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BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,
Petitioner,
v.
SHANGHAI MIRACOGEN INC.
Patent Owner.

Case IPR2025-00685
U.S. Patent No. 10,792,370

Title: Antibody-Drug Conjugate

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Patent Owner (“PO”) fails to overcome the prima facie case of obviousness in the Petition with its Response (“POR”). (POR, 1-4; EX1002, ¶¶1-16.) PO’s defense rests on three pillars, each of which collapses under scrutiny.

First, PO mischaracterizes the prior art and improperly narrows the POSA’s perspective to exclude well-established ADC design strategies. (EX1002, ¶¶177-201; EX1200, ¶¶4-11.) In its Institution Decision (“ID”), the Board rejected PO’s argument that Wei would have taught away from using a non-selective EGFR antibody such as BA03 because, among other things, BA03 could have presented advantages outweighing any alleged concerns. The POR offers no credible evidence of teaching away. To the contrary, PO’s own cited reference concedes that, for anti-EGFR therapies, “the risk associated with severe skin reaction is currently considered acceptable when managed properly” and that “[e]fforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater affinity for the target antigen.” (EX2011, 1:30-40.)

Second, PO’s pH selectivity and tumor-selective epitope theory finds no support from the prior art or the ’370 patent. (POR, 24-39; EX2027, ¶¶45-75.) The claims do not require pH selectivity, and Dr. Bournazos’s un rebutted testimony confirms that Wei’s data show no meaningful pH selectivity differences. (EX2026, 77:14-86:8.)

Third, Dr. Atanackovic’s deposition admissions fatally undermine his expert declaration. He conceded that his pH selectivity opinion for BA03 rested on post-filing evidence unavailable to a POSA (EX1246, 207:5-14), and he failed to analyze the very ADC design factors he faulted Dr. Bournazos for not addressing. (EX1200, ¶¶4-11; EX1246, 164:11-167:22; EX2027, ¶¶82-84.)

As the ID recognized, both Grounds of the Petition disclosed every claimed element, and the POR does not dispute this. Instead, PO recycles the same teaching-away and lack-of-motivation arguments the Board already rejected, without supplementing the record with credible evidence to compel any reversal of the Board’s findings.

Finally, the POR’s attempt to minimize the significance of BA03 by characterizing Liu as a “secondary” reference fails. Petitioner never listed Liu as a secondary reference, and in any event, characterizing references as primary and secondary has “no legal significance” to the obviousness analysis. *See Schwendimann v. Neenah, Inc.*, 82 F.4th 1371, 1384 (Fed. Cir. 2023). PO improperly limits the obviousness analysis by requiring the POSA to start with the ADCs disclosed in Wei or Leanna, and then requiring motivation to replace the antibody of these ADCs with Liu’s BA03 antibody. However, the POSA was not so constrained, and could have also started with the BA03 antibody and determined whether there

was prior art that disclosed modified cetuximab ADCs with the claimed linker-payload. As the Petition shows, Wei and Leanna each provided this to render the Challenged Claims obvious. In fact, this was the approach undertaken by PO. PO started with the prior art BA03 antibody, and simply purchased the claimed vc-MMAE linker-payload from a commercial catalog to create its alleged invention. Such an obvious invention cannot be allowed to survive this IPR challenge in view of the prior art.

II. CLAIM CONSTRUCTION

The parties agree on the ordinary meaning of the disputed terms as understood by a POSA. To the extent PO attempts to import limitations from the specification, such as pH selectivity or tumor-selective epitope binding, those are not in the claims and should not be read into them. (EX1001, Claims 1-23.)

III. GROUND 1: CLAIMS 1-23 ARE OBVIOUS OVER WEI AND LIU

A. Wei Teaches Humanized Cetuximab Variant ADCs with the Claimed Linker-Payloads

PO does not dispute that Wei discloses ADCs comprising humanized anti-EGFR antibodies (huY104D) conjugated to MMAE via cleavable valine-citrulline (vc) linkers. (EX1005, ¶¶1092-1127; POR, 25-34.) Wei's Example 20 discloses huY104D-vc-MMAE conjugates with potent anti-tumor activity against EGFR-expressing tumors. (EX1005, ¶¶1116-1127, Tables 42, 44-45.) That disclosure

provides the foundational ADC architecture claimed in the '370 patent: an anti-EGFR antibody covalently linked to a cytotoxic agent through a cleavable linker. (EX1002, ¶¶64-73.)

PO's attempt to distinguish Wei based on alleged pH selectivity of Y104D/huY104D fails. (POR, 24-39; EX2027, ¶¶51-59.) First, the claims do not require pH selectivity. (EX1001, Claims 1-23.) Claim 1 recites an ADC comprising "an anti-EGFR antibody" with specified CDR sequences covalently linked to a cytotoxic agent via a cleavable linker, with no pH-dependent limitation. (EX1001, Claim 1.) PO cannot avoid obviousness by relying on prior-art characteristics not required by its own claims.

Second, Wei's purported pH selectivity data does not establish a meaningful distinction. Petitioner's expert, Dr. Bournazos, testified that Wei's data does not demonstrate biologically meaningful pH selectivity for Y104D as compared to cetuximab. (EX2026, 77:14-86:8.) Wei's Tables 42, 44, and 45 show variable, inconsistent results between chimeric and humanized Y104D variants, undermining any claim of reliable pH-dependent superiority. (EX1005, Tables 42, 44-45.) Moreover, both BA03 and huY104D are humanized derivatives of cetuximab binding the same EGFR epitope; any difference in pH sensitivity is one of degree, not of kind, and is irrelevant to the claimed invention. (EX2026, 104:1-105:15.)

Third, the assumption by PO's expert, Dr. Atanackovic, that BA03 lacks pH selectivity rests on improper and inconsistent grounds. (EX1200, ¶¶90-91.) He relies in part on Petitioner's post-filing data (EX2008), filed about seven years after the priority date, which he conceded was unavailable to a POSA. (EX1246, 207:8-12.) He also asserts that pH-selective antibodies are typically generated by introducing charged residues, such as aspartic acid, into the CDRs (EX2027, ¶56), yet he could not explain why BA03 would not exhibit pH selectivity given that BA03 contains the very types of charged CDR mutations he identified as conferring that property (EX1246, 217-20:219:13; EX1008, 11). His opinions thus lack merit.

B. Liu Teaches BA03 as Superior to Cetuximab

Liu provides explicit motivation to select BA03 for an ADC. (EX1008, ¶¶0141-0160; EX1002, ¶¶185-187.) Liu teaches that BA03, a humanized anti-EGFR antibody, has multiple advantages over cetuximab directly relevant to ADC design. (EX1008, Tables 1-4, Figs. 2-6.)

First, Liu shows that BA03 rapidly internalizes upon EGFR engagement. (EX1008, ¶¶0154-0160.) Internalization is critical for ADC efficacy because the cytotoxic payload must be delivered intracellularly to kill the target cell. (EX1002, ¶¶45-53.) A POSA would therefore have recognized BA03 as a particularly attractive ADC candidate. (*Id.*) Indeed, PO's own Global Offering prospectus

identifies BA03's facilitation of "rapid internalization of MRG003 into tumor cells" as a "competitive advantage[]." (EX2032, 000310.)

Second, Liu teaches that BA03, as a fully humanized antibody, has lower immunogenicity than chimeric antibodies such as cetuximab. (EX1008, ¶¶0152-0153, Fig. 5.) Reduced immunogenicity is a well-recognized and material advantage for therapeutic antibodies intended for repeat administration, as required for ADC dosing regimens. (EX1002, ¶87.)

Third, Liu shows that BA03 inhibits EGFR phosphorylation more strongly than cetuximab. (EX1008, ¶0148, Fig. 3.) For an ADC targeting EGFR-expressing tumors, enhanced target engagement and signaling blockade improve therapeutic potential. (EX1002, ¶87.) Dr. Bournazos confirms that BA03's stronger phosphorylation inhibition is a therapeutically significant advantage, not a detriment, because receptor antagonism is a core therapeutic principle of the entire anti-EGFR antibody class, including cetuximab, and is preserved in ADCs such as T-DM1. (EX1200, ¶¶52-58.)

Fourth, Liu teaches that BA03 mediates higher antibody-dependent cellular cytotoxicity (ADCC) than cetuximab. (EX1008, ¶0150, Fig. 4.) ADCC is a well-established anti-tumor mechanism for therapeutic antibodies, and enhanced ADCC provides additional therapeutic benefit beyond the cytotoxic payload delivered by

the ADC. (EX1002, ¶87.) Dr. Atanackovic's contention that enhanced ADCC is irrelevant or even unfavorable for ADC design (EX2027, ¶64) is contradicted by both the prior art and his own testimony. As Dr. Bournazos explains, ADCC is among the well-established and deliberately engineered properties of anti-EGFR antibodies. (EX1200, ¶¶59-65.) Dr. Atanackovic himself admitted that ADCC "contribute[s] to antitumor effects." (EX1246, 306:9-307:20.)

Accordingly, PO's contention that BA03 offers no advantages over cetuximab-class antibodies is scientifically unsupported. (POR, 32-39; EX2027, ¶¶62-65.)

C. A POSA Would Have Been Motivated to Combine Liu and Wei

The motivation to combine Wei and Liu flows naturally from their teachings. (EX1002, ¶¶185-195.) Wei shows that humanized cetuximab variant ADCs with cleavable vc-MMAE linkers exhibit potent anti-tumor activity. (EX1005, ¶¶1116-1127, Tables 44-45.) Liu shows that BA03 is an improved humanized cetuximab variant with enhanced properties relevant to therapeutic efficacy. (EX1008, ¶¶0141-0160, Tables 1-4.) A POSA seeking to develop an optimized anti-EGFR ADC would have been motivated to use BA03, with its documented advantages in binding affinity, EGFR inhibition, ADCC activity, and internalization, to create a humanized cetuximab ADC which was disclosed in Wei's huY104D. (EX1002, ¶¶185-188.)

Because Wei does not teach away and Dr. Atanackovic cannot distinguish Wei's pH selectivity from BA03's, BA03's advantages outweigh any alleged toxicity concerns. As the Board recognized:

[T]he 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).

ID at 39-40.

Liu's express teaching of BA03's advantages over cetuximab (the parent of both BA03 and Y104D) supplies ample motivation to incorporate BA03 into Wei's ADC platform. (EX1002, ¶¶185-188.) A POSA could have started with BA03, recognized its critical attributes for ADC development, and turned to Wei, which already discloses a substantially similar humanized cetuximab antibody linked to the claimed vc-MMAE linker-payload.

The prosecution history confirms this. (EX1003, 405-407; EX1004, 245-247.) The Examiner repeatedly found that a POSA would be motivated to use BA03 in place of cetuximab in ADCs because BA03 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.” (EX1003, 406; EX1004, 247.) PO never challenged that finding. Its arguments focused exclusively on the alleged absence of cleavable linker teachings. (EX1004, 137-141, 199-207.)

Dr. Bournazos testified that BA03 and huY104D are “substantially identical” humanized cetuximab variants binding the same EGFR epitope: “They both originate from the same clone from cetuximab These are the siblings.” (EX2026, 101:19-23, 103:23-106:19). This substantial identity further supplied the motivation to combine Liu and Wei. (EX1002, ¶¶187-188.) Recognizing BA03’s ideal ADC characteristics, the POSA would have arrived at the Challenged Claims with a reasonable expectation of success because Wei discloses an ADC using a substantially identical antibody with the same claimed vc-MMAE linker-payload. (EX2026, 89:11-90:25.)

PO’s contention that there are “millions of ways to modify cetuximab” does not defeat obviousness. (POR, 37-38; EX2027, ¶¶78-80.) Liu specifically identifies BA03 and teaches its advantages. (EX1008, ¶¶0141-0160.) The prior art need not single out BA03 as the best option; it needs only motivation selecting BA03 as a suitable candidate with a reasonable expectation of success. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421-22 (2007).

D. PO's Therapeutic Window Framework Is Flawed

PO and Dr. Atanackovic frame the obviousness inquiry as if improving the therapeutic window through pH selectivity or tumor-selective epitope binding were the only motivation to develop an anti-EGFR ADC. (POR, 24-39; EX2027, ¶¶45-74.) That unduly narrow framing conflicts with prior art and ADC development practice.

Tikhomirov-346 itself contains statements Dr. Atanackovic failed to present to the Board: (1) “the risk associated with severe skin reaction is currently considered acceptable when managed properly” (EX2011, 1:30-40); and (2) “[e]fforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater affinity for the target antigen.” (*Id.*; EX1200, ¶¶29, 78-79.) Dr. Atanackovic conceded that he did not present either passage in his declaration (EX1246, 12:11-14:18), and this reflects a material gap in his presentation of the prior art.

Dr. Bournazos demonstrates that target-antigen expression on normal tissues has never been a prohibitive barrier to ADC development. (EX1200, ¶¶12-21.) Numerous ADCs against antigens expressed on normal cells entered clinical testing well before 2015, including trastuzumab emtansine (HER2), enfortumab vedotin (Nectin-4), mirvetuximab soravtansine (folate receptor alpha), sacituzumab govitecan (TROP-2), and MLN2704 (PSMA). (*Id.* ¶¶14-15, Table 1.) EGFR is no different. (*Id.* ¶15.) The relevant inquiry is whether tumor-associated overexpression

and biologic accessibility produce an acceptable therapeutic index, not the absolute absence of normal-tissue expression. (*Id.* ¶17.)

A POSA developing an anti-EGFR ADC would have considered multiple factors beyond therapeutic window, including binding affinity, internalization rate, ADCC and CDC activity, immunogenicity, manufacturability, pharmacokinetics, and overall anti-tumor efficacy. (EX1002, ¶¶32-58, 85-92; EX1015, 6-8; EX1019, 1-11; EX1010, 1-18.) The prior art confirms that desirable ADC antibody properties include “specificity; high binding affinity; long-circulation times; immune effector functions such as CDC, ADCC and antibody-dependent cellular phagocytosis; tumor-suppressing modulation of antigen’s biological activity when possible.” (EX1004, 177.) Liu teaches that BA03 has advantages in several of these parameters, providing ample motivation to select BA03 independent of any therapeutic window considerations. (EX1008, ¶¶0141-0160, Tables 1-4, Figs. 2-6; EX1002, ¶¶85-92.)

KSR rejected the rigid, formalistic approach PO advocates. *KSR*, 550 U.S. at 415-421. A POSA is “a person of ordinary creativity, not an automaton,” and would have been motivated to combine known ADC components for any number of legitimate scientific and commercial reasons. *Id.* at 421.

PO’s attempt to cabin the POSA’s motivation to a single objective (therapeutic window) improperly transforms obviousness into a hindsight-driven search for the

patentee's specific rationale. (EX2027, ¶¶51-59.) The proper question is whether the prior art as a whole suggests the desirability of the combination, not whether it suggests the most desirable one available. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Dr. Bournazos confirmed that a POSA would weigh various factors in assessing ADC success, including target, antibody, drug, linker, and overall ADC characteristics. (EX2026, 56:1-62:22.) PO's exclusive focus on therapeutic window ignores these other factors.

Even on PO's therapeutic window framework, a POSA would have understood that therapeutic selectivity can be achieved through mechanisms beyond pH selectivity or tumor-exclusive epitope binding. (EX1002, ¶¶32-58.) EGFR is overexpressed on many tumors relative to normal tissues, and that differential expression provides an alternative basis for selectivity. (EX1008, ¶¶0154-0160, Table 4; EX2026, 50:9-21, 149:15-150:12.) As the prior art confirms, "[t]he expression of an antigen of interest in some normal tissues does not necessarily preclude the development of an ADC targeting this antigen, if the normal tissue is either nonessential, or insensitive to the action of the drug." (EX1004, 174.)

E. The Crombet Model Is Unreliable

Dr. Bournazos explains that the Crombet model (EX2022) on which Dr. Atanackovic relies is scientifically unreliable and inapplicable to ADC design. (EX1200, ¶¶39-45.) Crombet was developed for naked antibodies and omits ADC-

specific parameters such as drug-to-antibody ratio, linker stability, or payload release kinetics. (*Id.* ¶41.) Crombet also compared h-R3 and cetuximab using data from different clinical trials at different dosages, introducing confounding variables. (EX1200, ¶44; EX1246, 88:8-89:2.) Crombet itself states only that “higher affinity is not necessarily the best,” not that higher affinity is disqualifying. (EX2022, 000007; EX1200, ¶46.)

ADCs differ from naked antibodies in dose. (EX1200, ¶¶34-38.) Clinical ADC doses are substantially lower than unconjugated antibody doses (*id.* ¶34), and at lower doses, high affinity becomes an advantage because the ADC must efficiently bind tumor cells with substantially less antibody administered (*id.* ¶36). Affinity also influences intracellular trafficking. (*Id.* ¶37.) HER2 data showed that internalization and catabolism generally increased with affinity. (*Id.*) Dr. Atanackovic himself admitted that “stronger binding affinity can result in a higher degree of internalization of ADC.” (EX1246, 50:19-51:4, 345:11-16.) PO’s own Global Offering prospectus likewise identifies BA03’s roughly six-to-sevenfold higher EGFR binding affinity over cetuximab, and its facilitation of “rapid internalization of MRG003 into tumor cells,” as “competitive advantages.” (EX2032, 000310.) The very property Dr. Atanackovic calls disqualifying is what PO promotes as a competitive advantage. (EX1200, ¶96.)

F. Neither Wei nor Leanna Teaches Away from Using BA03

PO's teaching-away argument fails because Wei does not criticize, discredit, or discourage humanized cetuximab variants lacking alleged pH selectivity. (POR, 27-39.) As the Board recognized, "teaching away requires a reference to actually 'criticize, discredit, or otherwise discourage the [claimed] invention.'" ID at 36-37, quoting *In re Fulton*, 391 F.3d at 1201 ("the prior art's mere disclosure of more than one alternative does not constitute a teaching away.").

Wei discloses Y104D as one approach to anti-EGFR ADCs but does not state or suggest that other humanized cetuximab variants would be unsuitable. (EX1005, ¶¶1092-1141; EX1246, 227:1-230:13, 326:17-329:22.) Wei's preference for Y104D based on its purported pH selectivity does not teach away from alternatives that work through different mechanisms. (EX2026, 77:15-20, 82:20-82:8, 87:18-86:8, 90:3-23, 108:16-109:19.) A POSA would have understood that Wei's ADC platform (a humanized anti-EGFR antibody conjugated to MMAE via a cleavable linker) could function with antibodies having different binding characteristics. (EX1002, ¶¶186-195.)

Wei in fact disclosed not only Y104D-MMAE but also a cetuximab-MMAE conjugate. (See EX1005, Example 21, ¶ [1128].) Both ADCs showed virtually identical cell growth inhibition ("CGI") on cancerous A431 cells. (*Id.*, ¶[1130].) Although Wei states that Y104D-MMAE exhibited less inhibition of non-cancerous

keratinocytes than the cetuximab-MMAE ADC, the actual data showed only a 10% difference: “[a]t the maximum doses, Cetuximab achieved about 80% CGI and Y104D-MMAE exhibited a CGI of about 70%.” (*Id.*, ¶[1131].) That ADCs made with cetuximab and a humanized cetuximab (Y104D-MMAE) displayed similar properties would not have discouraged a POSA from using another humanized cetuximab antibody, namely Liu’s BA03, to make ADCs with the claimed vc-MMAE linker-payload; if anything, it would have motivated the POSA to create a BA03-vc-MMAE ADC. As the Board recognized in its *KSR* discussion, “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.” (ID at 40.)

G. Reasonable Expectation of Success is Established

PO argues that the Petition fails to establish a reasonable expectation of success. (POR, 52-56; EX2027, ¶¶76-84.) The argument ignores the substantial supporting evidence. The legal standard requires only that a POSA would have had a reasonable expectation of successfully making and using the claimed invention, not a guarantee of clinical or therapeutic success. (EX1200, ¶97.) Dr. Atanackovic confirmed that claim 1 contains no language requiring the ADC to be therapeutically or clinically successful. (EX1246, 145:3-148:9.)

By the March 2015 priority date, two ADCs had received FDA approval: gemtuzumab ozogamicin (Mylotarg, 2000) and brentuximab vedotin (Adcetris,

2011). (EX1019, 2; EX1021, 1; EX1002, ¶51.) Both used cleavable linkers, clinically validating that strategy. (EX1020, 6; EX1010, 3; EX1026, 1-2.) Brentuximab vedotin used the same vc-MMAE configuration recited in the '370 patent, confirming that this drug-linker combination was well established and clinically successful. (EX1021, 1-2; EX1002, ¶¶51-55.)

Wei demonstrated that humanized cetuximab variant ADCs with vc-MMAE exhibit potent anti-tumor activity in preclinical models. (EX1005, ¶¶1116-1127, Ex. 20, Tables 42, 44-45.) That proof of concept would have given a POSA confidence that similar ADCs using other humanized cetuximab variants could achieve comparable results. (EX1002, ¶¶186-195; EX2026, 89:11-91:10.)

Liu demonstrated that BA03 has the key properties required for a successful ADC antibody: high-affinity target binding, efficient internalization, and anti-tumor activity. (EX1008, ¶¶0141-0160, Tables 1-4.) A POSA would have recognized that those characteristics, combined with Wei's validated vc-MMAE system, provide a reasonable expectation of generating a functional ADC. (EX1002, ¶¶181-201.)

The predictable nature of ADC construction further supports a reasonable expectation of success. ADCs are assembled from modular components (antibody, linker, payload) using established conjugation chemistry. (EX1015, 6-8; EX1020, 2-7; EX1026.) A POSA would have understood that substituting one humanized anti-

EGFR antibody (BA03) for another (huY104D) in a proven platform would yield a functional product with predictable properties. (EX1002, ¶¶181-201; EX2026, 89:11-91:10, 101:9-108:15.)

IV. GROUND 2: CLAIMS 1-23 ARE OBVIOUS OVER LEANNA, LIU AND WEI

Ground 2 is based on the combination of Leanna, Liu, and Wei. The motivation to combine and reasonable expectation of success arguments set forth in Section III with respect to BA03's advantages, the inapplicability of the Crombet model, the importance of high-affinity antigen recognition, and the absence of teaching away apply with equal force to Ground 2 and are incorporated here. The discussion below focuses on issues specific to Leanna.

A. Leanna Teaches Anti-EGFR ADCs with vc-MMAE

Leanna provides additional confirmation that anti-EGFR ADCs using cleavable vc linkers and MMAE payloads were known before the priority date. (EX1006, 26:1-32:18, Fig. 1; EX1002, ¶¶75-83.) Leanna discloses Antibody 1-vc-MMAE conjugates with anti-tumor activity against EGFR-expressing cancers. (EX1006, 32, 50-82.) The reference confirms that the claimed linker-payload architecture was well-established. (EX1002, ¶¶75-83.)

B. PO Mischaracterizes Leanna

PO mischaracterizes Leanna's scope and purpose. (POR, 39-46.) Leanna, entitled "Antibody Drug Conjugate (ADC) Purification," is directed to methods for obtaining ADC compositions with specified drug-to-antibody ratios (DARs). (EX1006, 1.) Leanna's claims and disclosure apply broadly to ADCs comprising "an antibody conjugated to an auristatin," and expressly state that suitable anti-EGFR antibodies "can include, for example, chimeric (e.g., having a human constant region and mouse variable region), humanized, or human antibodies; single chain antibodies; or the like." (EX1006, 4, 9, 18, 26, 83-89, Claims 1-50; EX1002, ¶¶74-83.) Leanna defines "anti-EGFR antibody" as "an antibody that specifically binds to EGFR" and identifies Antibody 1 only as "an example of an anti-EGFR antibody." (EX1006, 11; EX1200, ¶66.) Although Leanna uses Antibody 1-vc-MMAE as an exemplary embodiment, its methods are not limited to Antibody 1 or to any particular anti-EGFR antibody.

C. PO's Tumor-Selective Epitope Arguments Are Unavailing

PO contends that Leanna's Antibody 1 (mAb806) targets a tumor-selective EGFR epitope (de2-7 EGFR) and that substituting BA03 would eliminate tumor selectivity. (POR, 39-46; EX2027, ¶¶67-74.) This argument fails for several reasons.

First, as discussed above, Leanna's methods are not limited to Antibody 1. (EX1006, 4, 9, 18, 26, 83-89, Claims 1-50.) Antibody 1 is merely an exemplary anti-EGFR antibody used to demonstrate the purification methods, which apply to any

ADC comprising an antibody conjugated to an auristatin. (EX1006, Abstract, Claims 1-30.)

Second, the claims of the '370 patent do not require tumor-selective epitope binding. (EX1001, Claims 1-23.) The claims define the antibody by its CDR sequences and require binding to EGFR, not binding only to tumor-expressed EGFR variants. (*Id.*) PO cannot avoid obviousness by importing unclaimed limitations.

Third, Leanna is cited primarily to show that the claimed ADC architecture (an anti-EGFR antibody conjugated to MMAE via a cleavable vc linker) was known. (EX1002, ¶¶275-279.) The motivation to select BA03 comes from Liu's teaching of BA03's advantages, not from any desire to replicate Antibody 1's epitope specificity. (*Id.*, ¶¶280-282.)

Fourth, tumor selectivity can be achieved through means other than epitope-based selectivity. (EX1002, ¶¶32-58.) EGFR overexpression on tumor cells relative to normal cells provides an alternative basis for preferential targeting. (*Id.*) That overexpression-based strategy is well recognized in ADC development and yields a therapeutic window even when the antigen is also expressed on normal cells. (EX2026, 67:14-24, 129:11-131:8, 149:18-151:3.)

Fifth, Dr. Bournazos testified that Liu's BA03 and Leanna's Antibody 1 both recognize EGFR and, "in a bigger context, they both recognize EGFR." (*Id.*, 114:18-

115:19.) That they may bind different epitopes does not preclude using BA03 in an ADC platform like Leanna's. (*Id.*) This testimony undermines PO's claim that BA03 and Antibody 1 are fundamentally incompatible.

Sixth, Dr. Bournazos identifies significant advantages of BA03 over Antibody 1. (EX1200, ¶¶66-72.) EGFRvIII-specific antibodies like Antibody 1 can treat only a minority of patients: EGFRvIII is present in only "24-67% of cases," and tumors frequently lose EGFRvIII expression over time, with "82% of patients" losing it at recurrence. (*Id.* ¶¶68-70.) Dr. Atanackovic similarly confirmed that "not [] all the patients have this variant." (EX1246, 283:13-289:22.) A full-length EGFR antibody like BA03 avoids these problems because EGFR overexpression is an early, widespread feature of most tumor cells. (EX1200, ¶69.)

D. Leanna, Liu, and Wei Render the Claims Obvious

Leanna, Liu, and Wei together disclose every element of the claimed invention. (EX1002, ¶¶275-283.) Leanna and Wei show that anti-EGFR ADCs with cleavable vc linkers and MMAE payloads are effective against EGFR-expressing tumors. (EX1006, 32-34, 48-80; EX1005, ¶¶1116-1127.) Liu teaches BA03 as a superior humanized anti-EGFR antibody with enhanced properties relevant to ADC design. (EX1008, ¶¶0141-0160, Tables 1-4.) A POSA would have been motivated to incorporate BA03 into Leanna's and Wei's ADC platform with a reasonable expectation of anti-tumor activity. (EX1002, ¶¶282-283.)

V. CLAIM 13 IS OBVIOUS

PO separately argues that claim 13, which specifies the vc linker, MMAE payload, and DAR (p) of 1-8, is non-obvious based on the efficacy and safety of MYK-3 (now MRG003). (POR, 66-67; EX2027, ¶¶91-92.) The argument fails because PO conflates non-obviousness with clinical success, and the prior art teaches the vc-MMAE combination and DAR range recited in claim 13.

Wei discloses Y104D-Mc-vcPAB-MMAE ADCs with the same vc linker and MMAE payload recited in claim 13. (EX1005, ¶¶1092-1127, Example 18.) Wei further confirms that the “final conjugated product had a drug:antibody (DAR) ratio of approximately 4 as assessed by hydrophobic interaction chromatography,” within the claimed DAR range. (*Id.*, ¶[1103].) Leanna discloses Antibody 1-vc-MMAE conjugates with an average DAR of 3.85, also within the claimed 1-8 range. (EX1006, 32-51.) Wei and Leanna thus disclose the drug-linker architecture of claim 13, and Liu supplies the BA03 antibody with the CDR sequences completing the claim. (EX1002, ¶¶186-195, 275-283.) Leanna also provides complete, validated protocols for making and purifying anti-EGFR antibody-vcMMAE ADCs with controlled DARs, applicable to any IgG1 antibody with accessible interchain cysteines, including BA03. (EX1200, ¶¶99-100; EX1006, 35, 50-52.)

PO's reliance on the efficacy and safety data for MYK-3 in Examples 3 and 4 of the '370 patent does not establish non-obviousness of claim 13. The data

compared MYK-3 only to BA03 alone and BA03 plus free vcMMAE, with no comparison to any prior-art anti-EGFR ADC, such as Tikhomirov's cetuximab-vc-MMAE ADC (Cetux 2C9-MMAE), Wei's Y104D ADC, or Leanna's Antibody 1-vc-MMAE ADC. (POR, 66-67; EX2027, ¶¶91-92; EX1001, 19.) The reasonable-expectation-of-success standard requires only an expectation of successfully making and using the claimed invention, not a guarantee of clinical performance. (EX1200, ¶97.) The prior art easily clears that bar: vc-MMAE was a validated drug-linker system (EX1021, 1-2; EX1020, 6); anti-EGFR ADCs using that system showed potent anti-tumor activity (EX1005, ¶¶1116-1127); and BA03 had the key properties for a successful ADC antibody (EX1008, ¶¶0141-0160). MRG003's clinical results confirm, rather than negate, the predictability of combining these known elements. A predictable combination performing well in practice is evidence of obviousness, not non-obviousness. *See KSR*, 550 U.S. at 416.

VI. SECONDARY CONSIDERATIONS DO NOT REBUT OBVIOUSNESS

A. PO Fails to Establish Nexus

Secondary considerations are relevant only if PO establishes a nexus between the evidence and the merits of the claimed invention. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). PO's secondary-considerations evidence fails to establish that nexus.

PO points to MRG003's approval in China and FDA designations as evidence of commercial success and industry recognition. (POR, 60; EX2021.) But PO has not shown that MRG003's alleged success is attributable to the specific features claimed in the '370 patent, rather than to other factors such as clinical development expertise, manufacturing capability, regulatory strategy, or the dose and schedule used in trials.

The claims cover a broad genus of ADCs comprising an anti-EGFR antibody linked to any cytotoxic agent via any cleavable linker. (EX1001, Claims 1-23.) Dr. Atanackovic confirmed that the claimed anti-EGFR antibody, while having BA03's CDR sequences, can encompass millions of different antibodies. (EX1246, 142:2-144:18.) PO has not shown that MRG003's alleged success stems from features unique to the claims. Courts have held that when secondary considerations such as commercial success are based on a narrow species within very broad claims, there is insufficient nexus for those factors to rebut the prima facie case of obviousness over the full scope of the claims. *See ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1221-22 (Fed. Cir. 2016) (little weight to evidence of industry praise where claims were considerably broader than the praised features); *Palo Alto Networks, Inc. v. BT Americas Inc.*, IPR2023-00889, Paper 32, at 69–71 (PTAB Nov. 7, 2024) (no nexus

where challenged claims were “materially broader” and “not reasonably commensurate in scope” to commercial embodiment).

B. No Long-Felt Need and Failure of Others

While PO argues that MRG003’s approval addresses a long-felt need and that others failed to develop viable products (POR, 57-66.), the record undermines both arguments.

PO’s evidence of alleged failures by others involves ADCs with different antibodies, linkers, or payloads than those claimed. (EX2029, 1-3; EX2030, 1-2.) All four failed candidates cited by Dr. Atanackovic (ABT-414, ABBV-221, ABBV-321, and HTI-1511) used antibodies designed with tumor-selective or TME-selective properties, consistent with the strategies Dr. Atanackovic advocates, and none used a cetuximab-class antibody targeting wild-type EGFR. (EX1200, ¶72.) ABT-414 was terminated for “lack of survival benefit,” which Dr. Atanackovic confirmed is an efficacy failure, not a toxicity failure. (EX2030, 4; EX1246, 264:15-265:17.) As to the other three, he admitted he does not know the specific reasons for termination and conceded “there could be a number of reasons” beyond safety. (EX1246, 265:19-270:14.) Those failures undermine, rather than support, the position that tumor-selective strategies are superior. (EX1200, ¶72.)

The prior art further shows that anti-EGFR ADCs were actively and successfully pursued in preclinical models. (EX1002, ¶¶32-58.) Wei’s huY104D-vc-

MMAE and Leanna's Antibody 1-vc-MMAE each demonstrated anti-tumor activity. (EX1005, ¶¶1116-1127, Example 20, Tables 42, 44-45; EX1006, 50-60.) Nothing in the record supports the view that a POSA would have regarded anti-EGFR ADCs as a failed or abandoned approach. (EX1002, ¶¶32-58; EX2026, 69:20-71:7.)

C. No Alleged Copying

PO's allegation that Petitioner copied the claimed invention is unsupported. (POR, 62-66.) Petitioner's CPO301 product uses at least a different linker and a different cytotoxic payload (a topoisomerase I inhibitor) than the vc-MMAE system exemplified in the '370 patent specification and recited in claim 13. (EX2008, 000002; EX1100, 1-2; EX1103, 1; EX1001, claim 13.) That fundamental difference in drug-linker architecture defeats any inference of copying, which requires replication of a specific product, not merely use of an overlapping component. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

Finally, PO's allegations of copying are ironic given that all that PO did to "develop" its invention was to take a third-party prior art antibody – BA03, and attach this to a vc-MMAE linker-payload that PO admittedly purchased from a commercial source. *See* EX1001 at 19:26-28 ("To the reduced antibody was added 1.1 times the mole number of free thiol groups of vc-MMAE (purchased from Haoyuan Chemical Technology Co., Ltd., No. HY-15575)").

VII. DR. ATANACKOVIC'S DECLARATION IS UNRELIABLE AND WARRANTS LITTLE WEIGHT

PO relies heavily on Dr. Atanackovic's declaration to support its arguments on pH selectivity, tumor-selective epitopes, and lack of motivation to combine. (POR, 24-66; EX2027, ¶¶51-61, 67-71.) His opinions warrant little weight for at least the following reasons. (EX1200, ¶¶4-11.)

Dr. Atanackovic opines that a POSA would not have substituted BA03 for Wei's huY104D because doing so would sacrifice pH selectivity. (EX2027, ¶¶45-59.) But the claims do not require pH selectivity (EX1001, Claims 1-23), and Dr. Bournazos's unrebutted testimony confirms that Wei's data show no meaningful pH selectivity differences. (EX2026, 77:14-86:8.)

Dr. Atanackovic also opines that a POSA would have expected increased toxicity from a BA03-containing ADC due to BA03's binding to EGFR on normal cells. (EX2027, ¶¶62-65.) That opinion ignores that Wei itself recognized anti-EGFR ADCs would bind EGFR on normal cells (EX1005, ¶¶0009, 0476-0488); that the FDA approved cetuximab despite EGFR expression on normal tissues (EX1014, 1; EX1024, 2-3); and that the field developed strategies for managing on-target, off-tumor toxicity (EX1023, 6-7; EX1002, ¶¶32-58). Dr. Bournazos explains that anti-EGFR toxicities are predictable, well-characterized, and manageable through established monitoring and dose-modification protocols. (EX1200, ¶¶22-27.) The

same Tikhomirov-346 reference Dr. Atanackovic cites concedes that skin reaction risk “is currently considered acceptable when managed properly,” a passage he failed to disclose to the Board. (EX2011, 1:30-32; EX1200, ¶¶23; EX1246, 11:10-14:18.)

Dr. Atanackovic asserts that BA03’s increased EGFR phosphorylation inhibition and ADCC activity would produce “parallel changes” in killing activity against tumor and normal cells, yielding “no change to the ADC’s therapeutic window.” (EX2027, ¶¶63-64.) He cited no data or supporting reference for that assumption. (EX1200, ¶¶85-89.) He retreated at deposition, conceding that “parallel” meant only that the increase “happens in parallel” but “doesn’t mean it’s the same extent”; that measuring the impact “is not realistic”; and ultimately that “it’s possible that it won’t affect, at least not to a positive degree, the therapeutic window.” (EX1246, 293:10-301:6.) That shift from “no change” to “it’s possible” undercuts PO’s therapeutic-window theory. As Dr. Bournazos explains, tumor cells typically overexpress EGFR 10- to 100-fold relative to normal cells, so a stronger antagonist produces disproportionately greater signaling blockade in tumor cells. (EX1200, ¶¶12-21, 85-87.) That is the same differential-expression mechanism that has supported ADC development against HER2, Nectin-4, and TROP-2. (*Id.*)

Dr. Atanackovic’s analysis is further undermined by his failure to address the very factors he identified as relevant to ADC success. He listed five categories of

ADC design factors (EX2027, ¶82) but admitted at deposition that he did not analyze most of them, including antibody stability and payload characteristics, and that every ADC component “can potentially affect” safety. (EX1246, 164:22-165:9, 172:4-7.) Yet he criticized Dr. Bournazos for not discussing “the vast majority of these considerations.” (EX2027, ¶83.) He likewise conceded that he “could have mentioned internalization more often” and that internalization is “one of the factors that’s related to safety as well,” a factor favorable to BA03 that he omitted. (EX1246, 61:17-65:9; EX1200, ¶¶34-38.)

VIII. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that the Board find claims 1-23 of the ’370 patent unpatentable as obvious under 35 U.S.C. § 103.

Dated: May 1, 2026

By: /Joe Chen/
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner’s Reply to Patent Owner’s Response in *Inter Partes* Review of Claims 1–23 of U.S. Patent No. 10,792,370 contains, as measured by the word-processing system used to prepare this paper, 5,568 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting toward the word limit.

Dated: May 1, 2026

By: /Joe Chen/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on July 7, 2025, I caused a true and correct copy of the foregoing Petitioner’s Reply to Patent Owner’s Response in *Inter Partes* Review of Claims 1–23 of U.S. Patent No. 10,792,370 to be served by electronic mail, as authorized by Patent Owner, at the following email addresses:

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