015 LUNG CANCER: TARGETS AND THERAPY 6, 55-70 (July 31, 2015) (“González-Cao”)
1063	Merck & Co., Inc., <i>Merck Announces Generic Name for MK-3475, Merck’s Investigational anti-PD-1 Antibody: Pembrolizumab</i> , (May 30, 2014) available at https://www.merck.com/news/merck-announces-generic-name-for-mk-3475-mercks-investigational-anti-pd-1-antibody-pembrolizumab/ (“Merck-PR2014”)
1064	Walker, R.A., <i>Quantification of immunohistochemistry—issues concerning methods, utility and semiquantitative assessment I</i> , 2006 HISTOPATHOLOGY 49, 406-10 (“Walker”)

Exhibit No.	Description
1065	Taylor, C.R. & Levenson, R.M., <i>Quantification of immunohistochemistry—issues concerning methods, utility and semiquantitative assessment II</i> , 2006 HISTOPATHOLOGY 49, 411-24 (“Taylor”)
1066	Denkert, C., et al., <i>Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers</i> , 33 JOURNAL OF CLINICAL ONCOLOGY 9, 983-91 & Appendix (Mar. 20, 2015) (“Denkert”)
1067	Schalper, K.A., <i>PD-L1 expression and tumor-infiltrating lymphocytes: Revisiting the antitumor immune response potential in breast cancer</i> , 2014 ONCOIMMUNOLOGY 3, e29288-1-e29288-2 (June 25, 2014) (“Schalper”)
1068	Carbognin, L., et al., <i>Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers</i> , 10 PLoS ONE 6 (June 18, 2015) (“Carbognin”)
1069	Geissmann, F., et al., <i>Development of monocytes, macrophages, and dendritic cells</i> , 327 SCIENCE 5966, 656-61 (Feb. 5, 2010) (“Geissmann”)
1070	Muglia, V.F. & Prando, A., <i>Renal cell carcinoma: histological classification and correlation with imaging findings</i> , 48 RADIOLOGIA BRASILEIRA 3, 166-74 (May-June 2015) (“Muglia”)
1071	García-Tejido, P., et al., <i>Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cancer: The Future of Immune Targeting</i> , 10 CLINICAL MEDICINE INSIGHTS: ONCOLOGY SUPPL 1, 31-9 (Epub April 5, 2016) (“García-Tejido”)
1072	Fawcett, T., <i>An Introduction to ROC Analysis</i> , 27 PATTERN RECOGNITION LETTERS 8, 861-74 (Epub Dec. 19, 2005) (“Fawcett”)
1073	Almagro, J.C., et al., <i>Engineering strategies and binding mechanisms of therapeutic anti-PD-1 antibodies approved by regulatory agencies globally</i> , 17 FRONTIERS IN IMMUNOLOGY (May 21, 2026) (“Almagro”)
1074	Li, L., et al., <i>Overcoming resistance to anti-PD-1/PD-L1 therapy in cancer</i> , 9 CANCER DRUG RESISTANCE 18 & Supplementary Materials (May 15, 2026) (“Li”)

Exhibit No.	Description
1075	Cancer Research Institute, <i>Regulatory Approval Timeline of Active Immunotherapies</i> , available at https://www.cancerresearch.org/regulatory-approval-timeline-of-active-immunotherapies (accessed on Oct. 11, 2026) (“ <i>Cancer Research Institute</i> ”)
1076	--Intentionally Left Blank--
1077	Pardoll, D.M., <i>The blockade of immune checkpoints in cancer immunotherapy</i> , 12 NATURE REVIEWS CANCER 4, 252-64 (Mar. 22, 2012) (“ <i>Pardoll</i> ”)
1078	Merriam-Webster’s Collegiate Dictionary (11th ed. 2003) (excerpt p. 404) (“ <i>Merriam-Webster</i> ”)
1079	Dorland’s Illustrated Medical Dictionary (Saunders Elsevier, 31st ed. 2007) (excerpt pp. 284, 295-98) (“ <i>Dorland’s</i> ”)
1080	Hou, J., et al, <i>Correlation between infiltration of FOXP3+ regulatory T cells and expression of B7-H1 in the tumor tissues of gastric cancer</i> , 96 EXPERIMENTAL AND MOLECULAR PATHOLOGY 3, 284-91 (Epub Mar. 20, 2014) (“ <i>Hou</i> ”)
1081	USPTO, <i>July 2024 Subject Matter Eligibility Examples</i> (July 2024), available at https://www.uspto.gov/sites/default/files/documents/2024-AI-SMEUpdateExamples47-49.pdf (“ <i>USPTO Examples</i> ”)

X. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(b)(1). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 18,563 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24.

Respectfully submitted,

Dated: October 20, 2026

/ Lora M. Green /

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Post Grant Review (and accompanying Exhibits 1001-1028, 1030-1036, 1038-1042, 1045-1053, 1056-1075, 1077-1081) by overnight courier (Federal Express or UPS), on this 20th day of October, 2026, on the Patent Owner at the correspondence address of the Patent Owner Counsel as follows:

Agilent Technologies, Inc.
Global IP Operations
5301 Stevens Creek Blvd, 1A-PB
Santa Clara, CA 95051

Respectfully submitted,

Dated: October 20, 2026

/ Lora M. Green /

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