

IN THE 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.

Case No. IPR2025-00685

U.S. Patent No. 10,792,370

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER’S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	International Nonproprietary Names for Pharmaceutical Substances, WHO Drug Information, Vol. 38, No. 2, 2024
2002	Fei Han et al., Becotatug vedotin vs. chemotherapy in pre-heavily treated advanced nasopharyngeal carcinoma: A randomized, controlled, multicenter, open-label study
2003	Lepu Biopharma Co., Ltd., Voluntary Announcement, Breakthrough Therapy Designation Granted by the FDA to MRG003 for the Treatment of R/M NPC
2004	U.S. Food & Drug Administration, Fast Track
2005	U.S. Food & Drug Administration, Breakthrough Therapy
2006	EGFR expression in normal human tissues (HPA RNA-seq normal tissues) - https://www.ncbi.nlm.nih.gov/gene/1956
2007	CD30 expression in normal human tissues (HPA RNA-seq normal tissues) - https://www.ncbi.nlm.nih.gov/gene/943
2008	European Patent Application No. EP4434549A1
2009	CSPC Pharmaceutical Group Limited Voluntary Announcement, May 19, 2025
2010	Lu S. et al., “Abstract CT008: First-in-human study of SYS6010, a novel EGFR targeting antibody drug conjugate (ADC) for patients with advanced solid tumors,” <i>Cancer Res</i> (2025) 85 (8_Supplement_2): CT008
2011	International Publication No. WO2012/100346A1
2012	Huang L. et al., “Abstract 1217: Preclinical evaluation of a next-generation, EGFR targeting ADC that promotes regression in KRAS or BRAF mutant tumors,” <i>Cancer Res.</i> (2016) 76 (14_Supplement): 1217

2013	Phillips AC et al., “Characterization of ABBV-221, a Tumor-Selective EGFR-Targeting Antibody Drug Conjugate,” <i>Mol Cancer Ther</i> ; 17(4) April 2018 795-805
2014	Carneiro B. et al., “Phase I study of anti-epidermal growth factor receptor antibody-drug conjugate serclutamab talirine: Safety, pharmacokinetics, and antitumor activity in advanced glioblastoma,” <i>Neuro-Oncology Advances</i> 5(1), 1–12, 2022
2015	U.S. Patent Application Publication No. 2011/0076232 (“Old-232”)
2016	AbbVie, A Study Evaluating Safety and Pharmacokinetics of ABB-221 in Subjects With Advanced Solid Tumor Types Likely to Exhibit Elevated Levels of Epidermal Growth Factor Receptor. ClinicalTrials.gov Identifier NCT02365662 (March 30, 2018)
2017	Lepu Biopharma Co. Ltd. 2024 Annual Report
2018	Written Opinion of the International Searching Authority for WO2023/088382

I. Introduction

The '370 patent claims an ADC (antibody-drug conjugate) or a salt thereof that comprises an anti-EGFR (epidermal growth factor receptor) antibody linked to a cytotoxic agent via a cleavable linker. The antibody is defined with CDR sequences of antibody BA03, which is a humanized version of a human-murine chimeric antibody cetuximab (Erbix[®]). The Petition argues that the claims are obvious over Wei in view of Liu (Ground 1) and over Leanna in view of Liu and Wei (Ground 2).

The Petition should be denied institution for at least two reasons. First, the Petition does not articulate an adequate motivation to combine the prior art references in the proposed manner. Grounds 1 and 2 each proposes to modify the ADC of the primary reference (Wei/Leanna) by replacing its antibody with Liu's BA03 antibody. Wei and Leanna teach using antibodies designed with tumor-specific properties, which provide improvements over antibodies without such properties by mitigating the toxicity of anti-EGFR ADCs. Wei, Leanna, and Tikhomirov suggest that replacing Wei's/Leanna's antibodies with an antibody like BA03 would have reversed the toxicity improvements and strongly discourage a POSA from making the modification that the Petition proposes. Not only did Petitioner not address the teach-away, Petitioner also fails to provide any affirmative reason to make the proposed modifications. The Petition argues a

POSA would have been motivated to replace Wei's/Leanna's antibodies with Liu's antibody because a humanized antibody has benefits over its chimeric counterpart. However, this rationale is not logical because Liu's antibody is not the humanized version of Wei's/Leanna's antibodies, which have different properties and are already humanized.

Second, the Petition fails to address strong evidence of secondary considerations of non-obviousness despite Petitioner being aware of that evidence. First, Petitioner chose to copy the claimed ADC after evaluating alternatives. Second, despite relying on FDA's approval results for unrelated ADCs to support its argument, Petitioner fails to inform the Board that earlier attempts to conduct clinical trials of anti-EGFR ADCs failed. Finally, Petitioner fails to address the fact that Patent Owner's and Petitioner's ADC candidates that embody the claimed invention both have received FDA's Fast Track designations, demonstrating that the invention of the '370 patent addresses long-standing unmet needs in cancer treatment. By ignoring known secondary considerations evidence, Petitioner fails to meet its burden and cannot show a reasonable likelihood that the challenged claims are unpatentable.

II. Background

A. Antibody-Drug Conjugates

An antibody-drug conjugate (“ADC”) typically includes three main components: an antibody, a cytotoxic payload, and a linker connecting the payload to the antibody. The antibody, by virtue of its binding specificity to its antigen, targets the ADC to a cell that expresses the antigen. Upon internalization by the cell expressing the antigen, the cytotoxic payload exerts its cell-killing activity against the cell.

Antibodies obtained from animals can be subjected to humanization and affinity maturation. Humanization replaces non-critical amino acids with human counterparts in order to reduce immunogenicity. Affinity maturation identifies mutations that increase or decrease the binding affinity of the antibody to the antigen.

Cytotoxic payloads are typically anticancer agents on their own, albeit that they can afford to be more cytotoxic than conventional anticancer agents given their targeted delivery to tumor cells. Like anticancer agents, cytotoxic agents in ADCs are normally anti-proliferative agents that preferentially kill rapidly proliferating cells, a significant characteristic of tumor cells. Besides tumor cells,

normal skin cells also proliferate rapidly. *See, e.g., Ex-1009, 2.*¹ Accordingly, cytotoxic payloads can be associated with skin toxicities.

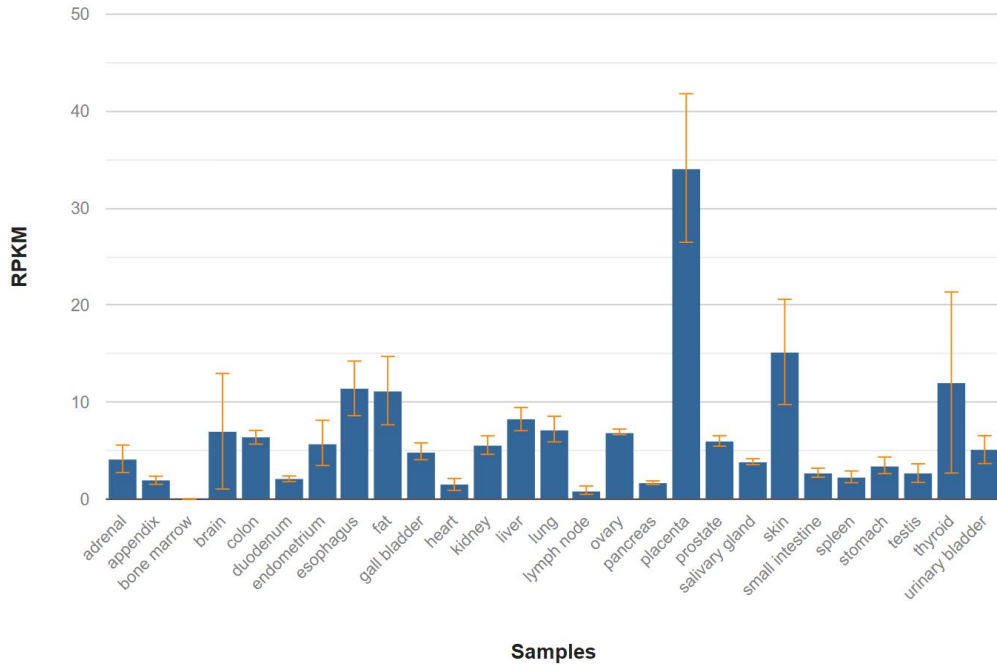
The linker that connects the payload to the antibody may be cleavable or non-cleavable. Cleavable linkers can be cleaved by a physiological stimulus, such as acidic pH, or an enzyme. Upon cleavage, whether inside or outside a cell, the free payload exerts its cytotoxicity against the cell. By contrast, a payload connected by a non-cleavable linker only becomes active when the antibody is degraded in the lysosome of the cell upon cellular internalization. ADCs with non-cleavable linkers generally have decreased cytotoxicity as compared to those with cleavable linkers.

B. EGFR and Anti-EGFR Antibodies

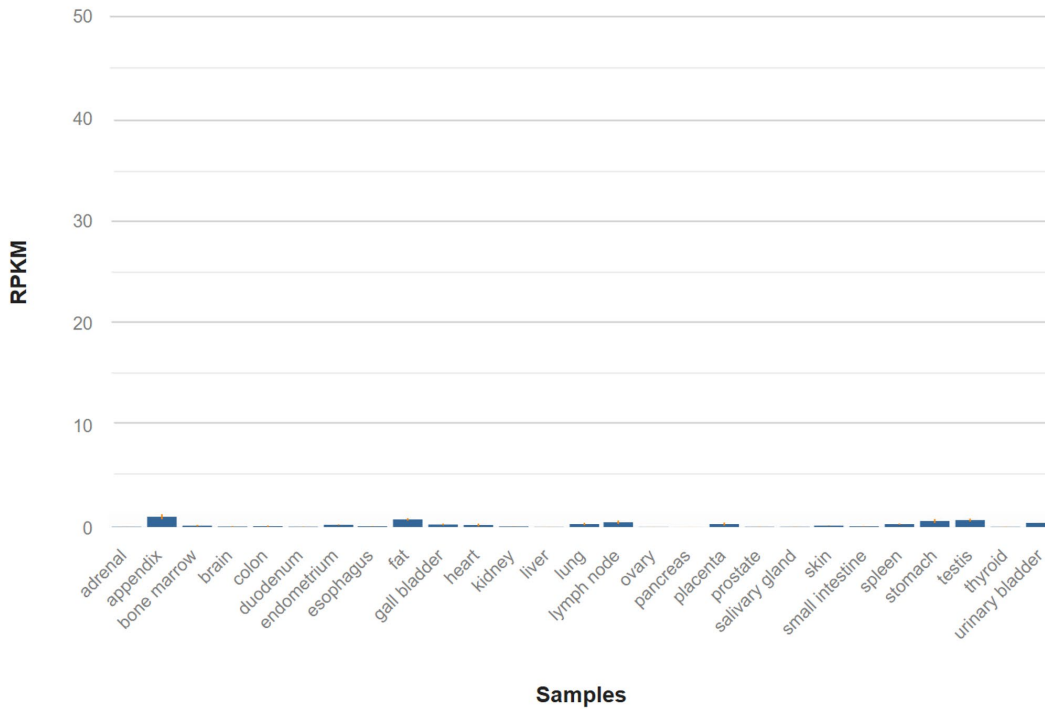
The epidermal growth factor receptor (EGFR) “is an attractive target” for anti-cancer therapies “because of the antigen’s expression by many tumors and its rapid internalization.” *Ex-1009, 2.* Unlike many other tumor-associated antigens, however, EGFR also has relatively high expression in other tissues such as the skin, and thus EGFR-targeting agents are associated with “skin toxicities that either demand dose reduction or in some cases are so severe as to warrant discontinuation of treatment.” *Id.*

¹ The citations to Exhibit 1009 use stamped page numbers.

EGFR's relatively high expression in normal tissues differentiates it from other antigens, including those that have been successfully targeted by ADCs. One of such other antigens is CD30, which Petitioner mentions to be targeted by Brentuximab vedotin (Adcetris[®]), one of the first approved ADCs that included a cleavable linker. Pet., 50. While both EGFR and CD30 are highly expressed in tumor cells, CD30's expression levels in normal tissues are minimal and considerably lower than that of EGFR. EGFR's and CD30's expression levels among 27 normal tissues, measured as RPKM (Reads Per Kilobase per Million reads) with RNA sequencing technology, are available from the NCBI (National Center for Biotechnology Information) database. As shown in the first (Ex-2006, 000002) and second (Ex-2007, 000002) figures below, the median expression levels of EGFR and CD30 among these tissues are about 5.1 RPKM and 0.17 RPKM, respectively, a 30-fold difference.



EGFR expression levels in 27 normal tissues. Ex-2006, 000002.



CD30 expression levels in 27 normal tissues. Ex-2007, 000002 (modified to the same y-axis scale as the figure above).

In addition to the overall higher expression among normal cells, EGFR is known to be expressed on skin cells. Ex-1009, 2. Given that skin cells tend to proliferate rapidly, they are susceptible to toxicity of a cytotoxic payload. An ADC that includes an anti-EGFR antibody, therefore, is significantly more likely cause skin toxicities than an ADC that targets a different antigen, such as CD30.

C. Prior Art Use of Anti-EGFR Antibodies in ADCs

EGFR's relatively high expression in normal tissues creates unique challenges faced by therapies targeting EGFR with respect to toxicity. Such challenges are emphatically acknowledged in Wei.

For example, anti-EGFR antibodies are associated with significant and characteristic adverse events including skin toxicities and digestive disturbances ..., that often lead to interruption of dosing and discontinuation of treatment. For example, EGFR, is highly expressed in pre-keratinocytes and basal cells of the skin. Blockade of EGFR signaling in the skin precursors by anti-EGFR antibodies leads to skin precursor growth inhibition, apoptosis and inflammation. This can result in skin toxicity, such as a rash and other skin lesions. In particular, existing anti-EGFR antibodies (e.g., cetuximab, panitumumab) exhibit high toxicity with up to 80% attributed to skin-related toxicity, including 25% that is Grade 3-4 (Cunningham et al. (2004) *NEJM*, 351:337). In particular, skin lesions can include rash with

itchy erythematous follicular papules that can evolve into pustules.

Ex-1005, ¶0477 (emphasis added).

Approaches have been taken to tackle these challenges, and three examples are discussed below.

1. Approach 1 – pH-sensitive antibodies (e.g., Wei)

The first approach aimed at increasing the tumor-specificity of the antibody activity. The tumor microenvironment is generally more acidic than non-tumor tissues. Therefore, if an antibody's activity depends on an acidic pH, the antibody is more likely inactive/safe in normal tissues (neutral pH) at a dose that is efficacious in tumors.

Wei is directed to such an approach. In the Background section, Wei points to the toxicity concerns associated with existing anti-EGFR antibodies (such as cetuximab) and states that its objective was to identify anti-EGFR antibodies, for use in ADCs, with tumor-specificity. Ex-1005, ¶0009.

Pursuing that objective, Wei found that mutations at Y104 of cetuximab rendered the antibody activity dependent upon pH. These Y104 mutants, Wei describes, “exhibit[ed] greater binding activity under acidic pH conditions and/or elevated lactate levels (e.g., present in a tumor microenvironment) than under neutral pH conditions/normal lactate levels” (Ex-1005, ¶476) and thus are tumor-

specific. Humanized versions of these mutants (Y104D and Y104E) were also prepared and tested, including huY104D and huY104E. Ex-1005, ¶1116.

The Y104D and Y104E mutants of cetuximab disclosed in Wei, as well as their humanized counterparts, “exhibit[ed] greater activity (binding affinity) under conditions of acidic pH, such as is present in a tumor microenvironment, than under conditions of neutral pH, such as exists in non-tumor tissue, such as that which exists in the basal layer of the skin.” Ex-1005, ¶10. With such tumor-specificity, Y104D and Y104E have greatly improved therapeutic index as compared to cetuximab.

2. Approach 2 – tumor epitope-specific antibodies (e.g., Leanna)

The second approach aimed at identifying antibodies that are specific to mutant forms of the antigen that are only present in tumor tissues.

The antibody of Leanna, “Antibody 1,” is such an antibody. Antibody 1 “recognizes de2-7 EGFR and amplified EGFR, but does not recognize normal, wild-type EGFR.” Ex-1006, 24:19-24. Since only “the tumor expresses the truncated version of the EGFR de2-7” (*id.*, 12:25-13:12), Antibody 1 does not bind normal cells, and thus avoids the safety concerns associated with cetuximab.

Notably, Antibody 1 is also a humanized antibody. Leanna states that the sequences of Antibody 1, “are described [in] WO 2011/041319 and US20110076232 (see, e.g., antibody sequence of Figure 55).” Ex-1006, 24:14-17.

U.S. Patent Application Publication No. 2011/0076232 (“Old-232”), which Leanna incorporates by reference, states that the antibody in FIG. 55 is hu806. Ex-2015, ¶ 177. hu806 is a humanized version of mouse antibody mAb806 (Ex-2015, ¶¶244-245), which was discussed in U.S. Patent No. 7,589,180 (“Old-180”) (Ex-2015, ¶ 935, Table 14, n.2-3).

3. Approach 3 – antibodies with reduced binding affinity (e.g., Tikhomirov-346)

The third approach aimed at reducing the general binding affinity of antibodies to the antigen.

The rationale of this approach and examples of such antibodies are provided in, for example, International Publication No. WO2012/100346A1 (“Tikhomirov-346,” Ex-2011). The example antibodies in Tikhomirov-346 had “a binding affinity for EGFR that is about 10 fold or more weaker than the EGFR binding affinity of cetuximab.” Ex-2011, 5:22-30. Such reduction of the affinity “substantially eliminates binding to [normal] cells presenting EGFR at a normal EGFR density, and retains effective binding at targeted disease cells that present EGFR at a greater density relative to normal cell EGFR density.” *Id.*, 3:12-16.

D. The ’370 Patent

The ’370 patent has a single independent claim:

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.

The anti-EGFR antibody of claim 1 is specifically defined with the six CDR sequences of antibody BA03, which is covalently linked to the cytotoxic agent via a cleavable linker. As noted in the application, BA03 was previously described in Liu, as a humanized version of cetuximab having increased EGFR-binding and inhibitory activity (Ex-1008, ¶140) and reduced immunogenicity (*id.*, ¶152).

Also, as compared to cetuximab, BA03 had “stronger activity in blocking the ligand from binding to the epidermal growth factor receptor on the cell surface” (Ex-1008, ¶144), and “stronger activity in inhibiting the phosphorylation of the epidermal growth factor receptor on the surface of A431 cells” (*id.*, ¶148). As noted in Tikhomirov, cetuximab is a “full antagonist” (Ex-1009, 11-12). Likewise, Liu has demonstrated that BA03 is a full antagonist as well, with strong activities in blocking ligand binding and inhibiting EGFR phosphorylation. Ex-1008, ¶144, ¶148.

BA03 and BA03-containing ADCs were also tested in an international patent application filed by Petitioner, WO2023/088382 (“the ’382 application,” filed on November 17, 2022), whose counterpart Europe Application No. EP4434549A1 (Ex-2008) is in English. The ’382 application describes four anti-EGFR ADC molecules. Three of them included pH-dependent antibodies, SWY2111, SWY2112 and SWY2113, and one of them used BA03 (SWY2110). See Ex-2008, ¶¶80-81 (showing sequences). As shown in Table 1, BA03’s binding to EGFR is not pH-dependent. *Id.*, 000035.

Moreover, as BA03 is a humanized version of cetuximab, it recognizes the normal EGFR molecule that is present in both tumor and normal cells. Accordingly, the ’370 patent does not use any of the three aforementioned approaches of using anti-EGFR antibodies in ADCs, as exemplified by Wei, Leanna, and Tikhomirov-346.

The prior art casted doubt on the viability of the ’370 patent’s approach. For example, Tikhomirov suggests that using a cleavable linker with cetuximab would increase toxicity against normal cells. Ex-1009, 30 (“[C]onjugation of cetuximab to MMAE by a cleavable linker (valine-citrulline) potentiates its toxicity against normal cells and MDA-MB-468 cancer cells.”) (emphasis added). Accordingly, Tikhomirov teaches that cleavable linkers should not be used with a full antagonist like BA03 in an ADC. Ex-1009, 31 (“[A] safe anti-EGFR ADC should incorporate

a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker.") (emphasis added).

1. The '370 patent issued over a combination of Tikhormirov and Liu

The '370 patent was issued from U.S. Patent Application No. 15/550,995, which was filed August 14, 2017 as a U.S. national phase application of International Patent Application No. PCT/CN2016/073844 (filed February 16, 2016) and claims priority to Chinese Patent Application No. 201510085038.8 (filed February 17, 2015.).

The '370 patent was allowed after three Office Actions. Each Office Action included a §103 rejection based on the combination of Tikhomirov, Liu, and other references. The Examiner cited Tikhomirov's teachings of an "EGFR antibody in a form conjugated with an anti-microtubule toxin," including an embodiment with "conjugation of cetuximab to MMAE anti-microtubule payload by a cleavable linker." Ex-1004, 153-54, 244. The Examiner cited Liu for its teaching of the BA03 antibody and argued that "[i]t would have been prima facie obvious as of the effective filing date to use the BA03 antibody in place of cetuximab in the conjugates and methods of using the conjugates of Tikhomirov." Ex-1004, 156, 247.

To overcome the Examiner's §103 rejections, the Applicant explained that a POSA would not have been motivated to use Liu's BA03 antibody as part of

Tikhomirov's ADC that has a cleavable linker, especially given that Tikhomirov teaches away from such a modification. For example, in the response to Office Action dated March 26, 2020, the Applicant explained that "one skilled in the art would not have been motivated ... to use a cleavable linker to arrive at the ADC ... as claimed." Ex-1004, 299. The Applicant pointed out that "Figure 13 [of Tikhomirov] shows that conjugation of cetuximab to MMAE by a cleavable linker (valine-citrulline) potentiates its toxicity against normal cells and MDA-MB-468 cancer cells, whereas conjugation via non-cleavable linker (SMCC) potentiates anti-cancer activity." *Id.* The Applicant noted that Tikhomirov teaches away from the Examiner's combination by stating "a safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker." Ex-1004, 299-300. Based on Tikhomirov's discussion of its Figure 13, the Applicant explained that "one of ordinary skill in the art would be discouraged from using a cleavable linker in incorporating a strongly antagonistic anti-EGFR antibody into an ADC due to potentiated toxicity against normal cells of such ADCs." Ex-1004, 299-300. The Examiner issued a Notice of Allowance thereafter. Ex-1004, 306-313.

E. The Parties' Relevant ADC Candidates

1. Clinical Development of MRG003

In 2020, Patent Owner started clinical testing for an ADC molecule, MRG003, which embodies claims of the '370 patent by using the BA03 antibody linked to a cytotoxic payload with a cleavable linker.

MRG003 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"). Ex-2003, 000001. Currently, 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. Ex-2017, 000005. If approved, to the best of Patent Owner's knowledge, MRG003 will likely be the first approved anti-EGFR ADC with a cytotoxic payload worldwide.

2. Petitioner's ADC Candidate CPO301

Petitioner's '382 application describes four anti-EGFR ADC molecules. Three of them included pH-dependent antibodies, SWY2111, SWY2112 and SWY2113, and one of them used BA03 (SWY2110). *See* Ex-2008, ¶¶80-87 (showing sequences).

Petitioner is conducting clinical trials for its anti-EGFR ADC drug candidate, CPO301 (or SYS6010). Petitioner stated in a voluntary announcement that "CPO301 is a humanized monoclonal antibody, optimized from cetuximab,

and conjugated with a topoisomerase I inhibitor.” Ex-2009, 000001-2. Further, the topoisomerase I inhibitor is connected to the antibody “via a cleavable glycine-glycine-phenylalanine-glycine tetrapeptide linker.” Ex-2010, 000001. Such description of CPO301 matches that of the SWY2110-ADC described in Petitioner’s patent application. Moreover, in Petitioners’ Response to Patent Owner’s Request For Discretionary Denial of Institution filed July 7, Petitioner acknowledges that the instant claims would “block Petitioner’s cancer treatments from the market.” Resp. to Discretionary Denial Request, 47. Accordingly, Patent Owner believes that CPO301, which includes the non-tumor specific antibody of the ’382 application, also embodies claim 1 of the ’370 patent. Like MRG003, CPO301 has also been granted Fast Track designations by the FDA. Ex-2009, 000001.

III. Petitioner fails to establish an adequate motivation to combine the prior art references.

As the Supreme Court recognized in *KSR*, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art” and “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The Petition fails to meet this requirement

of *KSR* because its articulation of the motivation to combine prior art references has at least two fatal flaws.

The Petition includes two obviousness grounds, respectively based on the combination of Wei and Liu (Ground 1) and the combination of Leanna, Liu, and Wei (Ground 2). Here, Liu is the same reference that the Examiner combined with Tikhomirov during prosecution. The Petition relies on Wei/Leanna for substantially the same teachings and recycles the Examiner's rationale in combining prior art references. *Supra* §II.D.1. Similar to the Examiner's use of Tikhomirov, Petitioner relies on Wei/Leanna for teaching an anti-EGFR antibody conjugated with the cytotoxic agent MMAE by a cleavable linker. Pet. 38, 65-66. And just like the Examiner's proposed combination, Petitioner proposes to use Liu's BA03 antibody in place of the antibody in Wei's/Leanna's ADC. Pet. 40-42, 67-69. Petitioner admits that it combines Wei/Leanna with Liu in the same way as the Examiner combined Tikhomirov with Liu. *See* Pet. 42 ("This reasoning—that the POSA would be motivated to replace cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu—was never even challenged, let alone overcome, by the Patent Owner during prosecution."), 69.

Petitioner's rehash of the Examiner's rationale to combine the prior art contains two glaring deficiencies. First, while Petitioner seeks to distinguish Wei and Leanna by arguing that they do not have the same teach-away as Tikhomirov

(Pet. 44-45), Petitioner ignores strong prior art teachings that specifically would have discouraged a POSA from modifying Wei and Leanna based on Liu in the manner Petitioner proposes and fails to explain how such teachings would not have refuted its motivation-to-combine showings. Wei and Leanna teach using antibodies designed with tumor-specific properties, which provide improvements over antibodies without such properties by mitigating the toxicity of anti-EGFR ADCs. Petitioner fails to explain why a POSA would not have been discouraged from replacing Wei/Leanna's antibody with that Liu, which would have reversed the toxicity improvements.

Second, in mechanically rehashing the Examiner's obviousness rationale, Petitioner fails to acknowledge a critical differences between Wei/Leanna and Tikhomirov and therefore fails to show how this rationale is applicable to the current grounds. Petitioner essentially argues that a POSA would have been motivated to replace a chimeric antibody with its humanized counterpart. Even if this rationale might be applicable to replacing Tikhomirov's chimeric antibody cetuximab with Liu's humanized cetuximab BA03 (as the Examiner proposed), it does not apply to making the same modification to Wei/Leanna's ADCs whose antibodies are already humanized and different from cetuximab.

A. Wei, Leanna, and Tikhomirov teach away from the claimed invention.

Petitioner fails to address strong prior art teachings that would have discouraged a POSA from replacing Wei's/Leanna's antibody with Liu's antibody.

1. Ground 1

In its "Background" section, Wei explains a problem with anti-EGFR antibodies such as cetuximab: that they can "bind to EGFR in healthy cells and tissue" and "exhibit limitations when administered to patients." Ex-1005, ¶9. Wei's objective is 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." Ex-1005, ¶9.

Wei's solution is to select antibodies whose pH selectivity make them more active in a tumor microenvironment than in non-tumor environment. 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." Ex-1005, ¶¶1016-17. The library of antibodies were screened for antibody binding results, antibody concentration, and specific activity to determine their pH selectivity. Ex-1005, ¶¶1018-26. Based on the screening, "[t]he variant anti-EGFR antibodies with an NSA>0.4 at pH 6.0 and an NSA<0.4 at pH 7.4 were identified and selected for further analysis." Ex-1005, ¶1026. Y104D is among the selected antibodies. *Id.*

Wei compared the pH-dependent effect of cetuximab-MMAE and that of Y104D-MMAE ADCs. Ex-1005, ¶¶1128-29. “The results showed that Cetuximab-MMAE and Y104D-MMAE exhibited inhibition of cell growth of A431 [tumor] cells, which was virtually identical between the tested agents.” Ex-1005, ¶1130. However, “Y104D-MMAE exhibited less keratinocyte growth inhibition compared to Cetuximab-MMAE.” Ex-1005, ¶1131. According to Wei, “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.” Ex-1005, ¶1132.

Wei further assessed the huY104D-MMAE ADC with the humanized huY104D antibody and confirmed that it is even better than the Y104D-MMAE ADC. Ex-1005, ¶¶1133-38. According to Wei, the assessment results “show that ADC conjugates of the humanized forms of the Y104D- and Y104E-anti-EGFR variants exhibit greater pH-dependent activity than the chimeric Y104D-MMAE conjugate.” Ex-1005, ¶1139. “[W]hile each [ADC with humanized antibody] are as effective as the chimeric Y104D-MMAE for inhibiting tumor cell growth at pH 6.8, each exhibit reduced growth inhibition of non-tumor keratinocytes at pH 7.4 compared to the chimeric Y104D-MMAE.” *Id.*

Therefore, Wei explicitly teaches that the Y104D-MMAE and huY104D-MMAE ADCs are as effective as the cetuximab-MMAE ADC in inhibiting tumor cells, but the Y104D-MMAE and huY104D-MMAE ADCs have less toxicity as they exhibit reduced growth inhibition of normal cells (*e.g.*, keratinocytes). In other words, Wei solves the problem that the cetuximab-MMAE ADC inhibits both tumor cells and normal cells by replacing cetuximab with the superior Y104D or huY104D antibody that selectively targets tumor cells more than normal cells.

Now, Petitioner proposes to 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).² According to Wei, this would remove the pH-selectivity of the

² Petitioner generalizes Wei's teaching that huY104D has better pH selectivity than Y104D to the case of cetuximab, arguing that "humanized cetuximab variant ADCs were more selective in targeting tumor cells than chimeric ADCs." Pet. 41. There is no support for this generalization, even from Petitioner's expert, who notes Wei's teaching but does not echo Petitioner's assertion about selectivity of humanized cetuximab. Ex-1002, ¶188. Petitioner's generalization is also refuted by Wei. Wei teaches using "a humanized variant of cetuximab" as "the unmodified anti-EGFR antibody," which confirms that humanized cetuximab similarly exhibits

Y104D-MMAE/huY104D-MMAE ADCs and increase their growth inhibition on normal cells, thereby making the ADC more toxic and reinstating the problem that Wei was set out to solve. This is a textbook example of teach-away, in which the prior art expressly explains the problem with and discourages a POSA from pursuing the proposed combination. *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) (“A reference teaches away 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 in the claim.”) (citation modified); *see Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (upholding the district court’s finding that the prior art teaches away from using 200 ppm benzalkonium chloride (“BAK”), even when 200 ppm falls within ranges disclosed by the prior art, because “the prior art

the problem of targeting health cells that is solved by using modified antibodies (e.g., Y104D, huY104D). *See, e.g.*, Ex-1005, ¶15. Nowhere does Wei indicate that its problem can simply be solved by humanizing cetuximab. Ultimately, as explained below, whether humanized cetuximab has better selectivity than chimeric cetuximab is irrelevant to the motivation to combine because neither grounds involves replacing chimeric cetuximab with humanized cetuximab. *Infra* §III.B.

taught that BAK should be minimized in ophthalmic formulations to avoid safety problems”); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355 (Fed. Cir. 2012) (holding that, when prior art teaches four medicine dosage options and “ruled out” the dosage forms according to one of the options, the prior art “teaches away from such formulations” and the district court erred by finding the dosage forms obvious); *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1372 (Fed. Cir. 2013), vacated on other grounds, 574 U.S. 318 (2015) (upholding the district court finding that the prior art teaches away from using lower molecular weight copolymer-1 when it “stated that copolymer-1 with a molecular weight lower than 17 kDa was ineffective for treating multiple sclerosis”).

2. Ground 2

The same teach-away applies to the combination of Leanna, Liu, and Wei.

Leanna indicates that the sequences of its Antibody 1, which the Petition relies on, “are described [in] WO 2011/041319 and US20110076232 (see, e.g., antibody sequence of Figure 55).” Ex-1006, 24:15-16. U.S. Patent Application Publication No. 2011/0076232 (“Old-232”, Ex-2015), which Leanna incorporates by reference, indicates that the antibody in FIG. 55 is hu806. Ex-2015, ¶177. hu806 is a humanized version of the mouse antibody mAb806 (Ex-2015, ¶¶244-245), which was discussed in U.S. Patent No. 7,589,180 (“Old-180”) (Ex-2015, ¶935, Table 14, n.2-3). Old-232 addresses a similar problem to that solved by

Wei—that the use of anti-EGFR antibodies is limited because EGFR is present in normal cells. *See* Ex-2015, ¶5 (“The use of [anti-EGFR] antibodies, however, may be limited by uptake in organs that have high endogenous levels of EGFR such as the liver and skin”). As a solution to this problem, Old-232 explains that hu806 (i.e., Leanna’s Antibody 1), and its mouse counterpart mAb806, were developed as antibodies that specifically target an EGFR epitope that is expressed only on tumor cells and not on normal cells:

The present inventors have discovered novel monoclonal antibodies, exemplified herein by the antibodies designated mAb806, ch806, hu806, mAb175, mAb124, and mAb1133, which specifically recognize aberrantly expressed EGFR. In particular, the antibodies of the present invention recognize an EGFR epitope which is found in tumorigenic, hyperproliferative or abnormal cells and is not generally detectable in normal or wild type cells, wherein the epitope is enhanced or evident upon aberrant post-translational modification. ... Importantly, these antibodies did not bind significantly to normal tissues such as liver and skin, which express levels of endogenous, wild type (wt) EGFR that are higher than in most other normal tissues, but wherein EGFR is not aberrantly expressed or amplified.

Ex-2015, ¶15.

Tikhomirov also discusses mAb806, the mouse version of Leanna's Antibody 1 (i.e., hu806), and explains its advantages over cetuximab. In its "Background" section, Tikhomirov identifies the same problem described by Wei and Old-232—that "current EGFR antibodies" "all display significant binding to normal organs such as skin in humans." Ex-1009, 3. Consistent with Old-232 (and Leanna, which incorporates Old-232 by reference), Tikhomirov explains that mAb806 provides a solution to this problem because it can selectively target cancer cells. In particular, mAb806 is special because it "targets an EGFR epitope found only on cancer cells" and not on normal cells. Ex-1009, 3. Tikhomirov explains that mAb806's selective binding with cancer cells makes it feasible to directly conjugate mAb806 with cytotoxic agents, while it is not feasible to do the same with anti-EGFR antibodies that bind with both cancer and normal cells because doing so would induce severe toxicity:

[I]t is recognized that "the most important advantage of MAb 806 compared to current EGFR antibodies, is that MAb 806 can be directly conjugated to cytotoxic agents", an approach not feasible with other EGFR antibodies since the "cytotoxic conjugation would almost certainly induce severe toxicity" (US 7589180).

Ex-1009, 3 (emphasis added). Tikhomirov explains that cetuximab, including humanized cetuximab, binds with both cancer and normal cells, which "show levels of skin toxicities that either demand dose reduction or in some cases are so

severe as to warrant discontinuation of treatment.” Ex-1009, 2, 6 (confirming that “standard methods” existed to humanize cetuximab).

Therefore, Leanna and Tikhomirov both would have discouraged a POSA from replacing Leanna’s Antibody 1 with an anti-EGFR antibody that binds with both cancer and tumor cells. Leanna teaches that its Antibody 1 is uniquely positioned to be used because it selectively targets tumor cells. Ex-2015, ¶15. Tikhomirov teaches that it is infeasible to replace Leanna’s Antibody 1 with humanized cetuximab, as doing so would “induce severe toxicity.” Ex-1009, 3. Leanna’s and Tikhomirov’s teachings reinforce Wei’s advice against replacing an antibody that selectively targets tumor cells with one that targets both tumor and normal cells.

Again, Petitioner’s proposal to replace Leanna’s Antibody 1 with Liu’s humanized cetuximab directly contradicts the teachings of Leanna and Tikhomirov. The modification proposed by Petition would have created the problem of severe toxicity and undermine, if not foreclose, the feasibility of the as-modified ADC. Leanna and Tikhomirov thus teach a POSA away from pursuing Petitioner’s proposed modification.

* * *

Petitioner extensively discusses Wei, Leanna, and Tikhomirov, and cannot reasonably argue that it overlooked the explicit teach-aways from these references.

Yet, nowhere does the Petition explain how Wei, Leanna, and Tikhomirov's teachings would not have discouraged a POSA from replacing Wei's/Leanna's antibody that has selective targeting capabilities with Liu's humanized cetuximab that has no selective targeting capabilities.³ Petitioner's failure to address the teach-away issue precludes a finding that a POSA would have found it obvious to modify Wei/Leanna based on Liu's teachings. Therefore, the Petition fails to show there is a reasonable likelihood that any of the challenged claims are unpatentable. *See Mylan Pharms. Inc. v. Novo Nordisk A/S*, IPR2023-00722, Paper 9 at 42-43 (P.T.A.B. October 2, 2023) (denying institution, finding "Petitioner's analysis incomplete for failing to address" prior art reference's teach-away from the proposed combination).

B. The Petition fails to provide any motivation for a POSA to replace the antibody of Wei or Leanna with that of Liu.

On top of its failure to address the teach-way issue, the Petition also fails to affirmatively provide a valid reason that would have motivated a POSA to replace the antibody of Wei or Leanna with that of Liu.

³ While Petitioner addresses the prosecution argument that Tikhomirov would have taught away from using a cleavable linker (Pet., 45-47), this argument is different from how Wei, Leanna, and Tikhomirov teach away from replacing Wei's/Leanna's antibody with that of Liu, leaving the latter undisputed.

The Petition provides four reasons in support of the combination of Wei and Liu:

- First, Liu’s humanized version of cetuximab “has numerous benefits over cetuximab.”
- Second, “both Wei and Liu disclose and characterize humanized anti-EGFR antibodies” that “are substantially identical.”
- Third, Wei’s use of a humanized antibody in ADCs with cleavable linkers would have motivated a POSA to create ADCs using the humanized antibody in Liu.
- Fourth, the “progression of antibody engineering, from murine to chimeric to humanized antibodies” would have motivated a POSA to use Liu’s humanized antibody in place of cetuximab.

Pet., 40-42.

However, the first, third, and fourth reasons are all directed to purported motivation to replace a chimeric antibody with its humanized counterpart. Even if these arguments were accepted, they at most provide a motivation to replace chimeric cetuximab with Liu’s humanized cetuximab. In fact, Petitioner admits that the Petition recycles the obviousness theory directed to replacing Tikhomirov’s chimeric cetuximab with Liu’s humanized cetuximab that the Examiner presented during prosecution. Pet. 42 (“This reasoning—that the POSA

would be motivated to replace cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu—was never even challenged, let alone overcome, by the Patent Owner during prosecution.”). These reasons do not suggest why a POSA would have replaced Wei’s antibody, which is NOT cetuximab, with humanized cetuximab.

Not only are Petitioner’s purported benefits of Liu’s humanized cetuximab over chimeric cetuximab irrelevant to Petitioner’s prior art combinations, they also contradict any motivation to combine. Petitioner alleges that “BA03 has numerous benefits over cetuximab, including higher ADCC activity and significantly lower immunogenicity.” Pet. 67-68. However, as explained above, the major concern in anti-EGFR ADC drug design was severe on-target toxicities against normal cells that express EGFR. *Supra* §II.C. On the issue of toxicity, the alleged higher ADCC (antibody-dependent cellular cytotoxicity) activity of BA03 would have been seen as a significant disadvantage, given that BA03 is not tumor-specific (as demonstrated in Table 1 of Ex-2008 (Petitioner’s patent application) and further explained below). With such higher ADCC activity, an ADC incorporating BA03 would kill EGFR-expressing normal cells more potently, leading to more severe toxicities. By contrast, the antibodies of Wei and Leanna are tumor-specific and would be seen by the POSA as significantly superior to BA03. *Supra* §III.A. Moreover, the purported lower immunogenicity of BA03 is at the best a less-

important advantage over cetuximab, and not an advantage at all over the already humanized antibodies of Wei and Leanna.

Regarding Petitioner's second reason, even if it was true that 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. If anything, 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. *See, e.g., Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (holding that when two references "independently accomplish similar functions" and "independently operates effectively," a POSA "would have no reason to combine the features of both devices into a single device.").

More importantly, Petitioner's premise of similarity between Wei's and Liu's antibodies is belied by Wei's extensive explanation of how its antibody is different from and superior to cetuximab in forming ADCs. *Supra* §III.A. The antibodies are not substantially identical simply because they differ "by only one amino acid." Pet., 40. As explained above, 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. *Supra* §III.A; Ex-1005, ¶¶1016-1026. This difference is material and would have

discouraged a POSA from replacing Wei's antibody with humanized cetuximab.

Supra §III.A.

Regarding Ground 2, the Petition presents reasons for combining Leanna, Liu, and Wei that are substantially similar to those for Ground 1. Pet., 67-69.

These reasons fail for the same reasons as explained above. Seemingly to address the fact that Leanna's antibody is not a modified version of cetuximab and is more different than Wei's antibody from cetuximab, Petitioner additionally alleges that cetuximab was one out of two FDA-approved anti-EGFR antibodies. Pet., 67.

However, this generic allegation does not provide any particular reason why a POSA 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.

As Petitioner provides no meaningful reason to replace Wei's/Leanna's antibody with Liu's antibody, all what is left is hindsight. The use of improper hindsight is evident from the Petition's reference to the '370 patent's claims as a roadmap in explaining a POSA would have been motivated to combine Wei and Liu. *See, e.g.*, Pet., 41 ("Wei discloses an ADC containing the cetuximab variant Y104D attached to the MMAE cytotoxic payload with a vc cleavable linker, the same vc-MMAE linker payload disclosed as preferred embodiments in the '370 patent and covered by the Challenged Claims.>"). Because Petitioner's motivation-to-combine theory is based on hindsight alone, it fails to show there is a reasonable

likelihood that any of the challenged claims are unpatentable. *KSR*, 550 U.S.at 421 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.”).

IV. Petitioner fails to address objective evidence of non-obviousness.

Petitioner failed to address various objective evidence of non-obviousness that it was aware of. It is well-established that objective evidence “must be considered in every case where present.” *Apple v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc). “A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors...,” which includes objective evidence. *Id.* Indeed, the Board “has cautioned petitioners ... that known evidence of secondary considerations should be addressed in the Petition.” *Aardevo North America, LLC v. Agventure B.V.*, IPR2025-00136, Paper 9 at (May 1, 2025) (denying institution based on “Petitioner’s failure to address any objective indicia offered by Patent Owner”).

Here, Petitioner failed to address evidence of copying, failure by others, and long-felt and unresolved need. Petitioner knew, or reasonably should have known, of secondary consideration evidence for non-obviousness including the development and clinical testing of its SYS6010 ADC cancer therapy that copies the claimed invention of the ’370 patent and termination of previous clinical trials for ADCs using other anti-EGFR antibodies. Petitioner’s failure to address any of

this evidence precludes a finding that there is a reasonable likelihood that any of the claims are unpatentable.

A. Petitioner considered different approaches in creating an anti-EGFR ADC and chose to copy the specific antibody claimed by the '370 patent.

As explained above, Petitioner filed a patent application, WO2023/088382 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 was granted (on October 6, 2020). 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. Ex-2018, 000002. Petitioner's patent application demonstrates that Petitioner prepared and tested four anti-EGFR ADC molecules with cleavable linkers. One of the four ADC molecules uses BA03 (referred to as SWY2110) as the antibody, the commercial exploitation of which would infringe the challenged claims. *See* Ex-2008, ¶¶80-81 (showing sequences of BA03). The other three ADC molecules use pH-dependent antibodies (SWY2111, SWY2112 and SWY2113) that have different CDRs from the challenged claims. Petitioner's patent application compared the efficacy and safety of the four ADC molecules. *See, e.g.*, Ex-2008, 57 (Tables 17, 18), 58 (Table 19) (showing efficacy comparison), 65 (Table 31) (showing safety comparison).

Despite its consideration of alternatives, Petitioner chose to copy Patent Owner's invention and initiate clinical trials for the cancer therapy candidate SYS6010 (CPO301). 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. Resp. to Discretionary Denial Request, 47. 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.

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. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016) ("The fact that a competitor copied technology suggests it would not have been obvious.") (citing *Windsurfing Int'l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1000 (Fed. Cir. 1986) ("[C]opying the claimed invention, rather than one within the public domain, is indicative of non-obviousness.")).

B. Petitioner fails to inform the Board that earlier clinical trials for ADCs with anti-EGFR antibodies and cleavable linkers have been terminated.

The Petition refers to the FDA approval results to argue that cleavable linkers are not disfavored:

At the filing of the Challenged Claims, there were only two FDA-approved ADCs—Mylotarg® (anti-CD33) and Adcetris® (anti-CD30)—for use in cancer treatments, yet both used cleavable linkers. . . . Currently, there are fourteen FDA-approved ADCs available, twelve of which use cleavable linkers.

Pet., 50. However, none of these ADCs include an anti-EGFR antibody, which, as explained above, creates unique challenges with respect to toxicity as compared with other antibodies. *Supra* §II.B-C.

Petitioner also failed to mention to the Board that several earlier attempts were made to advance anti-EGFR ADC drug candidates but all of these attempts have been terminated. A few examples are provided in the table below:

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)	EGFR _{vIII} -specific	Phase 1 testing reported in 2018; no subsequent report of further advancement
AbbVie	ABBV-321 (serclutamab talirine)	EGFR _{vIII} -specific	Phase I testing reported in 2022; no subsequent report of further advancement

Halozyme reported the preclinical testing of HTI-1511 in 2016. *See* Ex-2012. HTI-1511 is an anti-EGFR ADC that includes an antibody which “was engineered with increased tumor microenvironment (TME) specificity for EGFR” and a “vc-PAB cleavable” linker. Ex-2012, 000001. Since 2016, however, there

has been no report of clinical testing for HTI-1511, suggesting that its development has been terminated.

AbbVie's drug candidate ABBV-221 (losatuxizumab vedotin) is also an anti-EGFR ADC with a cleavable linker. The antibody in ABBV-221, AM1, is "an affinity-matured [anti-EGFR antibody] ABT-806" and binds EGFRvIII and the linker is a cleavable "valine–citrulline linker." Ex-2013, 000004. After the report in Ex-2013 that "ABBV-221 has advanced to a phase I clinical trial" as of 2018 (*id.*, 000001), there has been no report of phase I results or phase 2 or 3 testing. In fact, the Phase I study of ABB-221 has reportedly been terminated. Ex-2016, 000001.

Another ADC drug candidate by AbbVie is ABBV-321 (serclutamab talirine). This ADC includes the same AM-1 antibody as ABBV-221 and a cleavable "maleimidocaproyl-valine-alanine linker." Ex-2014, 000002. AbbVie reported phase 1 results in Ex-2014 in 2022. Nevertheless, no further phase 2 or 3 testing has been reported, suggesting that its development has been terminated.

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. *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) ("[E]vidence of failed attempts by others could be determinative on the issue of obviousness."); *Knoll Pharm. Co. v. Teva Pharms.*

USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004) (holding that “failure of two pharmaceutical companies to obtain FDA approval” constitutes objective indicia of non-obviousness that “must always be considered”).

Petitioner reasonably should have known about the evidence showing failure by others, but does not address such evidence. Petitioner investigated FDA approvals for ADCs unrelated to the claimed invention of the '370 patent to support its arguments in the Petition (Pet., 50), and cannot reasonably argue that its investigation somehow excluded ADC candidates that are much more relevant for this case—those that similarly use anti-EGFR antibodies. Yet, Petitioner withholds information about these anti-EGFR ADC candidates from the Board and does not address that the failure of earlier ADCs with different anti-EGFR antibodies shows that the claimed ADC, with the specific BA03 anti-EGFR antibody, was non-obvious.

C. Petitioner failed to dispute that the claimed invention addresses long-felt and unresolved needs as evidenced by the FDA’s Fast Track and Breakthrough Therapy designations.

EGFR “is an attractive target” for anti-cancer therapies “because of the antigen’s expression by many tumors and its rapid internalization.” Ex-1009, 2. As explained above, various attempts have been made to develop anti-EGFR ADCs for treating cancer but all failed. *Supra* §IV.B. This shows a long-felt and unresolved need to develop ADCs with anti-EGFR antibodies for cancer treatment.

Miracogen's ADC candidate MRG003, which is protected by the '370 patent, has been granted Fast Track designation and Breakthrough Therapy designation by FDA for the treatment of recurrent or metastatic nasopharyngeal cancer ("R/M NPC"). Ex-2003, 000001.

In its Response to Patent Owner's Discretionary Denial Request, Petitioner touts 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)." Resp. to Discretionary Denial Request, 46-47.

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." 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)." Ex-2005, 000001.

Both candidate ADCs that embody the claimed invention—including the specific claimed BA03 antibody connected to a cytotoxic payload using a cleavable linker—have been designated by the FDA as addressing unmet needs in cancer treatment. The use of the BA03 antibody, rather than antibodies according to prior art approaches (*supra* §II.C), caused the candidate ADCs to move much farther in the drug approval process. The evidence that Petitioner again fails to address demonstrate that the claimed invention was non-obvious. *Sun Pharm. Indus., Inc. v. Incyte Corp.*, No. 2019-2011, 2023 WL 5370639, at *6 (Fed. Cir. Aug. 22, 2023) (holding that “FDA’s designation of [drug candidate] for ‘Breakthrough Therapy’ and ‘Fast-Track’ approval are probative of nonobviousness” and “FDA approval is not a prerequisite to showing that a long-felt need has been met”).

V. Conclusion

The Petition has glaring omissions and gaps, including the failure to address strong teach-away from the cited prior art references, not providing any motivation for a POSA to combine prior art teachings in the proposed manner, and the failure to address known secondary consideration evidence of non-obviousness. Given these deficiencies, Patent Owner respectfully requests that the Board deny institution.

Date: July 15, 2025

Respectfully,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Patent Owner's Preliminary Response contains 7,825 words and therefore complies with the 14,000-word type-volume limit. The word count does not include those portions excepted by 37 C.F.R. §42.24(c) and was calculated by Microsoft Word 365.

Date: July 15, 2025

By: / Christopher Ponder /
Christopher Ponder

CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on this date, a complete copy of the foregoing Patent Owner's Preliminary Response was served via email to all parties to this proceeding at the addresses indicated:

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