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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MINH DIEM VU, KLAUS STREIN, EKKEHARD MOESSNER, RALF HOSSE, OLIVER AST, ANNE FREIMOSER-GRUNDSCHOBER, TANJA FAUTI, RAMONA MURR, CHRISTIAN KLEIN, PABLO UMANA, and SAMUEL MOSER

Appeal 2018-008737
Application 14/783,775
Technology Center 1600

Before JOHN G. NEW, RYAN H. FLAX, and JAMIE T. WISZ, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims to a method of treating an ROR1-positive hematological malignancy or a plasma cell disorder. Appellant appeals the Examiner's rejection of claims 18–21 under 35 U.S.C. § 103.[1,2,3] We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] "Appellant" herein refers to the "applicant" as defined by 37 C.F.R. § 1.42. Appellant identifies itself, "ENGMAB SÀRL," as the real party-in-interest. Appeal Br. 1.

[2] Oral argument was heard on November 1, 2019; a transcript of the hearing will be made a part of the record in due course.

[3] The Final Action also includes two maintained obviousness-type double patenting rejections of claim s 18–22; however, Appellant has not appealed these rejections. Final Action 11–12; Appeal Br. 5; Answer 10–12.

STATEMENT OF THE CASE

Independent claim 18, reproduced below, is representative of the claims on appeal:

> 18. A method of treating an ROR1-positive hematological malignancy comprising[:]
>
> administering a trivalent bispecific antibody which specifically binds human CD3ε (CD3) and the extracellular domain of human ROR1 (ROR1), wherein the antibody comprises ROR1 Fab-Fc-CD3 Fab-ROR1 Fab (FIG.1(1)), to a subject in need thereof,
>
> wherein the ROR1-positive hematological malignancy is selected from the group consisting of: chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), diffuse large B cell lymphoma (DLBCL), multiple myeloma (MM), and follicular lymphoma (FL).

Appeal Br. 22 (Claims Appendix) (formatting added for readability). Claim 18, and also independent claim 20, recite the antibody structure illustrated in the Specification at Figure 1.1, which is reproduced below:

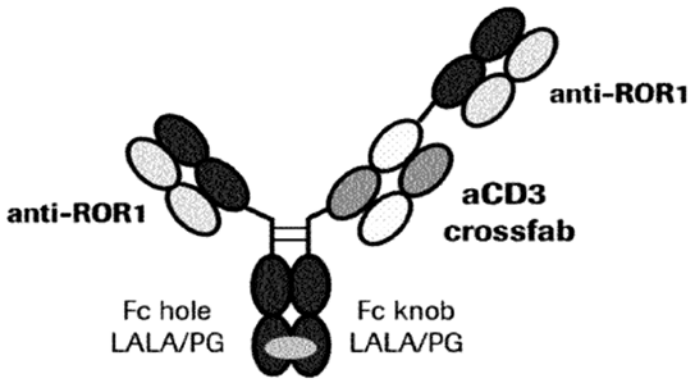


Figure 1(1), above, shows a trivalent, bispecific antibody structure having the following components or fragments: Fab ROR1-Fc-Fab CD3-Fab ROR1. *See* Spec. 12:31–32; Fig. 1.1.

The Specification defines "ROR1" as "humanROR1 (synonyms: tyrosine-protein kinase transmembrane receptor ROR1, EC=2.7.10.1, neurotrophic tyrosine kinase, receptor-related 1, UniPrtKB Q01973) which is a tyrosine-protein kinase receptor" and "CD3" as "human CD3ε described under UniProt P07766 (CD3E_human." Spec. 15:11–25. The Specification further states, "ROR1 is significantly and uniformly expressed on the cell surface of the[] [claimed] various blood cancers." *Id.* at 11:3–12. The Specification further defines the claim language "'[b]ispecific antibody specifically binding to CD3 and ROR1' . . . [as] refer[ing] to a respective definition for binding to both targets." *Id.* at 16:15–17.

The Specification states that "[t]he present invention relates to novel bispecific antibodies against CD3ε and ROR1." Spec. 1:3–4. The Specification explains, "[p]referably the bispecific antibody according to the invention is characterized in being trivalent and comprising a bivalent anti-ROR1 antibody specifically binding to ROR1, and a monovalent Fab fragment of an antibody specifically binding to CD3," thus, by trivalent, the claims refer to three antigen-binding sites on the antibody molecule: two for ROR1 and one for CD3. *Id.* at 5:10–12.

The antibody structure shown in the Specification's Figure 1.1, above, and claimed, includes a crossfab portion at the CD3 fragment. The Specification explains this means, "in the light chain and heavy chain of the CD3 Fab the variable domains VL and VH or the constant domains CL and

CH1 are replaced by each other (CD3 crossFab)." *Id.* at 5:13–14; *see also id.* at 19:10–20:3 (describing Fab fragments and preferred CD3 Fab crossFab). Figure 1.1, above, illustrates this configuration with white-speckled and gray shading at the CD3 fragment.

The following rejection is on appeal:

Claims 18–21 stand rejected under 35 U.S.C. § 103 over Rader[4] and Ast.[5] Final Action 4–10; Answer 4–9; *see also* Office Action dated Apr. 26, 2017, at 6–9 ("Non-Final Action").

Although, as noted *supra* at n.3, the Examiner's final rejection of the claims included a first provisional obviousness-type double patenting rejection of claims 18–21 over U.S. Patent Application No. 13/590,866 and Rader, and another over U.S. Patent Application No. 15/517,296, Appellant opens its briefing by stating, "[t]he only issue in this appeal is whether claims 18-21 are non-obvious under 35 U.S.C. § 103(a) over WO 2012075158 (Rader) in view of U.S. 2013/0078249 (Ast)," and presents no argument over these double patenting rejections. *See* Final Action 11–12; Appeal Br. 5; *see also* Answer 10–12 (maintaining these two double patenting rejections and withdrawing a third of claim 22). Therefore, we summarily affirm these two maintained double patenting rejections.

FINDINGS OF FACT

We agree with and adopt the Examiner's findings of fact and rationale for obviousness as set forth in the Final Action and Answer, as well as in the

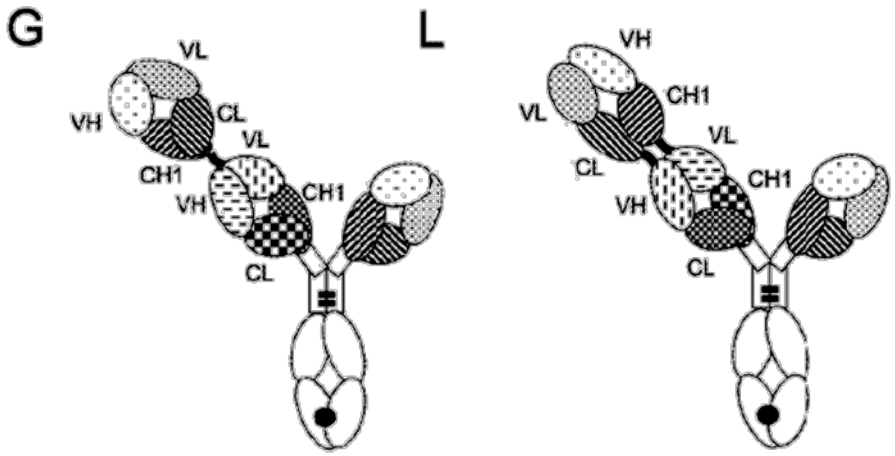
[4] WO 2012/075158 A1 (published June 7, 2012) ("Rader").
[5] US 2013/0078249 Al (published Mar. 28, 2013) ("Ast").

Non-Final Action. *See* Final Action 4–10; Answer 3–9, 12–22; Non-Final Action 6–10. The following findings of fact (FF) highlight certain evidence:

FF1. Ast discloses and "generally relates to novel bispecific antigen binding molecules for T cell activation and re-direction to specific target cells . . . [and] further relates to methods for producing the bispecific antigen binding molecules of the invention, and to methods of using these bispecific antigen binding molecules in the treatment of disease." Ast, Abstract.

FF2. Further to the preceding finding of fact, Ast discloses that such a T cell activating molecule is capable of binding CD3 and tumor cell antigens, and that such molecules can be provided in pharmaceutical compositions for use as a medicament to treat cancer upon administration of a therapeutically effective amount. Ast ¶¶ 21, 25–27.

FF3. Ast discloses 13 "[e]xemplary configurations of the T cell activating bispecific antigen binding molecules of the invention," including the following two antibody molecules:



Ast Figs. 1(G), 1(L). Fig. 1(G), above-left, is an "[i]llustration of the '2+1 IgG Crossfab' molecule with alternative order of Crossfab and Fab components ('inverted')" and Fig. 1(L), above-right, is an "[i]llustration of the '2+1 IgG Crossfab, inverted, linked light chain' molecule." Ast ¶ 28. Each of Figs. 1(G) and 1(L) shows a trivalent, bispecific antibody molecule having a crossfab CD3 fragment fused to other fragments at the Fab region. *Id.* ¶ 149.

FF4. Ast discloses that:

> it will be advantageous to have a T cell activating bispecific antigen binding molecule comprising two or more antigen binding moieties specific for a target cell antigen (see examples in shown in FIG. 1C, 1F, 1G, 1J or 1L), for example to optimize targeting to the target site or to allow crosslinking of target cell antigens.

Ast ¶ 159. And, further, "in certain embodiments, the T cell activating bispecific antigen binding molecule of the invention further comprises a third antigen binding moiety which is a Fab molecule capable of specific binding to a target cell antigen." *Id.* ¶ 160.

FF5. Further to the preceding finding of fact, Ast discloses, "[i]n a particular embodiment according to the invention, the T cell activating bispecific antigen binding molecule is capable of simultaneous binding to a target cell antigen, particularly a tumor cell antigen, and an activating T cell antigen," and "[i]n a particular embodiment the activating T cell antigen is CD3, particularly human CD3," particularly CD3ε. Ast ¶¶ 199, 203, 206.

FF6. Further to the preceding finding of fact, Ast further discloses "[i]n certain embodiments the target cell antigen binding

moiety is directed to an antigen associated with a pathological condition, such as an antigen presented on a tumor cell or on a virus-infected cell. Suitable antigens are cell surface antigens, for example, but not limited to, cell surface receptors." Ast ¶ 207.

FF7. Ast teaches using the above-noted antibody molecules in therapeutically effective amounts to treat a variety of cancers, including, *inter alia*, breast cancer, colorectal cancer, blood cancer, and proliferation disorders of the lymphatic system. Ast ¶¶ 259–265.

FF8. Ast discloses several working examples where a "2+1 IgG Crossfab" antibody molecule construct, like illustrated at Figures 1(G) and 1(L), was particularly effective at re-directing T cell cytotoxicity in tumor cells and inducing apoptosis therein, "via binding of the antigen binding moieties to their respective target antigens on cells." Ast ¶¶ 340–377 (Example 6: "the '2+1 IgG Crossfab' construct is the most potent molecule in this assay").

FF9. Rader is directed to and discloses "antibodies having specificity for human ROR1, compositions thereof; and methods for using such antibodies, including in the diagnosis and treatment of disorders associated with aberrant ROR1 expression." Rader, Abstract.

FF10. Further to the preceding finding of fact and FF5 and FF6, Rader discloses "[t]he invention provides an isolated antibody with specificity for the extracellular domain of receptor tyrosine kinase-like orphan receptor 1 (ROR 1), which is selectively expressed on the

surface of malignant cells, including B-cell tumors and other cancers." Rader ¶ 6; *see also id.* ¶¶ 60–61.

FF11. Rader discloses:

> In some embodiments, ***the antibody can also have specificity for one or more antigens in addition to ROR1***. For example, the antibody of the invention can be engineered (e.g., as a bivalent diabody or a conjugated Fab dimer or trimer) to have specificity for ROR1 and another tumor antigen, e.g., an antigen associated with ***B-CLL***, ***MCL***, Burkitt ***lymphoma***, renal cell carcinoma, ***colon cancer*** (e.g., colon adenocarcinoma), or ***breast cancer*** (e.g., breast adenocarcinoma). ***The antibody can be engineered to have specificity for ROR1 and an antigen that promotes activation or targeting of cytotoxic effector cells***.

Rader ¶ 58 (emphasis added); compare with FF4–FF7 (Ast is directed to an overlapping set of cancers to be treated with a bispecific antibody).

FF12. Further to the preceding finding of fact, Rader discloses that an anti-ROR1 antibody, IgG1 R12, demonstrated strong and homogenous (superior) binding at relatively low concentrations, recognizing cell surface human ROR1, including selective binding to CLL cells, but not normal B cells. Rader ¶¶ 101–104. And, furthermore, this R12 antibody had high binding activity, had some, albeit weak antibody-dependent cellular cytotoxicity (ADCC) activity (it is slow to internalize), and had no effect on apoptosis. *Id.* ¶¶ 113, 130.

FF13. Rader discloses that "[t]he antibody of the invention can be produced by any suitable technique, for example, using any suitable eukaryotic or non-eukaryotic expression system," "[b]acterial expression systems can be used to produce [antibody] fragments,"

[t]echniques for altering DNA coding sequences to produce such fragments are known in the art," and "[t]he antibody of the invention can be conjugated to a synthetic molecule using any type of suitable conjugation" where "it will be understood that the synthetic molecule can also be a protein (e.g., an antibody)." Rader ¶ 52–54.

FF14. Further to the preceding finding of fact, Ast similarly discloses that "[m]ethods to produce polyclonal antibodies and monoclonal antibodies are well known in the art," "[a] humanized or fully human form of the antibody can also be prepared in accordance with methods well known in the art," and "[h]uman antibodies and human variable regions can be produced using various techniques known in the art." Ast ¶¶ 239, 240. Furthermore, "T cell activating bispecific antigen binding molecules prepared as described herein may be purified by art-known techniques" and, similarly, the preparation of a pharmaceutical composition containing the T cell activating bispecific antigen binding molecule would also be accomplished by known techniques. *Id.* ¶¶ 242, 252.

DISCUSSION

I. LEGAL STANDARDS

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. [Once] . . . that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Arguments made by Appellant in the Appeal Brief and properly presented in the Reply Brief have been considered; arguments not

so-presented are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2017); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

"The combination of familiar elements [or steps] according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "[W]here a rejection is predicated on two references each containing pertinent disclosure . . . we deem it to be of no significance, but merely a matter of exposition, that the rejection is stated to be on A in view of B instead of on B in view of A, or to term one reference primary and the other secondary." *In re Bush*, 296 F.2d 491, 496 (CCPA 1961). The test for obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991). "What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *KSR*, 550 U.S. at 419.

"[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). Furthermore, "a reference is not limited to the disclosure of specific working examples." *In re Mills*, 470 F.2d 649, 651 (CCPA 1972)). That the prior art "discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true [when] the claimed composition is used for the identical purpose taught by the prior art." *Merck & Co. Inc. v. Biocraft Labs. Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. . . . [T]he proper standard [is that] the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (reasonable expectation of success, not absolute predictability, is required). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (citation omitted). "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980).

"One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of

ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014); *see also In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). Also, "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *In re Soni*, 54 F.3d at 751 (emphasis original). However, "'differences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—i.e., a new property dissimilar to the known property." *Bristol-Myers*, 752 F.3d at 977.

With these standards in mind and in view of the Findings of Facts set forth *supra* and as presented by the Examiner, we address the Examiner's rejection and Appellant's arguments there-over.

II. ANALYSIS

The Examiner determined the appealed claims would have been obvious over the combination of Rader and Ast. *See* Final Action 4–10, Answer 3–9, 12–22, and Non-Final Action 6–10 (collectively citing Rader in its entirety, but specifically at Abstract, ¶¶ 6, 58, 60, 61, 103, 104, 112–113, 118–119, 128–132, Figure 2; Ast in its entirety, but specifically at Abstract, ¶¶ 11, 12, 16, 21, 25–28, 159, 199–208, 217, 241, 259–265, 300, 340–377, Figures 1(G), 1(L). To summarize the Examiner's position, Ast discloses a T cell-activating/re-directing, bispecific antibody structure having a CD3

binding, 2+1 IgG Crossfab, portion that binds to CD3 and tumor cell antigens, thereby targeting cancer cells, including cells of blood cancers, breast cancers, colorectal cancers, and lymphatic cancers, thereby treating such cancers. *See* FF1–FF3, FF5–FF8. Further, Ast discloses that it would be advantageous to provide such an antibody structure with two or more antigen binding moieties, that is, make it bispecific, to optimize targeting to cell antigens, particularly on the cancer cells' surface. FF5, FF6; *see also* FF10 (Rader's ROR1 is just such a surface antigen). Further, Rader similarly discloses an antibody structure with specificity to human ROR1 and using such antibody structures to treat blood cancers and other cancers. FF9–FF10, FF12. Moreover, similar to Ast, Rader discloses such an antibody having specificity to one or more other antigens beyond ROR1, i.e., a bispecific antibody, for treating blood cancers (B-CLL or MCL), breast cancer, colon cancer, or lyphatic system cancer. FF11; *see also* FF7 (Ast teaches treating an overlapping set of cancers).

The Examiner's position is that "substitution of one known element (the anti-ROR1 Fab, which targets the tumor antigen ROR1 found on certain tumors [of Rader]) for another (any of the various antitumor antigen Fabs used in the construct of Ast)" would have been obvious to the skilled artisan "so that alternate constructs could be prepared that targeted an alternate tumor antigen." Answer 14. Furthermore, the Examiner also determined that "[b]ecause none of the antibodies of Rader were able to directly kill CLL cells from patients, the ordinary artisan would have been motivated to link the anti-ROR1 antibody to an anti-CD3 antibody [of Ast] to improve its ability to mediate killing of target tumor cells." Final Action 8. The

Examiner's position, stated more generally, was that the antibody fragments taught by Rader and Ast, one for ROR1 targeting and the other for CD3 targeting, each for treating cancers, including blood cancers, would complement one another if combined as suggested by each of Rader and Ast. This determination of obviousness is supported by the evidence of record, as exemplified by the findings of fact above.

As noted above, we find no error in, and agree with, the Examiner's determinations on and rationale for the obviousness of the appealed claims. We address Appellant's arguments below.

Appellant argues the Examiner's rejection does not articulate a rational reason to combine Rader and Ast. Appeal Br. 5. This argument is not persuasive.

As noted above, the Examiner articulated the following reasons the skilled artisan would have combined Rader and Ast: "Because none of the antibodies of Rader were able to directly kill CLL cells from patients, the ordinary artisan would have been motivated to link the anti-RORl antibody to an anti-CD3 antibody to improve its ability to mediate killing of target tumor cells" and "[t]he rationale to substitute anti-ROR1 tumor specific Fab units in a '2+1 Crossfab' for any of the tumor specific Fabs taught by Ast would have been to obtain an alternate construct that could be used in additional methods of treating cancer that expresses ROR1 and that could not have been effectively targeted using the anti-tumor antigen specificities exemplified by Ast." Final Action 8, 9. We agree with the Examiner that this is a rational reason to combine the teachings of the two references to achieve a trivalent, bispecific therapeutic antibody structure as claimed. *See*,

e.g., *In re Kerkhoven*, 626 F.2d at 850 (it is logical and obvious to combine compositions useful for the same purpose).

Appellant argues the claimed invention was not obvious to try because the prior art did not provide sufficient guidance to the skilled artisan because Rader only mentions once (at paragraph 58) that it would be desirable to engineer an antibody with specificity for ROR1 and also an antigen that promotes activation or targeting of cytotoxic effector cells. Appeal Br. 7–8. Appellant argues that, based on the prior art, there would have been over seven hundred possible antibody fragment combinations, and Rader does not provide a single example, so selecting the one that covers the claimed invention would not have been obvious. *See id.* at 10–11. This argument is not persuasive.

The Examiner did not premise the rejection on an obvious-to-try rationale, but rather on a conventional obviousness rationale based on the fact that each claim element is taught by the prior art combination, the fact that the skilled artisan would have been motivated to combine the Rader and Ast antibody constructs for advantages in cancer treatment, and the fact that the skilled artisan could have reasonably expected to successfully combine the references for such a purpose because each reference indicates that its molecules could be fabricated and provided as therapy by no more than routine, well-known techniques in the art. *See*, *e.g.*, Answer 3–9, 12–22; *see also* FF1–FF14. Thus, although the combination of Rader and Ast may well have been obvious to try based on what we find to be a limited number (13) of antibody molecules taught by Ast (*see* Ast, Fig. 1) and the limited number of effective antibody fragments taught by Rader (*see* Rader ¶¶ 99–132

(discussing R12 and other Mab)), the undeniably strong demand for new cancer treatments, and the presumed functionality of the antibody structures taught in Radar and Ast (*see Amgen*, 314 F.3d at 1355), such rationale was not necessary to the Examiner's position on obviousness and would only have served to supplement it.

Appellant argues there would not have been a reasonable expectation of success in combining the antibody fragments of Rader and Ast to treat the claimed cancers because the art includes many possible combinations, the art is complex, and the art is unpredictable. Appeal Br. 12–14. This argument is not persuasive.

Treating cancer is unpredictable, according to the Federal Circuit. *See, e.g.*, *OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375, 1376 (Fed. Cir. 2019). However, each of Rader and Ast discloses that its antibody fragments (ROR1-targeting for Rader and CD3-targeting for Ast) effectively target blood cancer cells for therapeutic treatment and we presume that these references' disclosures are enabling. *Amgen*, 314 F.3d at 1355; *see also* FF1–FF12. Moreover, each prior art reference discloses that, although its specific antibody therapy is inventive, the technology to prepare the antibody construct and practice such therapy was well-known to the skilled artisan. FF13, FF14. As noted above, "[t]he combination of familiar elements [or steps] according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. Although cancer treatment is generally unpredictable, the prior art references explain their cancer treatments, indicate that they worked, and suggest their combination to enhance cancer treatment using known methods.

Appellant argues the Examiner failed to establish that Ast's antibody structure shown at the reference's Figure 1G would be a lead compound and, so, selected by the skilled artisan for modification. Appeal. Br. 15–17. This argument is not persuasive.

A "lead compound" obviousness analysis is not warranted in this case. As explained in *Eisai Co. Ltd. v. Dr. Reddy's Labs, Ltd.*, a lead compound analysis is warranted when obviousness is based on structural similarity of two compounds and obviousness is supported when there would be some motivation to lead a skilled artisan to select and modify the prior art compound to achieve the claimed compound. 533 F.3d 1353, 1357 (Fed. Cir. 2008); *see also Bristol-Myers Squibb Co. v. Teva Pharma.s USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014) (patent cases involving new chemical compounds warrant a lead compound analysis). Here, the Examiner did not propose such a scenario, nor need she have. *See* Answer 19–20. Obviousness here is predicated on combining the teachings of two prior art references in ways taught or suggested to be advantageous by those references. The Examiner does not rely on modification of a proposed lead compound to create a new and closely related claimed chemical compound.

Appellant argues that the existence of prior art success in Tandem scFv and DART antibody treatment formats in a clinical setting teaches away from the claimed invention. Appeal Br. 17. Appellant's point is that, if prior art techniques were successful to some degree, the skilled artisan would use those and not try other, similar paths for cancer treatment. This argument is not persuasive.

As an initial matter, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d at 1201. BiTE and DART are merely alternatives to the claimed inventions, they do not criticize, discredit, or discourage the claimed invention. Thus, the existence of these alternatives does not teach away from the invention.

Furthermore, Appellant's argument does not follow logically. Appellant points out that the drug Blinatumomab (CD19 x CD3 bispecific BiTE® technology) was the first bispecific antibody with FDA approval for treating B-cell lymphoblastic leukemia (it underwent the clinical testing necessary therefore). Appeal Br. 17. Appellant next points out that a CD19 x CD3 bispecific antibody with a dual-affinity retargeting molecule (DART® technology) was then shown to be even more potent than the BiTE® molecule for the same treatment. *Id.* at 18. Under Appellant's reasoning, once BiTE was discovered and, in particular, FDA-approved, there would be no motivation to develop DART® absent some clinical testing to show it worked. Under such reasoning, however, how would one in the field get so far as to clinically test such a follow-on antibody treatment without first developing it to be tested? Under such reasoning, however, why would one develop such a new antibody treatment with no motivation to do so, as argued by Appellant? Thus, Appellant's own argument works to its unraveling.

There is a universal, strong motivation in the therapeutic arts to develop cancer treatments and there would be logical motivation to combine

cancer therapies in routine ways that have been identified as useful for a common purpose. *In re Kerkhoven*, 626 F.2d at 850; *see also Dystar Textilfarben Gmbh & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1368 (Fed. Cir. 2006) (universal, implicit motivating factors can contribute to obviousness, particularly where the skilled artisan is capable of combining the prior art references). Here, Rader teaches B-cell tumor (blood cancer) and other cancer treatment with anti-ROR1 antibodies and specifically states that such antibodies can also have specificity for antigens in addition to ROR1, e.g., specificity to promote activation or targeting of cytotoxic effector cells. *See* FF9–FF12. Ast similarly teaches bispecific antigen biding molecules (e.g., antibodies) for T cell activation and re-direction to specific target cells to treat cancer (including blood cancer). *See* FF1–FF8. The references suggest their combination.

Further to the discussion above, Ast discussed the shortcomings of BiTE® and DART® technologies, which it indicated motivated its disclosed invention. Ast ¶¶ 7–10 (short half-life, potential toxicity, and undesirable non-functional side products were problems to be overcome). Ast stated that

> the difficulties and disadvantages associated with currently available bispecific antibodies for T cell mediated immunotherapy, there remains a need for novel, improved formats of such molecules. The present invention provides bispecific antigen binding molecules designed for T cell activation and re-direction that combine good efficacy and produceability with low toxicity and favorable pharmacokinetic properties.

Id. ¶ 10. Thus, contrary to Appellant's arguments, Ast suggests that there is motivation to explore beyond the known technologies in cancer therapy, in spite of and based on the knowledge of those existing technologies.

At oral argument, Appellant focused its arguments on the absence of clinical trials relating to the subject matter of Rader and Ast as evidence that there would not have been motivation to combine Rader and Ast to formulate a cancer treatment, specifically, a hematological cancer treatment, or a reasonable expectation of success in doing so. *See, e.g.*, Hr'g Tr. 4:23–5:10, 5:18–25, 7:15–18, 11:5–18, 13:8–14:2, 16:11–17 (citing *OSI Pharm.*, 939 F.3d 1375 (Fed. Cir. 2019); *In re Copaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018); *Yeda Res. v. Mylan Pharm. Inc.*, 906 F.3d 1031 (Fed. Cir. 2018); and *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019)). Although this take on clinical trials evidence was not expressly presented in Appellant's briefing and, thus, could be considered waived, Appellant appears to assert that, as a matter of law, the lack of clinical trials for hematological cancer treatment with the Rader and Ast antibodies (or fragments) forecloses obviousness here. *See Borden*, 93 USPQ2d at 1474. Appellant's point appears to be that, under the law of our reviewing court, absent a clinical trial to support that the Rader and Ast technologies have some merit in cancer treatment, there would have been no reason to combine the references or expect to successfully do so. Appellant's argument is not persuasive.

OSI Pharmaceuticals begins with a statement that non-small lung cancer was the leading cause of cancer deaths in 2000, causing over 1 million deaths, followed by a statement that cancer treatment, in general, is of an unpredictable nature. *OSI Pharma.*, 939 F.3d at 1377–78. We noted this above as supporting strong motivation to develop new cancer treatments. While the Federal Circuit's identification that cancer research is

unpredictable is not a statement of law universally applicable to patentability, it underscores a well-known fact, *viz.*, that there is no cure for cancer and, therefore, drug development innovation is a continuing and quite necessary journey. The Federal Circuit held that the Board's conclusion of obviousness in an *inter partes* review (IPR), in particular, the Board's finding of a reasonable expectation of success, was not supported by substantial evidence. *Id.* at 1377. However, the holding in *OSI Pharmaceuticals* is specific to the facts of that case, which are different and distinguishable from the facts here.

In *OSI Pharmaceuticals*, the claims at issue were directed to the use of the drug compound *erlotinib* in the treatment of non-small cell lung cancer (NSCLC) and other cancers related to human papilloma virus, Barrett's esophagus, or neoplastic cutaneous diseases. *Id.* at 1378–79. In the IPR, the claims were found to be obvious over the combination of the "Schnur" and "Gibbs" references. *Id.* at 1379. As of the time of filing those claims, there had been over 1,600 new drugs tested in clinical trials directed to NSCLC therapies and all but 7 failed to show efficacy (in Phase II trials). *Id.* at 1378. The Schnur reference disclosed over 100 compounds, including erlotinib, useful in treating hyperproliferative diseases, such as cancer, including lung cancer (and head and neck tumors), but did not discuss treating NSCLC, specifically. *Id.* at 1329. The Gibbs reference disclosed erlotinib had good anti-cancer activity in preclinical models, particularly in patients with NSCLC, but provided no data on such treatment. *Id.* at 1379–80; *see also id.* at 1380 (an OSI 10-K statement had a similarly conclusory, but data-free disclosure). The Board found that the claims directed to

NSCLC treatment with erlotinib would have been obvious over Schnur and Gibbs (or the OSI 10-K), because Schnur taught all but the specific treatment of NSCLC and Gibbs taught (clearly inferred) that missing element because Gibbs's statement regarding preclinical anti-cancer activity could be relied upon as accurate (even in the face of a declaration statement by the author that the statement was not based on data). *Id.* at 1381.

The Federal Circuit found that the Board's reliance on Gibbs was error because Gibbs's statement regarding effectively treating NSCLC with erlotinib was based only on Gibbs's cited references Woodburn, which related to a different compound (not erlotinib), and Moyer, which disclosed treatment of cancers other than NSCLC with erlotinib. *Id.* at 1383. Thus, there was no real evidence that erlotinib could be used to treat NSCLC and the Board's finding that there was a clear inference in Gibbs to that end was not supported by substantial evidence. *Id.* at 1384.

Similarly, the court found that the Board's finding of reasonable expectation of success in the asserted combination of Schnur and Gibbs (or the OSI 10-K) was not supported by substantial evidence because Schnur did not disclose or provide data on treating NSCLC with erlotinib and Gibbs could not cure this deficiency. *Id.* The court held that this lack of disclosure and data was significant in view of the evidence of a 99.5% failure rate in 1,630 NSCLC-treatment Phase II clinical trials. There was a complete absence of data on NSCLC treatment with erlotinib and a complete absence of teaching of the indicator or mechanism on which a skilled artisan could rely to reasonably expect success. *Id.* at 1384–85. The Federal Circuit concluded its analysis as follows:

> To be clear, we do not hold today that efficacy data is always required for a reasonable expectation of success. Nor are we requiring "absolute predictability of success." *See* Appellee's Br. 39. We conclude only that, on these particular facts, a reasonable fact finder could not find a reasonable expectation of success. The Board's finding is thus not supported by substantial evidence, and accordingly we reverse its obviousness determination.

Id. at 1385.

The facts before this Panel are different from those that were determinative in *OSI Pharmaceuticals* and compel a different result. Here, there is no evidence of over a thousand, or even a few, clinical trials relating to antibody therapies for blood cancers, much less evidence of a 99.5% failure rate in such an impressive number of clinical trials as in *OSI Pharmaceuticals*. And, while cancer treatment is an unpredictable field, each of Rader and Ast discloses an antibody therapy useful to treat blood cancer (as well as breast cancer, colorectal/colon cancer, lymphatic cancers, and other cancers). *See* FF2, FF7, FF9, FF11. Furthermore, each of Rader and Ast teaches that no more than well-known techniques would be required to produce and therapeutically use their disclosed antibody structures. FF13, FF14. Finally, each of Rader and Ast suggests its own antibody structure's combination with other antibody structures, like the antibody constructs taught by the other reference. FF4, FF7, FF11. Therefore, *OSI Pharmaceuticals* is not determinative on the evidence before this panel.

In *In re Copaxone*, the Federal Circuit affirmed a district court's ruling that claims to a multiple sclerosis (MS) drug, glatiramer acetate (GA), dosed at 40mg 3x/week, were obvious. *See* 906 F.3d at 1016–17, 1024. Some of the prior art cited in that case consisted of clinical trials for GA for

MS treatment. The Federal Circuit stated, "[w]e recognize that the prior art did not conclusively teach that a regimen of 40mg GA 3x/week would be effective. However, '[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Id* at 1026 (quoting *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014)). Other than "obviousness [being] proven through human clinical studies establishing the safety, efficacy, and tolerability of GA at dose and dose frequencies similar to the claimed regimen," the Federal Circuit did not discuss the significance of clinical trials, per se. *See id.* at 1028. While the court in *In re Copoxone* held that clinical testing data can be evidence supporting a reasonable expectation of success, it did not hold that the converse is also true, i.e., that a lack of clinical trial data supports a finding of no reasonable expectation of success. *Id.* at 1031. Therefore, *In re Copoxone* is not on point here and is not supportive of Appellant's arguments on appeal.

Yeda relates to substantially the same patented subject matter as *In re Copoxone* and the Federal Circuit affirmed the Board's conclusion that the claims would have been obvious over the same, or at least substantially similar, prior art as at issue in *In re Copoxone*. 906 F.3d at 1035–37. The Federal Circuit's conclusions and ultimate holding on the Board's obviousness determination are also substantially the same as presented in *In re Copoxone*, therefore, we find *Yeda* not to be determinative here for the same reasons. *See id.* at 1042–48. Furthermore, we note that in *Yeda* the Federal Circuit stated:

> The Board's finding that the uncertainty around GA's mechanism of action would motivate a POSITA to stick to

> dosing regimens with existing clinical support, such as 20mg and 40mg, is supported by substantial evidence from Dr. Green. *Id.* at 18. Because "the expectation of success need only be reasonable, not absolute," we find no error in these findings.

Id. at 1044. Here, although cancer treatment is somewhat unpredictable in general, we do not have similar evidence that the mechanism of action for Rader's ROR1 antibody fragments or Ast's CD3 antibody fragments have an uncertain mechanism of action; quite the contrary, the references explain such action. *See e.g.*, FF8, FF12 (and related portions of the references). Thus, as in *In re Copoxone*, *Yeda* supports that clinical trial evidence can support the existence of a reasonable expectation of success in the face of uncertainly or unpredictability, but does not support that the lack of such trials is proof of an absence of such an expectation. Appellant's arguments are not supported by *Yeda*.

In *Grunenthal*, the Federal Circuit affirmed a district court's ruling of infringement and also non-infringement, and of no invalidity of claims directed to a drug, a *polymorph of tapentadol hydrochloride*, for treating polyneuopathic pain. *See* 919 F.3d at 1336. In affirming the district court's ruling that the claims were not obvious, the Federal Circuit noted that the claimed technology, i.e., polymorphism of tapentadol hydrochloride, was unknown at the time of the filing of the patent. *Id*. at 1341. Further, the Federal Circuit observed that these characteristics of compounds in the relevant field could not be extrapolated from other compounds and the reference cited for teaching polymorphism discussed a "huge variety" of variables without specifying or providing guidelines therefor. *Id*. at 1341–42. The Federal Circuit found that this evidence, in view of the expert testimony thereon, supported the district court's ruling that the claims were

not proved to be obvious; there was no reasonable expectation of success. *Id*. at 1342–43. After discussing several precedential cases regarding the need for support for a reasonable expectation of success, rather than proof of absolute certainty in an obviousness analysis, the Federal Circuit went on to conclude that the skilled artisan's total lack of understanding as to the claimed polymorphic nature of tapentadol hydrochloride supported that there was no reasonable expectation of success in the case. *Id*. at 1344 (discussing *Pfizer*, 480 F.3d 1348 (reasonable to combine narrowed list of compounds of prior art based on known characteristics); *AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999 (Fed. Cir. 2015) (actual success not required; use of known techniques would be reasonably expected to be successful); and *Cubist Pharm., Inc. v. Hospira, Inc.*, 805 F.3d 1112, (Fed. Cir. 2015) (obvious to use known techniques to achieve claimed purity levels with reasonable expectation of success)). *Gruenthal* does not address evidence of clinical trials as supporting or refuting a reasonable expectation of success.

As discussed above, the case law cited by Appellant does not support Appellant's position that the existence or absence of clinical trials would have either led the skilled artisan toward therapies other than the claimed antibody or would have established that the skilled artisan would not have had a reasonable expectation of successfully combining the antibody components taught by Ast and Rader to achieve the claimed trivalent, bispecific antibody therapeutic.

Finally, Appellant argues that evidence of unexpected results refutes the Examiner's position on obviousness. Appeal. Br. 18. Appellant points to the disclosure at page 63 and Figure 10B of its Specification as evidence

of unexpected results relating to "the EC50 value of a bispecific anti-CD3ε anti-ROR1 antibody having the claimed format for killing the multiple myeloma cell line RPMI8226 is approximately 5-fold lower than for a bispecific anti-CD3ε anti-ROR1 antibody having an alternative format 'ROR1 TCB 1 + 1 Fe'." *Id.* at 19–20.

We reproduced Appellant's Figure 10B below:

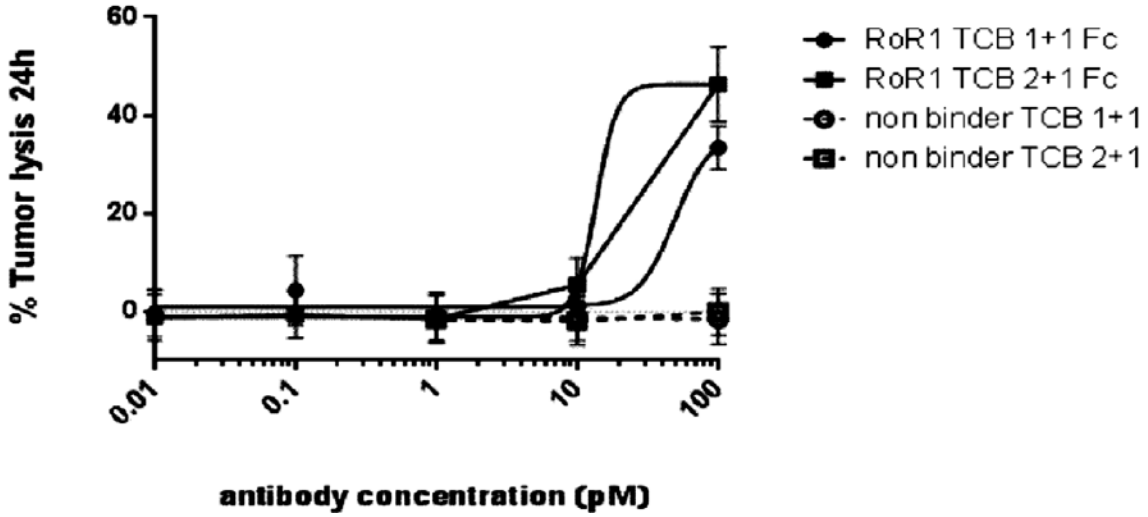


Figure 10B is a graph comparing percentage of tumor lysis (at 24 hours) along the Y axis to antibody concentration along the X axis, showing data points for the following four samples: ROR1 TCB 1+1 Fc; ROR1 TCB 2+1 Fc; non-binder TCB 1+1; and non-binder TCB 2+1. The graph shows the data points for each of these samples at concentrations of 0.01, 0.1, 1, 10, and 100 pM. Although the graph purports to depict differences in the rate of tumor lysis among these samples between the 10 and 100 pM concentrations, it is unclear why because there are no intermediary data points shown to support the differing slopes of the lines drawn. The portion of the Specification cited by Appellant as directed to this figure states:

> Experiment 2 (20h time point): The study was repeated in RORI-positive RPMI8226 and measurement of LOH release was assessed after 20h incubation. 30-40% target cell lysis was observed with anti-ROR1/anti-C03 TCBl+l and TCB2+ 1 antibodies at a concentration of 100 pM while non-binder TCB controls at 100 pM did not induce any tumor lysis. The results corroborate with an increase in T cell activation as 25 measured by upregulation of C025 marker on the C08 T cells (Figure 9B).

Spec. 63:20–25. The EC50 value of a bispecific anti-CD3ε anti-ROR1 antibody is not expressly discussed, other than a preceding statement that "EC50 could not be calculated." *See id.* at 63:13.

Appellant's evidence of unexpected results is not sufficient to overcome the Examiner's prima facie case for obviousness. Although Appellant has presented some evidence of improvements with an embodiment appearing to fall within the scope of the invention over comparative examples, the evidence does not clearly compare the results achieved in the invention with the closest prior art and does not clearly show an improvement in kind versus a mere improvement by degree so as to be particularly persuasive. *See Bristol-Myers Squibb*, 752 F.3d at 977; and *In re Soni*, 54 F.3d at 751. Furthermore, there is no evidence that the results shown in Figure 10B were unexpected. "Attorneys' argument [which is all we have here,] is no substitute for evidence." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989).

We discern no error in the Examiner's determinations, which we conclude presented a prima facie case for the claims' obviousness over the cited prior art combination. We have considered Appellant's arguments over the rejections in their entirety, but find them unpersuasive on the record on appeal.

CONCLUSION

In summary, the obviousness rejection of claims 18–21 is affirmed.

The obviousness-type double patenting rejection of claims 18–21 over U.S. Patent Application No. 13/590,886 and Rader is affirmed.

The obviousness-type double patenting rejection of claims 18–21 over U.S. Patent Application No. 15/517, 296 is affirmed.

Claims Rejected	Basis	Affirmed	Reversed
18–21	§ 103 over Rader and Ast	18–21	
18–21	obviousness-type double patenting over 13/590,886 and Rader	18–21	
18–21	obviousness-type double patenting over 15/517,296	18–21	
Overall Outcome		18–21	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED