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Paper 10
Date: October 14, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

SHANGHAI MIRACOGEN INC.,

Patent Owner.

IPR2025-00685
Patent 10,792,370 B2

Before JEFFREY N. FREDMAN, JOHN G. NEW, and RYAN H. FLAX, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner CSPC Megalith Biopharmaceutical Co., Ltd., ("Petitioner") has filed a Petition (Paper 1, "Pet.") seeking *inter partes* review of claims 1–23 (all claims) of U.S. Patent 10,792,370 B2 (Ex. 1001, the "'370 patent"). Patent Owner Shanghai Miracogen Inc. ("Patent Owner") filed a Preliminary Response (Paper 8, "Prelim. Resp.").

Patent Owner also filed a Request with the Acting Director of the USPTO seeking discretionary denial of institution of *inter partes* review (Paper 6, the "Request"). Petitioner subsequently filed a brief opposing Patent Owner's Request (Paper 7). On July 31, 2025, the Acting Director denied Patent Owner's Request for discretionary denial of institution of *inter partes* review and referred the case to the panel for an institution decision on the merits (Paper 9).

Under 35 U.S.C. § 314, the Board "may not authorize an *inter partes* review to be instituted unless … the information presented in the petition … and any response … shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." For the reasons we explain below, we institute *inter partes* review of claims 1–23 of the '370 patent.

II. BACKGROUND

A. Real Parties-in-Interest

Petitioner identifies CSPC Pharmaceutical Group Limited, CSPC NBP Pharmaceutical Co., Ltd, CSPC Innovation Pharmaceutical Co., Ltd, and CSPC Megalith Biopharmaceutical Co., Ltd., as the real parties-in-

interest. Pet. 3. Patent Owner identifies Shanghai Miracogen Inc. and Lepu Biopharma Co., Ltd., as the real parties-in-interest. Paper 3, 2.

B. Related Matters

Both Petitioner and Patent Owner state that they are unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition. Pet. 3, Paper 3, 2.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1–23 of the '370 patent are unpatentable, based upon the following Grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–23	103	Wei[1], Liu[2,3]
2	1–23	103	Leanna[4], Wei, Liu

Pet. 5. Petitioner also relies upon the Declaration of Stylianos Bournazos, Ph.D. (the "Bournazos Declaration," Ex. 1002).

[1] Wei et al. (US 2015/0071923 Al, March 12, 2015) ("Wei") Ex. 1005.

[2] Liu (CN 103772504 A, May 7, 2014) ("Liu") Ex. 1007.

[3] The Liu reference is written in Simplified Chinese. *See generally* Ex. 1007. Petitioner has produced a certified English translation of Liu. *See* Ex. 1008. Patent Owner does not contest the accuracy of the certified English translation, and all references and citations to Liu in this Decision cite to the translation.

[4] Leanna et al. (WO 2014/152199 A1, September 25, 2014) ("Leanna") Ex. 1006.

D. The '370 Patent

The '370 patent is directed to an antibody-drug conjugate and, in particular, to an antibody-drug conjugate targeting an epidermal growth factor receptor ("EGFR"). Ex. 1001, code (57). The '370 patent discloses that its antibody-drug conjugates ("ADCs") usually consist of three constituent parts: (1) a monoclonal antibody with specific binding affinity to a target; (2) a small-molecule drug with cytotoxic activity; and (3) a linker molecule linking the small molecule drug and the monoclonal antibody. *Id.* at col. 2, ll. 60–65.

The '370 patent discloses a number of embodiments of monoclonal anti-EGFR antibodies comprising different complementarity-determining regions (CDR1, CDR2, CDR3) with specific sequences and homology to these sequences based on percentages ranging from greater than 70% to 99%. Ex. 1001, cols. 3–4, ll. 50–63). The '370 patent also discloses various candidate cytotoxic agents that were well-known in the art, including monomethyl auristatin E ("MMAE"). *Id.* at col. 5, ll. 6–22. The '370 patent additionally lists well-known cleavable and non-cleavable linkers, including the cleavable linker valine-citrulline ("vc"). *Id.* at col. 5, ll. 23–38. The '370 patent discloses that an embodiment of the linker and cytotoxic portion of the ADC is vc-MMAE, and provides the chemical structure of this prior art embodiment. *Id.* at col. 5, ll. 39–53.

Example 1 of the '370 patent discloses the preparation of a specific ADC (MYK-3), in which the previously-known BA03 anti-EGFR antibody, is connected to a commercially-obtained vc-MMAE linker-cytotoxic agent molecule. Ex. 1001, col. 19, ll. 26–29. Examples 2–5 of the '370 patent disclose various *in vitro* and *in vivo* assays comparing the inhibitory

activities of the MYK-3 ADC *versus* the BA03 antibody against various cancer cell lines and tumors, in which the activity of the MYK-3 ADC was demonstrated to be generally superior. In Example 6, the *in vitro* inhibitory activity of BA03-MMAE ADCs with three different linkers (BA03-vc-MMAE, BA03-MC-MMAE, and BA03-MCC-MMAE) was compared, and in which inhibition of tumor cell proliferation by MYK-3 was demonstrated to be significantly higher than that demonstrated by BA03-MC-MMAE or BA03-MCC-MMAE.

E. Representative Claim

Claim 1 is the sole independent claim of the '370 patent and recites:

> 1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.

Ex. 1001, col. 33, ll. 2–11.

III. ANALYSIS

A. A Person of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art would typically have had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an M.D. with similar experience. Pet. 32. The Petitioner further states that a person of ordinary skill would typically have

had at least five years of experience with antibodies and antibody engineering, or access to other individuals with that knowledge and experience. *Id.* Patent Owner does not contest Petitioner's proposed definition or offer an alternative. *See generally* Prelim. Resp.

Petitioner's proposed definition of the level of ordinary skill in the art appears to be generally consistent with the level of skill presented in the cited prior art. *See generally, e.g.*, Exs. 1005–1008; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself may reflect an appropriate level of skill in the art). However, at this point we reject the portion of Petitioner's proposed definition that includes having "access to other individuals with that knowledge and experience," as not reflecting the individual level of skill of a given skilled artisan. *See, e.g.*, *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (holding that "[t]he person of ordinary skill is a hypothetical *person* who is presumed to be aware of all the pertinent prior art. The actual inventor's skill is not determinative") (emphasis added, footnotes omitted).

Consequently, and for the purposes of this Decision, we adopt Petitioner's proposed definition as defining a person of ordinary skill in the art as a person who would have had "a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an M.D. with similar experience, and would further have had at least five years of experience with antibodies and antibody engineering."

B. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claims in a civil action under 35 U.S.C. § 282(b). *See*

37 C.F.R. § 100(b) (2020). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Petitioner states that no term of the challenged claims requires construction to resolve the challenges in this Petition. Pet. 32. Patent Owner does not contest Petitioner's assertion. *See generally* Prelim. Resp.

We find, for the purposes of this Decision, that no terms of the challenged claims require construction beyond the ordinary and customary meaning of the terms, as understood by a person of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312–13.

C. Ground 1: Alleged Obviousness of Claims 1–23 over Wei and Liu

1. Principles of law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that

subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness, if present. *KSR*, 550 U.S. at 406.

"[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art "to combine … known elements in the fashion claimed by the patent at issue." *Id.* at 418.

"[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (C.C.P.A. 1968). Moreover, a precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness over a combination of references must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the

claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

2. Petitioner's arguments

a. Claim 1

Petitioner provides the following claim chart to establish that the combination of Wei and Liu teaches or suggests all of the limitations of claim 1:

Claim 1 of the '370 patent	**Prior Art**
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker,	**Wei** discloses: An anti-EGFR antibody-drug conjugate (EX1005, [0229]), including the Y104D-Mc-vcPAB-MMAE ADC (*id.*, [0742], [1092]-[1141])) and a humanized version of this antibody, huY104D-MMAE ADC (*id.*), that comprises an anti-EGFR antibody (*e.g.*, Y104D,

wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.	huY104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (*id.*, [0742], [1092]-[1127], claims 27-40.) **Liu** discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a light chain (EX1008, Examples 1-5, [00141]-[0146], Tables 1-3), wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7 (*id.*, [0085], [0123], [0124]), and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 (*id.*, [0108], [0123], [0124]).

Pet. 37–38. The claim chart provides each limitation of claim 1 and a description of where each limitation is supported by the cited prior art references.

Petitioner argues that Wei teaches anti-EGFR ADCs, including Y104D-Mc-vcPAB-MMAE ADC (also referred to as "Y104D-MMAE ADC") and an ADC with a humanized version of the antibody, huY104D-Mc-vcPAB-MMAE ADC (also referred to as "huY104D-MMAE ADC"), that comprise a modified cetuximab[5] antibody covalently linked to a cytotoxic agent, monomethyl auristatin E ("MMAE"), *via* a maleimidocaproyl-valine-citruline-p-aminobenzyl linker (a cleavable valine-

[5] Cetuximab is a human-mouse chimeric C225 monoclonal anti-EGFR antibody that is also known by its commercial name of Erbitux®. *See* Ex. 1014.

citrulline ("vc") linker). Pet. 38 (citing Ex. 1005 ¶¶ 1092–1127). According to Petitioner, the Y104D antibody is a cetuximab variant in which the tyrosine (Y) at a position corresponding to position 104 is replaced with D [aspartic acid]." *Id.* (quoting Ex. 1005 ¶ 660, also citing *id.*, Examples 1–2).

Petitioner points to Example 18 of Wei, which discloses the formation of the Y104D-MMAE ADC by conjugating Y104D to MMAE *via* the cleavable linker. Pet. 38–39. Petitioner also points to Example 20 of Wei, which demonstrates that the Y104D-MMAE ADC and a humanized variant, huY104E-MMAE, were administered in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors and were shown to exhibit strong anti-tumor response and tumor regression. *Id.* at 39 (citing Ex. 1005 ¶¶ 1122–1127).

Petitioner argues that Liu discloses the humanized anti-EGFR antibody BA03, an IgG1 isotype anti-EGFR antibody, which is the same BA03 antibody used in the '370 patent to generate its preferred embodiment, MYK-3 ADC, and which is a humanized cetuximab antibody. Pet. 39 (citing Ex. 1008 ¶¶ 60; Ex. 1001, col. 18, ll. 3–6). Petitioner contends that the heavy chain variable region, light chain variable region, heavy chain constant region, and light chain constant region sequences of the BA03 antibody disclosed by Liu are identical to those of the BA03 antibody used and claimed in the '370 patent to obtain the MYK-3 ADC. *Id.* (citing Ex. 1008 ¶¶ 85, 133; Ex. 1002, 90–92). Therefore, argues Petitioner, all of the CDR sequences (SEQ ID NOs: 5–7 and 12–14) recited in claim 1 of the '370 patent are taught by Liu. *Id.*

Petitioner argues further that Liu teaches that among its disclosed humanized anti-EGFR antibodies, BA03 demonstrated the highest binding

affinity to EGFR, and antagonistic activity inhibiting EGF–EGFR binding. Pet. 39 (citing Ex. 1008 ¶¶ 141–146, Examples 1–5, Tables 1–3). Additionally, argues Petitioner, BA03 demonstrates several advantageous properties, including: (1) stronger EGFR phosphorylation inhibition than cetuximab; (2) higher ADCC activity than Erbitux® (i.e., cetuximab); and (3) significantly lower immunogenicity compared to Erbitux®. *Id.* at 39–40 (citing Ex. 1008 ¶¶ 148, 150, 152–160, Figs. 3–5, Table 4).

Petitioner contends that a person of ordinary skill in the art would have been motivated to combine the teachings of Wei and Liu, because Liu discloses and claims a humanized version of cetuximab, BA03, and states that BA03 has numerous benefits over cetuximab, including stronger EGFR phosphorylation inhibition, higher antibody-dependent cell-mediated cytotoxicity ("ADCC") activity, and significantly lower immunogenicity. Pet. 40 (citing Ex. 1008 ¶¶ 148–152). Petitioner argues that both Wei and Liu disclose and characterize humanized anti-EGFR antibodies, which a person of ordinary skill in the art would have recognized as having lower immunogenicity than murine and chimeric antibodies. *Id.* (citing Ex. 1008 ¶¶ 148–152; Ex. 1005 ¶¶ 1116–1127). Petitioner points to the testimony of its Declarant, Dr. Bournazos, who states that the humanized anti-EGFR antibodies disclosed by these references are substantially identical: Liu discloses a humanized cetuximab BA03 and Wei discloses a humanized cetuximab variant huY104D as part of the huY104D-MMAE ADC. *Id.* (citing Ex. 1002 ¶ 188). Petitioner notes that Wei's Y104D antibody differs from cetuximab by only a single amino acid, out of several hundred. *Id.* (citing Ex. 1002 ¶ 187).

Petitioner argues that Wei also teaches an ADC containing the cetuximab variant Y104D attached to the MMAE cytotoxic payload with a vc cleavable linker; the same preferred vc-MMAE linker payload disclosed in the Specification of the '370 patent and recited by the challenged claims. Pet. 41 (citing Ex. 1005 ¶ 1103). Petitioner adds that Dr. Bournazos explains that a skilled artisan would have recognized that if ADCs with cleavable linkers were being made in the prior art using a modified version of the chimeric version of M225 (i.e., Wei's cetuximab variant Y104D), they would have been strongly motivated to create ADCs using the humanized version of M225 (BA03), because humanized antibodies had several advantages over chimeric antibodies, including lower immunogenicity. *Id.* (citing Ex. 1002 ¶ 188). Dr. Bournazos adds that Wei teaches a humanized version of its cetuximab variant ADC, huY104D-MMAE, which is substantially identical to the preferred humanized cetuximab-vc-MMAE (MYK-3) disclosed in the '370 patent. *Id.* (citing Ex. 1002 ¶ 188).

Furthermore, argues Petitioner, the humanized cetuximab variant ADCs of Wei exhibited reduced growth inhibition of non-tumor cells compared to the chimeric antibody at physiological pH. Pet. 41 (citing Ex. 1005 ¶ 1139). Petitioner contends that this would have provided additional motivation to create the humanized ADCs of claim 1 because humanized cetuximab variant ADCs were more selective in targeting tumor cells than chimeric ADCs. *Id.*

b. Claim 2

Dependent claim 2 recites that "FR1, FR2, FR3, FR4 of the variable region of the heavy chain of the anti-epidermal growth factor receptor

antibody respectively comprise sequences as shown in SEQ ID NOs: 8 to 11." Ex. 1001, col. 33, ll. 13–16.

Petitioner argues that SEQ ID NOs: 8–11 of the '370 Specification are the respective amino acid sequences of FR1, FR2, FR3, and FR4 of the variable region of the heavy chain of the BA03 antibody. Pet. 51 (citing Ex. 1001, col. 18, ll. 1–36). Petitioner argues that Liu teaches that FR1, FR2, FR3, and FR4 of the variable region of the heavy chain of the anti-EGFR receptor antibody respectively comprise the sequences shown in SEQ ID NOs: 8 to 11. *Id.* (citing Ex. 1008 ¶ 85; Ex. 1002, 90–92).

c. Claim 3

Dependent claim 3 recites that "FR1, FR2, FR3, FR4 of the variable region of the light chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18." Ex. 1001, col. 33, ll. 18–22.

Petitioner argues that Liu discloses that FR1, FR2, FR3, and FR4 of the variable region of the light chain of the anti-EGFR antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18. Pet. 52 (citing Ex. 1008 ¶ 85; Ex. 1002, 90–92).

d. Claim 4

Dependent claim 4 recites that "the heavy chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human IgG constant region, a human IgM constant region, a human IgA constant region, and a human IgD constant region." Ex. 1001, col. 33, ll. 23–39.

Petitioner argues that the BA03 antibody taught by Liu and the Y104D antibody disclosed in Wei have a human IgG1 constant region. Pet. 53 (citing Ex. 1008 ¶ 37; Ex. 1005 ¶¶ 558, 559).

e. Claim 5

Dependent claim 5 recites that "the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4." Ex. 1001, col. 33, ll. 41–43.

Petitioner contends that the BA03 antibody taught by Liu and the Y104D antibody disclosed in Wei have a human IgG1 constant region. Pet. 53 (citing Ex. 1008 ¶ 37; Ex. 1005 ¶ 328).

f. Claim 6

Dependent claim 6 recites that "the constant region of the heavy chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3." Ex. 1001, col. 33, ll. 45–48.

Petitioner argues that the Specification of the '370 patent discloses that the "BA03 antibody of the present invention" was described in Liu. Pet. 53 (citing Ex. 1001, col. 18, ll. 3–6). Therefore, Petitioner asserts, Liu discloses that "the constant region of the heavy chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3." *Id.* at 53–54.

g. Claim 7

Dependent claim 7 recites that "the light chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the

group consisting of a human lambda constant region, and a human kappa constant region." Ex. 1001, col. 33, ll. 50–54.

Petitioner contends that Liu teaches that the BA03 antibody has a human kappa light chain constant region. Pet. 54 (citing Ex. 1008 ¶ 37). Petitioner also asserts that Wei teaches that the anti-EGFR antibody can be IgG1 antibody containing a human lambda light chain constant region. *Id.* (citing Ex. 1005 ¶¶ 558, 559).

h. Claim 8

Dependent claim 8 recites that "the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4." Ex. 1001, col. 33, ll. 56–59.

Petitioner argues that the '370 Specification acknowledges that Liu teaches that "the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4." Pet. 55 (citing Ex. 1001, col. 18, ll. 3–6).

i. Claim 9

Dependent claim 9 recites:

> The antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1, which has a structure as shown in Formula I,
>
> Ab-(L-D)p Formula I
>
> wherein:
>
> Ab represents the anti-epidermal growth factor receptor antibody;
>
> L represents a cleavable linker;
>
> D represents the cytotoxic agent;

p represents 1–9.

Ex. 1001, cols. 33–34, ll. 6–3.

Petitioner argues that Wei teaches that Y104D-MMAE ADC has an average drug antibody ratio ("DAR") of 4, which falls within the recited range of 1–9. Pet. 56 (citing Ex. 1005 ¶ 1103).

j. Claims 10 and 11

Dependent claim 10 recites that: "the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, radioisotopes, antibiotics, enzymes, and biologically active peptides." Ex. 1001, col. 34, ll. 5–9. Dependent claim 11 recites that "the cytotoxic agent is selected from the group consisting of Monomethyl auristatin E (MMAE), Monomethyl auristatin F (MMAF), maytansinoid alkaloids, Calicheamicin, duocarmycin MGBA, doxorubicin, ricin, diphtheria toxin, I131, and tumor necrosis factors." *Id.* at col. 34, ll. 11–15

Petitioner argues that Wei teaches that its Y104D-MMAE ADC contains the cytotoxic agent MMAE, which is a chemotherapeutic agent that interferes with microtubule dynamics and GTP hydrolysis. Pet. 56 (citing Ex. 1005 ¶ 434).

k. Claim 12

Dependent claim 12 recites that "the linker is selected from the group consisting of valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), N-succinimidyl 4-(2-pyridylthio)valerate (SPP), and 6-maleimidocaproyl-

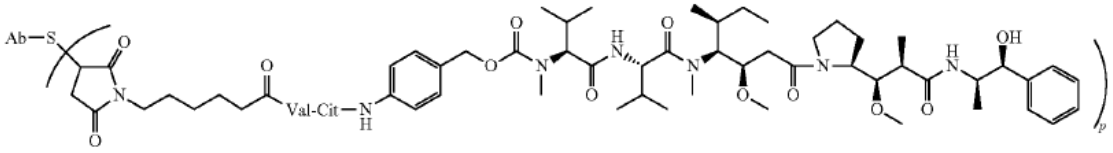
valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB)." Ex. 1001, col. 34, ll. 17–22.

Petitioner argues that Wei teaches that its Y104D-MMAE ADC contains the val-cit cleavable linker. Pet. 57 (citing Ex. 1005 ¶ 1103).

l. Claim 13

Dependent claim 13 recites:

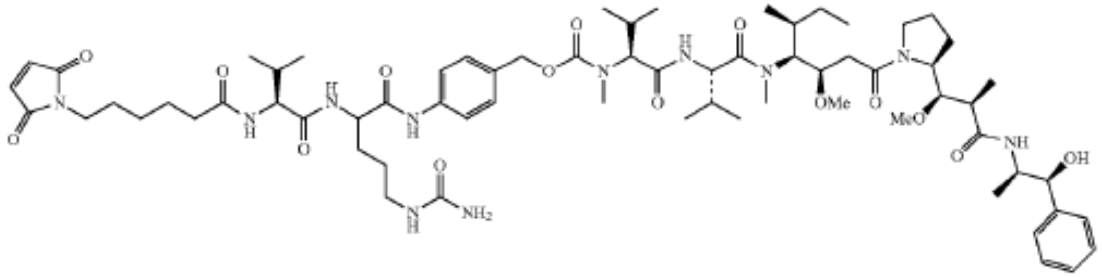
> The antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 9, which is:



> wherein Ab represents the anti-epidermal growth factor receptor antibody, p is 1–8.

Ex. 1001, col. 34, ll. 23–36.

Petitioner argues that Wei teaches the same chemical structure of the linker-drug payload of claim 13, as depicted below:



Pet. 58 (citing Ex. 1005 ¶¶ 740, 742, 1102, 1103, claim 40).

Petitioner also notes that Wei discloses that Y104D-MMAE ADC has an average DAR of 4, which falls within the claimed range of 1–9. *Id.* at 59 (citing Ex. 1005 ¶ 1103).

m. Claim 14

Dependent claim 14 recites "wherein the linker is 6-maleimidocaproyl-valine-citrulline-p-amino benzyloxycarbonyl (MC-vc-PAB)." Ex. 1001, col. 34, ll. 38–40.

Petitioner argues that Wei discloses Y104D-MMAE ADC, in which Y104D "was conjugated to MMAE via the cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyl linker (maleimidocaproyl -vc-PAB-MMAE) as described in Francisco et al. Blood 102:1458–1465 (2003)." Pet. 59 (citing Ex. 1005 ¶ 1103).

n. Claim 15

Dependent claim 15 recites "A composition, which comprises the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1, optionally, further comprises at least one pharmaceutically acceptable carrier, diluent or excipient." Ex. 1001, col. 34, ll. 41–45.

Petitioner contends that Wei discloses that its ADCs can be formulated into "pharmaceutical compositions" comprising "a pharmaceutically acceptable carrier or excipient." Pet. 60 (citing Ex. 1005 ¶¶ 1103, 238, 861–875).

o. Claim 16

Claim 16 recites "[a] method for treatment of a disease associated with epidermal growth factor receptor (EGFR), comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug

conjugate or the pharmaceutically acceptable salt thereof according to claim 1." Ex. 1001, col. 34, ll. 46–50.

Petitioner argues that Wei teaches that its anti-EGFR ADCs:

> [C]an be used for targeted delivery of cytotoxic or cytostatic agents, *i.e.*, drugs to kill or inhibit tumor cells expressing EGFR in the treatment of cancer, … such conjugates exhibit selectivity to tumor cells that are desired to be eliminated over non-diseased cells, and thereby do not result in unacceptable levels of toxicity to normal cells. Therefore, the conjugates achieve maximal efficacy with minimal toxicity and reduced side effects.

Pet. 60 (citing Ex. 1005 ¶ 666). Petitioner also points to Wei's teaching that a pharmaceutical composition comprising its anti-EGFR ADCs can be used in:

> [M]ethods of treating a condition responsive to treatment with an anti-EGFR antibody in a subject, including administering to the subject a pharmaceutically effective amount of a pharmaceutical composition provided herein, … [including] conditions that are responsive to treatment with an anti-EGFR antibody include a tumor, such as a solid tumor, cancer or metastasis, particularly when the tumor expresses EGFR.

Pet. 60–61 (citing Ex. 239) (internal quotes omitted).

p. Claim 17

Dependent claim 17 recites that "the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR." Ex. 1001, col. 34, ll. 51–53.

Petitioner argues that Wei discloses that its ADCs can be used to treat a solid tumor having overexpression of EGFR. Pet. 61 (citing Ex. 1005 ¶¶ 239, 442).

q. Claim 18

Dependent claim 18 recites "[a] method for inhibiting tumor angiogenesis, delaying tumor progression, inhibiting tumor growth, or inhibiting tumor cell proliferation, comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1." Ex. 1001, col. 34, ll. 54–59.

Appellant contends Wei discloses methods for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC, in which the subject has a disorder, such as a tumor, a cancerous condition, a precancerous condition, and any condition related to or resulting from hyperproliferative cell growth to alleviate the symptoms and/or tumor progression. Pet. 62 (citing Ex. 1005 ¶¶ 441–458, 1086–1127, claims 48, 58.). Petitioner also points to Wei's teaching that treating "means that the subject's symptoms are partially or totally alleviated, or remain static following treatment," and prevention of worsening of symptoms or progression of a cancer. *Id.* (citing Ex. 1005 ¶ 443).

r. Claim 19

Dependent claim 19 recites that "the tumor is selected from colon cancer, rectal cancer, head and neck cancer, lung cancer, ovarian cancer, cervical cancer, bladder cancer, esophageal cancer, breast cancer, renal cancer, prostate cancer, gastric cancer, pancreatic cancer and brain glioma." Ex. 1001, col. 34, ll. 60–64.

Petitioner contends that Wei teaches that "[ex]emplary tumors that can be treated" by its ADC inventions:

> [A]re those that overexpress EGFR. Some tumors observed to overexpress EGFR that can be treated include, but are not limited to, colorectal and head and neck tumors, especially squamous cell carcinoma of the head and neck, brain tumors such as glioblastomas, and tumors of the lung, breast, pancreas, esophagus, bladder, kidney, ovary, cervix, and prostate.

Pet. 63 (citing Ex. 1005 ¶ 903; *see also id.* ¶¶ 239, 442).

s. Claims 20 and 22

Dependent claims 20 and 22 both recite "wherein the tumor is a tumor with KRAS gene mutation." Ex. 1001, col. 34, ll. 66–67, col. 35, ll. 3–4.

Petitioner contends that Wei teaches that the Y104D-MMAE and huY104D-MMAE ADCs were tested against breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors, and that both ADCs "exhibit a strong anti-tumor response in KRAS mutated, EGFR+ tumor model" and that "[t]he anti-tumor response of each of the tested antibodies achieves tumor growth regression." Pet. 63–64 (citing Ex. 1005 ¶¶ 1116–1127).

t. Claims 21 and 23

Both claims 21 and 23 recite "wherein the tumor is a tumor with BRAF gene mutation." Ex. 1001, col. 35, ll. 1–2, 5–6.

Petitioner points to Wei's teaching that the Y104D-MMAE and huY104DMMAE ADCs were tested in breast cancer xenograft models (MDA MB 231M TNBC) and exhibited a strong anti-tumor response and achieved tumor growth regression. Pet. 64–65. Petitioner contends that, as

of the earliest possible effective filing date of the Challenged Claims, it was known in the art that the MDA MB 231M TNBC tumors tested with Wei's ADCs are BRAF-mutated tumors. *Id.* at 64 (citing Ex. 1018, 939, 942 ("MDA-MB-231 (KRASG13D and BRAF-G464V mutations)")).

3. Patent Owner's preliminary response

a. Wei allegedly teaches away from the claimed invention

Patent Owner first argues that Wei teaches away from the claimed invention. Prelim. Resp. 19. Patent Owner points to Wei's explanation, in its "Background" section, that anti-EGFR antibodies, such as cetuximab, can "bind to EGFR in healthy cells and tissue" and "exhibit limitations when administered to patients." Prelim. Resp. 19 (quoting Ex. 1005 ¶ 9). According to Patent Owner, Wei seeks to solve this problem by "provid[ing] improved anti-EGFR antibodies that exhibit increased EGFR binding activity in a tumor microenvironment compared to in a non-tumor environment." *Id.*

Patent Owner argues that Wei's solution is to select antibodies whose pH selectivity make them more active in a tumor microenvironment than in non-tumor environment. Prelim. Resp. 19. Patent Owner asserts that Wei teaches constructing "[a] library of single point mutants of the Cetuximab anti-EGFR antibody," where "each member contained a single amino acid mutation compared to the reference [cetuximab] antibody." *Id.* (citing Ex. 1005, ¶¶ 1016–1017). Patent Owner states that Wei's library of antibodies was then screened and, based on the screening, "[t]he variant anti-EGFR antibodies with [a normalized specific activity ('NSA')] > 0.4 at pH 6.0 and an NSA < 0.4 at pH 7.4 were identified and selected for further

analysis." *Id.* (citing Ex. 1005 ¶¶ 1018–1026). Wei's Y104D was among these selected antibodies. *Id.*

Patent Owner continues, explaining that Wei compared the pH-dependent effect of cetuximab-MMAE and that of Y104D-MMAE ADCs demonstrating that "Cetuximab-MMAE and Y104D-MMAE exhibited inhibition of cell growth of A431 [tumor] cells, which was virtually identical between the tested agents." Prelim. Resp. 20 (citing Ex. 1005 ¶¶ 1128–1130). However, Patent Owner argues, Wei also demonstrated that "Y104D-MMAE exhibited less keratinocyte growth inhibition compared to Cetuximab-MMAE." *Id.* (citing Ex. 1005 ¶ 1131). Wei states that "these results confirm that the MMAE ADC conjugate of Y104D anti-EGFR retains the pH-dependent activity of Y104D anti-EGFR, such that the Y104D-MMAE exhibits less cell growth inhibition activity of skin keratinocytes than the A431 tumor cells." *Id.* (citing Ex. 1005 ¶ 1132).

Patent Owner additionally notes that Wei also assessed the huY104D-MMAE ADC and confirmed that it exhibited greater pH-dependent activity than the chimeric Y104D-MMAE conjugate. Prelim. Resp. 20 (citing Ex. 1005 ¶¶ 1133–1139).

Summarizing these studies of Wei, Patent Owner asserts that Wei solves the problem that the cetuximab-MMAE ADC inhibits both tumor cells and normal cells by replacing cetuximab with the better-performing Y104D or huY104D antibody that selectively targets tumor cells more than normal cells. Prelim. Resp. 20. However, argues Patent Owner, Petitioner's arguments would reverse Wei's improvement by replacing the Y104D/huY104D antibody back with a cetuximab derivative that does not have tumor-specific properties (i.e., Liu's BA03 antibody, which is a

humanized cetuximab). *Id.* According to Patent Owner, this would remove the pH-dependent activity of the Y104D-MMAE/huY104D-MMAE ADCs and increase the growth inhibition on normal cells, thereby making the ADC more toxic; negating Wei's purported solution to the problem. *Id.* at 21. Patent Owner asserts that this is a teaching away, in that the prior art expressly explains the problem with, and would discourage a person of ordinary skill in the art from, pursuing the proposed combination. *Id.* at 22 (citing *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017)).

b. Motivation to combine

Patent Owner next argues that the Petition fails to provide a reason why a person of ordinary skill in the art would have been motivated to replace the antibody of Wei with that of Liu. Prelim. Resp. 27.

According to Patent Owner, the Petition provides four reasons in support of the combination of Wei and Liu:

1. Liu's humanized version of cetuximab "has numerous benefits over cetuximab."
2. "[B]oth Wei and Liu disclose and characterize humanized anti-EGFR antibodies" that "are substantially identical."
3. Wei's use of a humanized antibody in ADCs with cleavable linkers would have motivated a skilled artisan to create ADCs using the humanized antibody in Liu.
4. the "progression of antibody engineering, from murine to chimeric to humanized antibodies" would have motivated a skilled artisan to use Liu's humanized antibody in place of cetuximab.

Prelim. Resp. 28 (citing Pet. 40–42).

However, Patent Owner argues, reasons 1, 3, and 4 are all directed to a purported motivation to replace a chimeric antibody with its humanized

counterpart. Prelim. Resp. 28. Patent Owner contends that, even if these arguments were accepted, they would at most provide a motivation to replace chimeric cetuximab with Liu's humanized cetuximab. *Id.* Patent Owner asserts that Petitioner acknowledges that the Petition recycles the obviousness theory advanced by the Examiner during prosecution, directed to replacing Tikhomirov's[6] chimeric cetuximab with Liu's humanized cetuximab. *Id.* at 28–29 (citing Pet. 42). Patent Owner asserts that these reasons do not suggest why a person of ordinary skill in the art would have been motivated to replace Wei's antibody, which is not cetuximab, with humanized cetuximab. *Id.* at 29.

Patent Owner contends that, not only are Petitioner's alleged benefits of Liu's humanized cetuximab over chimeric cetuximab irrelevant to Petitioner's prior art combinations, they also contradict any motivation to combine. Prelim. Resp. 29. Patent Owner notes that Petitioner argues that "BA03 has numerous benefits over cetuximab, including higher ADCC activity and significantly lower immunogenicity." *Id.* (citing Pet. 67–68). But, Patent Owner argues, a major concern in anti-EGFR ADC drug design was on-target toxicities against normal cells that express EGFR. *Id.* Patent Owner argues, with respect to this toxicity, that the higher ADCC (antibody-dependent cellular cytotoxicity) activity of BA03 would have been perceived as a significant disadvantage, given that BA03 is not tumor-specific. *Id.* citing Ex-2008, Table 1). Patent Owner contends that, with higher ADCC activity, an ADC incorporating BA03 would kill EGFR-expressing non-tumor cells more potently, leading to more severe toxicities. *Id.*

[6] Tikhomirov (WO 2015/000062 Al, January 8, 2015) ("Tikhomirov") Ex. 1009.

By contrast, argues Patent Owner, the antibodies of Wei are tumor-specific and would have been seen by a skilled artisan as significantly superior to BA03. Prelim. Resp. 29. Patent Owner also contends that the lower immunogenicity of BA03 is, at best, a less-important advantage over cetuximab, and not an advantage at all over the already humanized antibodies of Wei. *Id.* at 29–30.

With respect to Petitioner's reason 2 above, Patent Owner argues that even if it is true that Wei's and Liu's humanized anti-EGFR antibodies are "substantially identical," Petitioner does not provide a reason to replace the former with the latter. Prelim. Resp. 30. According to Patent Owner, the alleged similarity between the antibodies suggests that there would have been no reason to modify Wei based on Liu's teachings, which would have been redundant. *Id.* (citing, e.g., *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012)).

Importantly, argues Patent Owner, Petitioner's argument concerning the similarity between Wei's and Liu's antibodies is contradicted by Wei's extensive explanation of how its antibody is different from and superior to cetuximab in forming ADCs, as argued above. Prelim. Resp. 30. Petitioner contends that the antibodies are substantially identical simply because they differ "by only one amino acid." *Id.* (quoting Pet. 40). Petitioner again notes that Wei constructed a library including hundreds of "single point mutants of the Cetuximab anti-EGFR antibody," all of which differ from cetuximab by one amino acid, and picked Y104D from the library for its desirable pH selectivity that offers advantages over cetuximab. *Id.* (citing Ex. 1005 ¶¶ 1016–1026). Petitioner asserts that this difference is material

and would have discouraged a person of ordinary skill in the art from replacing Wei's antibody with humanized cetuximab. *Id.* at 30–31.

c. Objective indicia of non-obviousness

Patent Owner argues that Petitioner failed to address various evidence of objective indicia of non-obviousness of which it was allegedly aware. Prelim. Resp. 32 (citing *Apple v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc)). Patent Owner contends that Petitioner's failure to address such objective indicia is itself sufficient reason for the Board to deny the Petition. *Id.* (citing *Aardevo North America, LLC v. Agventure B.V.*, IPR2025-00136, Paper 9 at (May 1, 2025)).

Patent Owner asserts that Petitioner failed to address evidence of: (1) copying; (2) failure by others; and (3) long-felt and unresolved need. Prelim. Resp. 32. Patent Owner contends that Petitioner knew, or reasonably should have known, of such secondary evidence of non-obviousness, including the development and clinical testing of its SYS6010 ADC cancer therapy that copies the claimed invention of the '370 patent and the termination of previous clinical trials for ADCs using other anti-EGFR antibodies. *Id.* According to Patent Owner, Petitioner's failure to address this evidence precludes a finding that there is a reasonable likelihood that any of the claims are unpatentable. *Id.* at 32–33 (citing *KSR*, 550 U.S.at 421).

i. Copying

Patent Owner begins by pointing out that Petitioner filed a patent application, WO2023/088382 (the "'382 application), on

November 17, 2022, more than six years after the PCT application of the '370 Patent was published (on August 25, 2016) and more than two years after the '370 Patent issued (on October 6, 2020). Prelim. Resp. 33. Patent Owner notes that the PCT counterpart of the '370 patent (WO2016/131409) was cited in the February 11, 2023, Written Opinion of the International Search Authority for Petitioner's '382 application. *Id.* (citing Ex. 2018, 000002).

Patent Owner argues that Petitioner's '382 application demonstrates that Petitioner prepared and tested four anti-EGFR ADC molecules with cleavable linkers, and that one of these ADCs used BA03 (referred to as SWY2110) as the antibody, the commercial exploitation of which would infringe the challenged claims. *Id.* (citing Ex. 2008 ¶¶ 80–81 (showing the sequences of BA03)). The other three ADC molecules use pH-dependent antibodies (SWY2111, SWY2112 and SWY2113) having different CDRs from the challenged claims. *Id.* Petitioner's '382 application compared the efficacy and safety of the four ADC molecules. *Id.* (citing Ex. 2008, 57 (Tables 17, 18), 58 (Table 19) (showing efficacy comparison), 65 (Table 31) (showing safety comparison)).

Patent Owner contends that, despite its consideration of alternatives, Petitioner chose to copy Patent Owner's invention, and initiated clinical trials for the cancer therapy candidate SYS6010 (CPO301). Prelim. Resp. 34. In Petitioner's Response to Patent Owner's Discretionary Denial Request, Petitioner admits that the '370 patent would "block Petitioner's cancer treatments from the market," thereby admitting that its drug candidate SYS6010 (CPO301) copies the specific BA03 antibody. *Id.* (citing Paper 7, 47). Because the PCT counterpart of the '370 patent was cited against

Petitioner's '382 application, Patent Owner asserts that Petitioner knowingly made the decision to copy Patent Owner's patented invention. *Id.*

Patent Owner contends that Petitioner's decision to copy the claimed ADC, including the specific sequence of the BA03 antibody, after considering multiple options, indicates that the claimed invention was non-obvious. Prelim. Resp. 34 (citing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016); *Windsurfing Int'l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1000 (Fed. Cir. 1986)).

ii. Failure of others

Patent Owner next argues that the Petition refers to the FDA approval results to argue that cleavable linkers are not disfavored, noting that there were only two FDA-approved ADCs for use in cancer treatments, both of which used cleavable linkers, and that there are currently "fourteen FDA-approved ADCs available, twelve of which use cleavable linkers." Prelim. Resp. 35 (citing Pet. 50). However, Petitioner notes, none of these ADCs include an anti-EGFR antibody, which, as Wei acknowledges, creates unique challenges with respect to toxicity compared to other antibodies. *Id.* (citing, e.g., Ex. 1005 ¶ 477).

Patent Owner further asserts that Petitioner also failed to mention that several earlier attempts were made to advance anti-EGFR ADC drug

candidates but all of those attempts have been terminated. Prelim. Resp. 35. Patent Owner provides the following table, providing a few examples:

Sponsor	ADC Name	EGFR antibody	Status
Halozyme	HTI-1511	Tumor microenvironment (TME)-specific	Pre-clinical testing reported in 2016; no subsequent report of clinical development
AbbVie	ABBV-221 (losatuxizumab vedotin)	EGFRvIII-specific	Phase 1 testing reported in 2018; no subsequent report of further advancement
AbbVie	ABBV-321 (serclutamab talirine)	EGFRvIII-specific	Phase I testing reported in 2022; no subsequent report of further advancement

Patent Owner explains that, in 2012, Halozyme reported the preclinical testing of HTI-1511, an anti-EGFR ADC that includes an antibody which "was engineered with increased tumor microenvironment (TME) specificity for EGFR" and possessed a "vc-PAB cleavable" linker. Prelim. Resp. 35 (citing Ex. 2012, 000001). Patent Owner reports that, since 2016, there have been no reports of clinical testing for HTI-1511, suggesting that its development has been terminated. *Id.* at 35–36.

Patent Owner next points to AbbVie's drug candidate ABBV-221 (losatuxizumab vedotin), also an anti-EGFR ADC with a cleavable linker. Prelim. Resp. 36. The antibody in ABBV-221, AM1, is "an affinity-matured [anti-EGFR antibody] ABT-806" that binds EGFRvIII, and the linker is a cleavable "valine–citrulline linker." *Id.* (citing Ex. 2013, 000004). Patent Owner notes that, although it was reported in 2018 that "ABBV-221 has advanced to a phase I clinical trial," there have been no reports of phase I results or phase 2 or 3 testing. *Id.* (citing Ex. 2013, 000004). Patent Owner further notes that the Phase I study of ABB-221 has reportedly been terminated. *Id.* (citing Ex. 2016, 000001).

Patent Owner next notes that another ADC drug candidate by AbbVie is ABBV-321 (serclutamab talirine). Prelim. Resp. 36. According to Patent Owner, this ADC includes the same AM-1 antibody as ABBV-221, as well as a cleavable "maleimidocaproyl-valine-alanine linker." *Id.* (citing Ex. 2014, 000002). Patent Owner asserts that AbbVie reported phase 1 results in 2022, but that no further phase 2 or 3 testing has been reported, suggesting that its development has also been terminated. *Id.* (citing, generally, Ex. 2014).

Summarizing these studies, Patent Owner argues that the failures by others in moving candidate anti-EGFR ADCs with cleavable linkers past pre-clinical testing or early-stage clinical trials demonstrate that the claimed ADC was non-obvious. Prelim. Resp. 36–37 (citing *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000); *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)).

Patent Owner argues that Petitioner reasonably should have known about the evidence showing failure by others, but does not address any such evidence in its Petition. Prelim. Resp. 37. Patent Owner points out that Petitioner investigated FDA approvals for ADCs unrelated to the claimed invention of the '370 patent to support its arguments in the Petition, and so cannot reasonably argue that its investigation somehow excluded ADC candidates that similarly use anti-EGFR antibodies and that are therefore more relevant to this case. *Id.* (citing Pet. 50).

iii. Long-felt and unresolved needs

Patent Owner emphasizes that EGFR "is an attractive target" for anti-cancer therapies "because of the antigen's expression by many tumors and

its rapid internalization." Prelim. Resp. 37 (quoting Ex. 1009, 2). Despite this, and as documented in the preceding section, Patent Owner argues, various attempts have been made to develop anti-EGFR ADCs for treating cancer, but all failed. *Id.* Patent Owner asserts that these failed attempts demonstrate a long-felt and unresolved need to develop ADCs with anti-EGFR antibodies for cancer treatment. *Id.*

Patent Owner asserts that its ADC candidate MRG003, which is protected by the '370 patent, has been granted Fast Track designation and Breakthrough Therapy designation by the FDA for the treatment of recurrent or metastatic nasopharyngeal cancer ("R/M NPC"). Prelim. Resp. 38 (citing Ex. 2003, 000001). Furthermore, Patent Owner argues that Petitioner, in its Response to Patent Owner's Discretionary Denial Request, states that its ADC candidate SYS6010 (CPO301), which admittedly uses the '370 patent's claimed invention, "has received three Fast Track Designations from the FDA," including for treating "non-small cell lung cancer (NSCLC)." *Id.* (citing Paper 7, 46–47).

Patent Owner explains that Fast Track "is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need," with a purpose of "get[ting] important new drugs to the patient earlier." Prelim. Resp. 38 (quoting Ex. 2004, 000001). "Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy." *Id.* "Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over

available therapy on a clinically significant endpoint(s)." *Id.* (quoting Ex. 2005, 000001).

Patent Owner argues that both candidate ADCs that embody the claimed invention, including the specific claimed BA03 antibody connected to a cytotoxic payload using a cleavable linker, have thus been designated by the FDA as addressing unmet needs in cancer treatment. Prelim. Resp. 39. The use of the BA03 antibody, rather than antibodies according to prior art approaches, caused the candidate ADCs to move much farther in the drug approval process. *Id.* Patent Owner asserts that the Petitioner's failure to address this evidence is probative of the claimed invention's nonobviousness. *Id.* In support of this contention, Patent Owner points to the non-precedential *Sun Pharms. Indus., Inc. v. Incyte Corp.*, in which our reviewing court found that the "FDA's designation of [drug candidate] for 'Breakthrough Therapy' and 'Fast-Track' approval are probative of nonobviousness" and that "FDA approval is not a prerequisite to showing that a long-felt need has been met." *Id.* (quoting No. 2019-2011, 2023 WL 5370639, at *6 (Fed. Cir. Aug. 22, 2023)).

4. Analysis

With respect to at least challenged claim 1, we are persuaded that Petitioner has established a reasonable likelihood of prevailing at trial in showing that a person of ordinary skill in the art would have found claim 1 to be obvious over the combination of Wei and Liu. Wei teaches an anti-EGFR antibody-based ADC (Y104D), which is a variant of cetuximab differing by a single amino acid substitution at the 104 position of the variable heavy chain. Ex. 1005 ¶ 10. Wei teaches that its antibody is

covalently linked to a cytotoxic agent (MMAE) via a cleavable linker (vc). *See, e.g.*, *id.* ¶¶ 10, 742, 1103. Wei also teaches a humanized version of this antibody (huY104D) that is similarly covalently linked to MMAE via the vc cleavable linker. *See, e.g., id.* ¶¶ 15, 36–42, 1116. Wei teaches that its ADCs are effective in inhibiting tumor cells, KRAS-mutated EGFR+ tumors both *in vitro* and *in vivo*. *Id.* at Examples 17–20.

Liu teaches a humanized anti-EGFR antibody (BA03) comprising a heavy chain and a light chain, in which the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences SEQ ID NOs: 5–7, and a light chain variable region comprising CDR1, CDR2 and CDR3 having sequences SEQ ID NOs: 12–14. Ex. 1008 ¶¶ 85, 108, 123, 124, 141, 146, Examples 1–5, Tables 1–3. Patent Owner, in its Preliminary Response, does not contest that the combination of Wei and Liu thus teaches all of the limitations of challenged claim 1.

Petitioner argues that a person of ordinary skill in the art would have been motivated to combine the teachings of Wei and Liu, because Liu's humanized version of cetuximab, BA03, has numerous benefits over cetuximab, including stronger EGFR phosphorylation inhibition, higher ADCC activity, and significantly lower immunogenicity. *See* Pet. 40 (citing Ex. 1008 ¶¶ 148–152); Ex. 1002 ¶ 187. Petitioner's declarant, Dr. Bournazos, further testifies that the anti-EGFR antibodies taught by Wei and Liu are "substantially identical." Ex. 1002 ¶ 187.

We are persuaded that, on the record as presently developed, Petitioner has met its burden of establishing a reasonable likelihood of prevailing at trial. We find, and Patent Owner does not contest, that the combination of Wei and Liu teach all of the limitations of at least challenged

claim 1, and, based upon the present record, we agree with Petitioner that a person of ordinary skill in the art would likely have found it obvious to substitute the cetuximab-variant, anti-EGFR antibody of Wei with the similar and effective cetuximab-variant, BA03 anti-EGFR antibody of Liu to arrive at the claimed invention.

Patent Owner makes three principal arguments in opposition to the Petition, namely that: (1) Wei teaches away from the claimed invention; (2) a person of ordinary skill in the art would not have been motivated to substitute Liu's antibody for that of Wei; and (3) secondary objective evidence of non-obviousness, not addressed by Petitioner, is strong enough to overcome Petitioner's arguments. Prelim. Resp. 16–39. We address each of these in turn below.

a. Whether Wei teaches away

With respect to (1), Patent Owner argues that Wei teaches away from the claimed invention, because Wei teaches that the binding of its antibody is pH dependent, and thus selectively targets tumor cells, and Liu does not teach this feature. *See* Prelim. Resp. 19–21. Consequently, Patent Owner argues, Petitioner's argument reverses Wei's alleged improvement over the prior art, by making the ADC more toxic to non-tumor cells, and "reinstating the problem that Wei was set out to solve." *Id.* at 21–22. This, Patent Owner alleges, is a teaching away from Petitioner's proposed combination. *Id.* (citing, e.g., *Meiresonne*, 849 F.3d at 1382; *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015)).

We are not persuaded, on the record thus far developed, that Wei's silence with respect to the teaching of Liu amounts to a "teaching away." A

teaching away requires a reference to actually "criticize, discredit, or otherwise discourage the [claimed] solution." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *see also In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (holding that "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant").

Liu is silent with respect to whether its modified cetuximab EGFR antibody exhibits any pH selectivity in its binding affinity. Nor does Patent Owner point to any express teaching or suggestion of Wei that expressly criticizes, discredits, or would have otherwise discouraged a person of ordinary skill in the art from combining its linker-cytotoxin constituent with other anti-EGFR antibodies. To be sure, Wei teaches that its modified cetuximab anti-EGFR has the advantage of being pH selective in its binding affinity, such that it binds preferentially to EGF receptors in the more acidic extracellular microenvironment of tumor tissue compared to receptors in non-tumor tissues at a physiological pH of 7.0–7.2. But, Patent Owner points to no teaching that would have discouraged a skilled artisan from combining its vc-MMAE moiety with another modified cetuximab anti-EGFR antibody whose pH binding affinity is unknown.

As such, we find, based upon the record as presently developed, that the evidence likely does not support Patent Owner's argument that Wei not teaches away from combining its vc-MMAE moiety with Liu's BA03 antibody. Patent Owner may wish to develop this argument further at trial, but as it presently stands, Patent Owner's argument speaks more to a skilled

artisan's motivation to combine the references than to a teaching away. We therefore consider that argument next.

b. Motivation to combine

Patent Owner's argument (2) is that a person of ordinary skill in the art would not have been motivated to substitute Liu's antibody for that of Wei. Patent Owner contends that the cytotoxic activity of Liu's BA03 anti-EGFR antibody would have been seen as a disadvantage, given that BA03 is not tumor-specific, and would kill EGFR-expressing non-tumor cells more potently, leading to more severe toxicities. *See* Prelim. Resp. 29. Patent Owner contends that the antibodies of Wei and Leanna are tumor-specific and would been seen by the POSA as significantly superior to BA03.[7] *Id.*

Patent Owner argues further that even if Wei's and Liu's humanized anti-EGFR antibodies are "substantially identical," it does not provide a reason to replace the former with the latter, as it would have been redundant. Prelim. Resp. 30. Patent Owner also contends that, because Wei explains in detail how its antibody is different from and superior to cetuximab in forming ADCs, a skilled artisan would have been discouraged from replacing Wei's antibody with Liu's humanized cetuximab. *Id.* at 30–31.

[7] As evidence of this, Patent Owner points to Petitioner's patent application EP 4 434 549 A1, published on September 25, 2024 (the "'549 application"). Ex. 2008. However, the '549 application claims the priority benefit of CN 202111365644, filed November 17, 2021, whereas the '370 patent claims a priority date of February 16, 2016. Ex. 2008, code (30); Ex. 1001, code (22). Consequently, the '549 application is not prior art to the '370 patent and a person of ordinary skill in the art would not have known of its disclosures at the time the application for what issued as the '370 patent was filed.

Based upon the record as presently developed, and for the purposes of this Decision, we are not persuaded that Patent Owner's argument (2) is sufficiently strong to overcome Petitioner's reasonable likelihood of success at trial. We acknowledge that Wei teaches that "administered [cetuximab] anti-EGFR antibodies can bind to EGFR in healthy cells and tissue. This limits the dosages that can be administered. Hence, Cetuximab and other anti-EGFR antibodies exhibit limitations when administered to patients." Ex. 1005 ¶ 9. Nevertheless, Liu teaches that its humanized cetuximab (BA03) has superior activity and decreased immunogenicity than chimeric cetuximab: "The humanized antibodies BA03 and BD03 of the present invention have higher ADCC activity than [chimeric cetuximab] at 0.l μg/ml and l μg/ml, both higher than [chimeric cetuximab]." Ex. 1008 ¶ 130.

We find, based upon the present record and for the purposes of this Decision, that Petitioner has sufficiently established that a person of ordinary skill in the art would have been motivated to combine the teachings of Wei and Liu to determine the activity and suitability of Liu's humanized anti-EGFR antibodies in an ADC. We acknowledge that Liu is silent regarding the pH selectivity or tissue preference of its binding affinity, but Patent Owner points to no prior art reference that would have informed a skilled artisan upon this point or that would have discouraged a person of ordinary skill in the art from combining the references. *See* fn.7, *supra*. And, even if a skilled artisan might have recognized that Liu's humanized cetuximab might have been potentially problematic if it failed to show pH-selective activity like Wei's Y104D, the mere fact that some disadvantage may come with an advantage when combining prior art does not foreclose their combination under § 103. *Medichem, S.A. v. Rolabo S.L.*, 437 F.3d 1157,

1165 (Fed. Cir. 2006). In the instance of Liu's humanized anti-EGFR antibody, a person of ordinary skill in the art would have recognized that its advantages (enhanced activity against tumor cells compared to chimeric cetuximab, thus requiring smaller dosages) could balance or outweigh its possible disadvantages (e.g., possible activity against non-tumor cells).

Furthermore, it is in the nature of scientific research to continue to try new substitutions in drug therapy, even if a promising candidate has been discovered. As the Supreme Court stated in *KSR*:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421.

Petitioner and Patent Owner may wish to further develop their arguments and evidence with respect to Patent Owner's argument (2) at trial.

c. Objective indicia of nonobviousness

Patent Owner's argument (3) is that evidence of objective indicia of nonobviousness, not addressed by Petitioner, is strong enough to overcome Petitioner's arguments. *See* Prelim. Resp. 32–39. "For objective evidence of secondary considerations to be relevant, there must be a nexus between the merits of the claimed invention and the objective evidence." *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023) (citing *In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). A showing of nexus can be made in two ways: (1) *via* a presumption of nexus,

or (2) *via* a showing that the evidence is a direct result of the unique characteristics of the claimed invention. *Id.* Patent Owner does not expressly address this threshold issue in its Preliminary Response, and its argument is consequently deficient in this respect.

However, if we assume, for the purposes of this Decision, that such a nexus exists, objective evidence of nonobviousness can include: (1) commercial success; (2) copying; (3) industry praise; (4) skepticism; (5) long-felt but unsolved need; and (6) failure of others. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling U.S., Inc.*, 699 F.3d 1340, 1349–56 (Fed. Cir. 2012). The weight to be given to evidence of secondary considerations is a factual determination. *In re Couvaras*, 70 F.4th 1374, 1380 (Fed. Cir. 2023). Patent Owner argues that: (a) objective evidence of copying; (b) failure of others; and (c) long-felt but unsolved need in this case are such that they overcome the reasonable likelihood that Petitioner will prevail at trial. Prelim. Resp. 32–39. Patent Owner argues further that, because Petitioner has not addressed this evidence, or reported it to the Board, institution of *inter partes* review should be denied. *Id.* at 32 (citing *Aardevo North America, LLC v. Agventure B.V.*, IPR2025-00136, Paper 9 at 34–35 (May 1, 2025) (denying institution based on "Petitioner's failure to address any objective indicia offered by Patent Owner")).

As evidence of copying, Patent Owner points to Petitioner's Response to Patent Owner's Discretionary Denial Request, in which Petitioner allegedly admits that the '370 patent would "block Petitioner's cancer treatments from the market," admitting that its drug candidate SYS6010 (CPO301) copies the specific BA03 antibody. Prelim. Resp. 34 (quoting Paper 7 at 47). Patent Owner asserts that, because the PCT counterpart of

the ’370 patent was cited against Petitioner’s ’382 application, Petitioner knowingly made the decision to copy Patent Owner’s patented invention. *Id.* Patent Owner therefore contends that Petitioner’s decision to copy the claimed ADC, including the specific sequence of the BA03 antibody, after considering multiple options indicates that the claimed invention was non-obvious. *Id.*

With respect to failure of others, Patent Owner cites three studies of ADCs with anti-EGFR antibodies, none of which apparently progressed beyond pre-clinical or Phase 1 testing. Prelim. Resp. 35. According to Patent Owner, these failures by others in moving candidate anti-EGFR ADCs with cleavable linkers past pre-clinical testing or early-stage clinical trials are evidence that the claimed ADC was non-obvious. *Id.* at 36.

Patent Owner additionally argues that its claimed invention satisfies a long-felt and unresolved need to develop ADCs with anti-EGFR antibodies for cancer treatment. Prelim. Resp. 37. Patent Owner points to its ADC candidate MRG003, which is protected by the ’370 patent, which has been granted Fast Track and Breakthrough Therapy designations by the FDA for the treatment of recurrent or metastatic nasopharyngeal cancer. *Id.* at 38. Patent Owner acknowledges that Petitioner’s ADC candidate SYS6010 (CPO301), which allegedly uses the ’370 patent’s claimed invention, “has received three Fast Track Designations from the FDA,” including for treating “non-small cell lung cancer (NSCLC).” *Id.* (quoting Paper 7 at 46–47). Patent Owner argues that the success of these drug candidates as evidence of the claimed inventions fulfillment of a long-felt and unresolved need. *Id.* at 39.

Although Patent Owner's arguments concerning objective indicia of nonobviousness appear to have some merit, and have not yet been addressed by Petitioner, we conclude, based upon the record presently before us, that the balance of the arguments and evidence weigh in favor of institution of *inter partes* review. Patent Owner makes a colorable argument that Petitioner has copied its invention; however, Petitioner may have done so in anticipation of challenging the validity of the '370 patent. Indeed, we concluded in Section III.C.4.a–b above that Petitioner has demonstrated a reasonable likelihood of success in prevailing in challenging the '370 patent's claims. Also, *Liqwd* explained the difference between infringement and copying focused on "whether there was actual evidence of copying efforts as opposed to mere allegations regarding similarities between the accused product and a patent; the focus was not whether the copying efforts involved a 'specific product.'" *Liqwd, Inc. v. L'Oreal USA, Inc*., 941 F.3d 1133, 1138 (Fed. Cir. 2019). Further evidence may clarify this issue.

Moreover, although Patent Owner points to the alleged failure of three other ADCs incorporating anti-EGFR antibodies to advance beyond phase 1 clinical trials, Patent Owner is still faced with the evidence of Wei, which appears to have very successfully demonstrated pre-clinical success of such an antibody.

Finally, with respect to the claimed invention's fulfillment of a long-felt and unresolved need, Patent Owner's arguments may be premature. Patent Owner points to the fact that a new drug application ("NDA") for MRG003 has been accepted by the National Medical Products Administration (NBPA) of China for the treatment of nasopharyngeal cancer (NPC), and was included in priority review, arguing that, if approved,

MRG003 will likely be the first approved anti-EGFR ADC with a cytotoxic payload worldwide. Prelim. Resp. 15 (citing Ex. 2017, 000005). Such an approval may yet be a long time forthcoming, if it comes at all. Similarly, Fast Track and Breakthrough Therapy designations indicate that a developing drug or therapy exhibits considerable promise, but both designations are similarly a long way from *fulfilling* a long-felt and unresolved need.

Given these considerations, we conclude that, on the record presently before us, Patent Owner's arguments with respect to objective indicia of nonobviousness do not outweigh Petitioner's demonstration of a reasonable likelihood of prevailing in demonstrating that the claims are obvious over the cited prior art. The parties are free to continue to develop these arguments at trial. Furthermore, although the ultimate burden of proof on patentability never shifts from Petitioner, the burden (of production) of coming forward with arguments concerning objective indicia rests upon Patent Owner, and not Petitioner. So the fact that Petitioner has yet to argue against such issues is not determinative at this point. **See, e.g., ZUP, LLC v. Nash Mfg., Inc.**, 896 F.3d 1365, 1373 (Fed. Cir. 2018).

5. Summary

Based upon the record as presently developed, we conclude that Petitioner has met its burden of showing a reasonable likelihood of showing at trial that at least claim 1 of the '370 patent is obvious over the cited prior art. Because we determine that Petitioner has demonstrated a reasonable likelihood of success at trial in showing that at least one claim is unpatentable on at least one of the stated Grounds, we institute *inter partes*

review of all challenged claims of the '370 patent, based on all of the remaining grounds identified in the Petition. *See* 37 C.F.R. § 42.208(a); *SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 371 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

We offer the following views on the remaining claims and second Ground for the parties' consideration.

6. Dependent claims 2–23

Based upon the record presently before us, we conclude that Petitioner has similarly established a reasonable likelihood of success in prevailing at trial in demonstrating that these challenged claims are unpatentable on Ground 1. *See* Section III.C.2.b–s above. We note that Patent Owner has not argued these claims separately in its Preliminary Response, and our reasoning is consequently based upon the evidence of record cited by Petitioner and our reasoning in the preceding Sections of this Decision.

D. Ground 2: Alleged Obviousness of Claims 1–23 over Wei, Liu and Leanna

1. Petitioner's arguments

a. Claim 1

Petitioner provides the flowing claim chart to illustrate Ground 2 with respect to challenged claim 1:

Claim 1 of the '370 patent	**Prior Art**
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody	**Leanna** discloses: An anti-EGFR antibody-drug conjugate, including Antibody 1-vc-MMAE ADC that comprises a humanized anti-EGFR antibody (*i.e.*, Antibody 1) covalently

covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.	linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1006, 34). **Liu** discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a light chain (EX1008, Examples 1-5, [00141]-[0146], Tables 1-3), wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7 (*id.*, [0085], [0123], [0124]), and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 (*id.*, [0108], [0123], [0124]). **Wei** provides further motivation to combine the anti-EGFR ADCs of Leanna with the Liu, which discloses the BA03 antibody claimed in the Challenged Claims. **Wei** discloses the Y104D-Mc-vcPAB-MMAE ADC, containing a modified cetuximab antibody (*i.e.*, Y104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1005, [0742], [1092]-[1141]). In view of Wei, a POSA would have been motivated to combine the humanized ADC of Leanna with a modified (humanized) cetuximab antibody – BA03 – as taught by Liu, to arrive at the Challenged Claims.

Pet. 65–66. The claim chart provides each limitation of claim 1 and a description of where each limitation is supported by the cited prior art references.

Petitioner argues that, in addition to the teachings of Wei and Liu argued above in Section III.*C*.2.a, Leanna teaches ADCs comprising an anti-EGFR antibody and a cytotoxic agent, such as MMAE or MMAF. Pet. 67 (citing Ex. 1006, 1, 5, 6). Petitioner contends that Leanna discloses that MMAE is conjugated to the antibody via a cleavable valine-citrulline (vc) linker. *Id.* (citing Ex. 1006, 8). Specifically, argues Petitioner, Leanna specifically discloses an Antibody 1-vc-MMAE ADC, in which Antibody 1 is a humanized IgG1 isotype anti-EGFR antibody disclosed previously WO 2011/041319 and US 2011/0076232. *Id.* (citing Ex. 1006, 26).

Petitioner argues that a person of ordinary skill in the art would have been motivated to combine the teachings of Leanna, Liu, and Wei to arrive at claim 1 because Leanna discloses anti-EGFR ADCs with the cleavable linker vc, which is disclosed as a preferred embodiment of the '370 patent. Pet. 67 (citing Ex. 1006, 50–60). According to Petitioner, at the time of filing, there were only two FDA-approved anti-EGFR antibodies for therapeutic use, one of which was cetuximab. *Id.* (citing Ex. 1014). Furthermore, argues Petitioner, Liu discloses and claims BA03, a humanized version of cetuximab, and states that BA03 has numerous benefits over cetuximab, including higher ADCC activity and significantly lower immunogenicity. *Id.* at 67–68 (citing Ex. 1008 ¶¶ 141–160).

Petitioner argues that both Leanna and Liu disclose humanized anti-EGFR antibodies, which a skilled artisan would have recognized as having lower immunogenicity compared to murine and chimeric antibodies. Pet. 68 (citing Ex. 1006, 26, 34). Additionally, Petitioner contends, Wei discloses a humanized cetuximab variant huY104D as part of the huY204D-MMAE ADC. *Id.* (citing Ex. 1005, Example 20). Petitioner argues that Wei's

Y104D-MMAE ADC contains the cetuximab variant Y104D attached to the MMAE cytotoxic payload with a vc cleavable linker, as in challenged claim 1. *Id.* (citing Ex. 1005 ¶¶ 740, 742, 1103).

Petitioner points to Dr. Bournazos' testimony, in which he explains that those of ordinary skill in the art would have recognized that, if ADCs with cleavable linkers were being made in the prior art using a modified version of the chimeric version of M225 (i.e., cetuximab variant Y104D, as shown by Wei), they would have been strongly motivated to create ADCs using the humanized version of M225 (BA03), because humanized antibodies had several advantages over chimeric antibodies, including lower immunogenicity, as disclosed by Liu. *Id.* (citing Ex. 1002, 188).

Additionally, argues Petitioner, a person of ordinary skill in the art would have recognized the standard progression of antibody engineering, from murine to chimeric to humanized antibodies. Pet. 68. Petitioner notes that this was the primary basis for the Office to conclude, during prosecution, that ADCs incorporating the claimed antibody of claim 1 were obvious over the prior art. *Id.* at 68–69 (citing Ex. 1003, 148–162). According to Petitioner, the Office was correct when it found that a skilled artisan "would have been motivated" to replace the BA03 antibody in place of cetuximab ADCs "because the BA03 antibody is the full-length antibody that is an antagonist of EGFR as demonstrated by Liu and has higher binding affinity and ligand blocking abilities than cetuximab." *Id.* at 70 (citing Ex. 1003, 406–407). Petitioner asserts that this reasoning—that a person of ordinary skill in the art would have been motivated to replace cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu—was never challenged by Patent Owner during prosecution. *Id.*

b. Claims 2–23

Petitioner essentially repeats the arguments concerning challenged dependent claims 2–23 presented in Sections III.*C*.2.b–t above, and adding Leanna's relevant teachings concerning the Antibody 1-based ADCs. *See* Pet. 69–75.

2. Patent Owner's preliminary response

Patent Owner responds that Petitioner's arguments fail for the same reasons as in Ground 1. Prelim. Resp. 31. Patent Owner notes that Leanna's antibody is not a modified version of cetuximab and is more different than Wei's antibody from cetuximab and that Petitioner alleges that cetuximab was one out of two FDA-approved anti-EGFR antibodies. Prelim. Resp. 31 (citing Pet. 67). Patent Owner contends that this allegation does not provide any particular reason why a person of ordinary skill in the art would have been motivated to modify Leanna's ADC, especially given that Liu's BA03 antibody is not covered by the FDA's approval of cetuximab. *Id.* Patent Owner argues that, because Petitioner provides no meaningful reason to replace Wei's/Leanna's antibody with Liu's antibody, all that is left is impermissible hindsight. *Id.* Patent Owner contends that Petitioner's alleged reliance upon hindsight is evident from the Petition's reference to the '370 patent's claims as a roadmap in explaining why a skilled artisan would have been motivated to combine Wei and Liu. *Id.* (citing, e.g., Pet. 41).

3. Analysis

Because we have concluded that, based upon the record as presently developed, Petitioner has established a reasonable likelihood of prevailing in

demonstrating that claims 1–23 are unpatentable as being obvious over Wei and Liu, we similarly conclude, for the same reasons, that Petitioner has met its burden of demonstrating a reasonable likelihood of prevailing in showing that claims 1–23 are unpatentable as being obvious over Wei, Liu, and Leanna. Additionally, Leanna teaches that its humanized cetuximab anti-EGFR antibody, when incorporated into an ADC (an "immunoconjugate" in Leanna) "displays enhanced cytotoxicity against cancer cells without a corresponding increase in cytotoxicity against skin cells," similar to the ADCs of Wei. Ex. 1006, 3, 24. We invite the parties to continue to develop their arguments and evidence at trial.

IV. CONCLUSION

Because we have determined that Petitioner has demonstrated a reasonable likelihood of success at trial in showing that at least one claim is unpatentable on at least one of the stated Grounds, we institute *inter partes* review of all challenged claims of the '370 patent, based on all of the remaining grounds identified in the Petition. *See* 37 C.F.R. § 42.208(a); *SAS*, 584 U.S. at 371; *PGS Geophysical*, 891 F.3d at 1360.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or to the construction of any claim term. Therefore, our view with regard to any conclusion reached in the foregoing may change upon consideration of Patent Owner's merits response and the completion of the record.

Consequently, and in keeping with our mission of resolving patentability disputes in a just, speedy, and efficient manner, and for the

reasons we have explained in the foregoing Sections, we institute *inter partes* review as set forth in the following Order.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), that the Petition for *inter partes* review of challenged claims 1–23 of U.S. Patent 10,792,370 B2 is GRANTED with respect to all grounds in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '370 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of trial.

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