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Sanofi/Genzyme c/o Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, CA 94304

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* PASCALE LEJEUNE and PATRICIA VRIGNAUD

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Appeal 2017-001518
Application 13/130,867
Technology Center 1600

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Before MICHAEL J. FITZPATRICK, ULRIKE W. JENKS, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants[1] submit this appeal under 35 U.S.C. § 134(a) involving claims to a pharmaceutical combination comprising cytarabine and an antibody recognizing CD38. The Examiner rejected the claims as obvious and for obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellants identify the Real Party in Interest as Sanofi. App. Br. 3.

## STATEMENT OF THE CASE

Appellants' "invention relates to combinations of monoclonal antibodies directed against CD38 and cytarabine which are therapeutically useful in the treatment of neoplastic diseases." Spec. 1:4–6. CD38 is a transmembrane glycoprotein that "is upregulated and has been implicated in many hematopoietic malignancies." *Id.* at 1:8–12. The Specification notes that "[m]onoclonal antibodies . . . which specifically recognize CD38, are described in PCT application WO2008/047242 [Park][2]" and that these "antibodies are capable of killing $CD38^+$ cells" by several mechanisms (e.g., induction of apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC)). "Cytarabine is an anti-metabolic agent used in chemotherapy." *Id.* at 1:20–21. Cytarabine converts into a compound that damages DNA during DNA synthesis and also damages other enzymes required for DNA synthesis, which most affects rapidly dividing (e.g., cancerous) cells that require DNA replication for mitosis. *Id.* at 6:25–30.

According to the Specification:

> It has now been found, and for this invention, that the efficacy of the humanized anti-CD38 antibodies may be considerably improved when it is administered in combination with at least one substance which is therapeutically useful in anticancer treatments and has a mechanism identical to or different from the one of the humanized anti-CD38 antibodies and which is limited in the present invention to cytarabine.

*Id.* at 1:24–28.

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[2] Park et al., WO 2008/047242 A9, published Apr. 24, 2008.

Claims 1, 2, 11, and 30–32 are on appeal. Claim 1 is illustrative and is reproduced below:

> 1. A pharmaceutical combination comprising an antibody specifically recognizing CD38 and at least cytarabine, wherein said antibody comprises at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity determining regions comprising the amino acid sequences of SEQ ID NOs: 13, 81 and 15, and wherein said light chain comprises three sequential complementarity determining regions comprising the amino acid sequences of SEQ ID NOs: 16, 17 and 18, and wherein the antibody and cytarabine constituents of the combination are physically separate.

App. Br. 29 (Claims App'x).

The claims stand rejected[3] as follows:

I. Claims 1, 2, 11, and 30–32 under 35 U.S.C. § 103(a) as obvious over Weers,[4] Park, Romaguera,[5] and Piccaluga.[6]

II. Claims 1, 2, 11, and 30–32 for obviousness-type double patenting over: (i) claims 1–30 of the '765 patent;[7] (ii) claims

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[3] The Examiner, "in order to simplify the issues for appeal," withdrew some of the § 103 and double patenting rejections. Ans. 14–15. We do not address those withdrawn rejections in this decision.

[4] Weers et al., WO 2006/099875 A1, published Sept. 28, 2006.

[5] Jorge E. Romaguera et al., *High Rate of Durable Remissions After Treatment of Newly Diagnosed Aggressive Mantle-Cell Lymphoma With Rituximab Plus Hyper-CVAD Alternating With Rituximab Plus High-Dose Methotrexate and Cytarabine*, 23:28 JOURNAL OF ONCOLOGY 7013–7024 (2005).

[6] Pier Paolo Piccaluga et al., *First experience with gemtuzumab ozogamicin plus cytarabine as continuous infusion for elderly acute myeloid leukaemia patients*, 28 LEUKEMIA RESEARCH 987–990 (2004).

[7] Park et al., US 8,153,765 B2, issued Apr. 10, 2012 ("the '765 patent").

1–12 of the '406 patent;[8] and (iii) claims 1–8 of the '301 patent.[9] The double patenting rejections rely on the claims of the above-noted patents in further view of Weers, Romaguera, and Piccaluga. Ans. 11–12.[10]

I – OBVIOUSNESS

*Claim 1*

*Issue*

According to the Examiner, Weers, Park, Romaguera, and Piccaluga render obvious the anti-CD38 antibody and cytarabine combination recited in claim 1. Ans. 3–11.

Appellants respond that no adequate motivation to combine the prior art references has been provided. App. Br. 8–9; *see also id.* at 11–12. Appellants further argue that the claimed combination displays unexpected synergism and, thus, that claim 1 is nonobvious. *Id.* at 14–23.

The issue on appeal is whether the preponderance of the evidence on this record supports the Examiner's conclusion that claim 1 would have been obvious over the cited prior art. We discuss further below.

*Findings of Fact (FF)*

The Examiner's findings of fact, statement of the rejection, and supporting reasoning are provided at pages 3–11 and 16–25 of the

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[8] Lejeune et al., US 9,259,406 B2, issued Feb. 16, 2016 ("the '406 patent").
[9] Lejeune et al., US 8,633,301 B2, issued Jan. 21, 2014 ("the '301 patent").
[10] The Examiner provisionally rejected the appealed claims for double patenting over claims in U.S. Application No. 13/131,389. Ans. 12. Based on Patent Office records, that application went abandoned on November 30, 2016 and the provisional rejection is, accordingly, moot.

Examiner's Answer. *See also* Adv. Act. (dated Feb. 25, 2016); Adv. Act. (dated May 18, 2016). The following findings are provided for emphasis and convenient reference.

FF 1. Weers relates to "[i]solated human monoclonal antibodies which bind to human CD38, and related antibody-based compositions." Weers, Abstract. Weers teaches that such antibodies are useful for treating, for example, multiple myeloma, which is a B cell malignancy and disease that attacks bones and bone marrow, resulting in tumors throughout the skeletal system. *Id.* at 1:3–9. According to Weers, about 1% of all cancers and more than 10% of all hematologic malignancies can be attributed to multiple myeloma. *Id.* at 1:10–11.

FF 2. Weers describes "CD38 binding peptides ('CD38BPs')" useful for the treatment "of disorders involving cells expressing CD38, such as multiple myeloma." *Id.* at 20:17–19. Weers teaches the CD38BP may be an antibody, including a humanized or chimeric antibody. *Id.* at 26:21–24.

FF 3. Weers describes methods for treating or preventing a disorder involving cells expressing CD38 by administering a therapeutically effective amount of the CD38BP. *Id.* at 168:3–7. According to Weers, "[t]he CD38BP composition may be administered alone or along with another therapeutic agent, such as described elsewhere [in Weers] which acts in conjunction with or synergistically with the CD38BP composition to treat or prevent the diseases." *Id.* at 168:4–7. Weers also teaches that its compositions may be "administered in combination therapy, i.e., combined with other therapeutic agents . . . [and that] [s]uch administration may be simultaneous, separate or sequential." *Id.* at 175:19–22.

FF 4. Weers teaches "a method for treating multiple myeloma, which comprises administration of a therapeutically effective amount of a CD38BP . . . and at least one chemotherapeutic agent to a subject in need thereof." *Id.* at 176:7–10. Weers teaches that "such a chemotherapeutic agent may be selected from an antimetabolite, such as methotrexate, . . . *cytarabine*, fludarabine, . . . and similar agents." *Id.* at 176:14–17 (emphasis added).

FF 5. Park relates to antibodies, including humanized antibodies, which bind to CD38 and are capable of killing $CD38^+$ cells by apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and/or complement-dependent cytotoxicity (CDC). Park, Abstract. Park teaches that such antibodies may be used to treat tumors that express CD38 protein, such as in multiple myeloma. *Id.*; *see also id.* at 64:10–15 (disclosing that CD38 is expressed in a variety of other malignant hematological disorders, including B-cell acute lymphocytic leukemia, mantle-cell lymphoma, and chronic or acute myeloid leukemia).

FF 6. Park teaches that a therapeutic composition may comprise an anti-CD38 antibody and a second therapeutic agent. According to Park, "[t]his second therapeutic agent can be also chosen from the group of chemotherapeutic or immunomodulatory agents." *Id.* at 6:12–30.

FF 7. Park tested the in vivo activities of the anti-CD38 antibody hu38SB19. *See*, *e.g.*, *id.* at 84–86 (Example 9). In a multiple myeloma tumor model, Park reports that "hu38SB19 and mu38SB19 antibodies or a chimeric IgG1 control antibody were given to mice intravenously at a dose of 40 mg/kg, twice per week, in three successive weeks." *Id.* at 85:13–18. According to Park, none of the tumors in the control groups (IgG1 or PBS controls) regressed, yet "treatment with hu38SB19 or mu38SB19 led to

tumor regression in 8 of 10 or 6 of 10 animals, respectively." *Id.* at 85:18–23; *see also id.* at 84:29–30 ("The treatment with either mu38SB19 or hu38SB19 significantly extended the survival of mice compared to that of PBS-treated mice . . . .").

FF 8. Romaguera relates to a study on survival rates of subjects with mantle-cell lymphoma (MCL) receiving combination therapy with rituximab and a chemotherapy regimen including hyper-CVAD,[11] methotrexate, and cytarabine. Romaguera, Abstract. As explained in Romaguera, "[t]he monoclonal anti-CD20 antibody rituximab has shown activity in untreated patients with MCL." *Id.* at 7014, left col. Romaguera also explains that therapy with hyper-CVAD, methotrexate, and cytarabine has proven effective in patients with aggressive MCL variants. *Id.* Regarding combination therapy, Romaguera reports that "the results of this trial show that rituximab plus hyper-CVAD alternating with rituximab plus methotrexate-cytarabine is an effective regimen for induction of complete remissions in patients with newly diagnosed aggressive MCL and produces prolonged remissions in patients 65 years of age or younger." *Id.* at 7022.

FF 9. Piccaluga relates to a study on administration of gemtuzumab ozogamicin (a humanized anti-CD33 antibody conjugated to calicheamicin) in combination with cytarabine for the treatment of acute myeloid leukemia. Piccaluga, Abstract. Piccaluga discloses that, following administration of the above combination, "[f]ive out of nine patients achieved a CR [complete

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[11] Hyper-CVAD includes fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. Romaguera, 7014, left col.

remission]. In particular, 3/5 untreated and 2/4 relapsed/refractory patients obtained a CR." *Id.* at 987.

FF 10. Table 1 from Appellants' Specification is below.

Table 1: Combination of hu38SB19 and Palmo Ara-C against advanced human T-cell acute lymphoblastic leukemia DND-41 implanted in SCID female mice.

| agent, route Dose in mg/kg/inj (total dose) | | Schedule in days | Drug death | % BWC at nadir (day) | T-C in days (750 mg) | $\log_{10}$ cell kill | TFS on day 160 | Comments |
|---|---|---|---|---|---|---|---|---|
| hu38SB19 IV | Palmo Ara-C SC | | | | | | | |
| 40.0 (160.0) | - | 18, 21, 24, 27 | 0/6 | -2.1 (19) | 6.1 | 0.5 | 0/6 | HDT - Inactive |
| - | 96.3 (385.2) | 18, 21, 24, 27 | 6/6 | -26.6 (31) | - | - | - | Toxic |
| - | 58.0 (232.0) | | 0/6 | -6.1 (31) | 60.5 | 5.4 | 3/6 | HNTD – highly active |
| - | 36.0 (144.0) | | 0/6 | -4.6 (30) | 48.6 | 4.3 | 0/6 | Highly active |
| - | 22.3 (89.2) | | 0/6 | -0.5 (32) | 22.1 | 2.0 | 0/6 | Active |
| 40.0 (160.0) | 96.3 (385.2) | 18, 21, 24, 27 | 5/6 | -21.6 (34) | - | - | - | Toxic |
| 40.0 (160.0) | 58.0 (232.0) | | 0/6 | -6.5 (30) | | | 5/6 | HNTD - Highly active |
| 40.0 (160.0) | 36.0 (144.0) | | 0/6 | -3.2 (31) | 90.9 | 8.1 | 3/6 | Highly active |
| 40.0 (160.0) | 22.3 (89.2) | | 0/6 | -1.7 (19) | 30.8 | 2.7 | 0/6 | active |

Tumor doubling time = 3.4 days. Median tumor size at start of therapy = 124-136 mg. Time for median control tumor to reach 750 mg = 26.9 days. BWC = body weight change, T-C = tumor growth delay, HDT = highest dose tested, HNTD = highest nontoxic dose, TFS = tumor free survivors, IV = intravenous, SC = subcutaneous. Formulations: hu38SB19 = phosphate buffer saline without $Ca^{2+}$ and $Mg^{2+}$, pH 7.4, Palmo Ara-C = 3 % ethanol, 1 % polysorbate 80, 96 % water.

Spec. 12;[12] App. Br. 15. Table 1 relates to a tumor model for a human T-cell acute lymphoblastic leukemia cell line implanted in mice, and shows results (e.g., log cell kill, tumor-free survival (TFS), etc.) for mice receiving the anti-CD38 antibody hu38SB19 or Palmo Ara-C (a cytarabine derivative), or a combination of hu38SB19 and Palmo Ara-C. Spec. 10:5–11:31, 12. An antibody formulation was administered intravenously (40 mg/kg) and a formulation of Palmo Ara-C was administered subcutaneously to mice at

[12] Table 1, reproduced here, reflects the amendments to the Specification submitted on January 22, 2016.

specific dosage levels (e.g., 58.0 mg/kg, 22.3 mg/kg, etc.), and those administrations were given at 18, 21, 24, and 27 days after implantation. *Id.* at 10:13–21; *id.* at 12 (Table 1). Certain mice received only the antibody formulation (total dose of 160 mg/kg (40 x 4)), certain mice received only the Palmo Ara-C formulation (e.g., total dose 233 mg/kg (58.0 x 4)), and certain mice received both the antibody and Palmo Ara-C formulations. For example, as shown in the bottom row of Table 1, six mice received a total dose of 160 mg/kg of the antibody formulation *along with* a total dose of 89.2 mg/kg (22.3 x 4) of the Palmo Ara-C formulation. *Id.* at 12 (Table 1).

*Principles of Law*

"[T]he burden of showing unexpected results rests on he who asserts them. Thus it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). Moreover, "[i]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

"[W]e attribute no magic status to synergism per se since it may be expected or unexpected." *In re Huellmantel*, 324 F.2d 998, 1003 (CCPA 1963); *see also In re Kollman*, 595 F.2d 48, 55 n.6 (CCPA 1979) ("Synergism, in and of itself, is not conclusive of unobviousness in that synergism might be expected.").

*Analysis*

The Examiner finds that Weers teaches "a composition comprising an antibody that binds CD38 and cytarabine and that the antibodies can have ADCC, CDC and/or cause apoptosis and be humanized for treating multiple myeloma." Ans. 3. The Examiner finds that Weers "specifically teach[es] at page 176 that 'In one embodiment, the present invention provides a method for treating multiple myeloma, which method comprises administration of a therapeutically effective amount of a CD38BP . . . and at least one chemotherapeutic agent." *Id.* And, the Examiner highlights, Weers identifies cytarabine as one such chemotherapeutic agent. *Id.*

As for an anti-CD38 antibody having the specific complementarity determining regions (CDRs) and sequences as claimed, the Examiner turns to Park. *Id.* According to the Examiner, Park teaches "an antibody that specifically binds to CD38 that comprises the amino acid sequences of SEQ ID Nos: 62, 64, 66 that are 100% identical to the instant SEQ ID Nos: 62, 64, 66." *Id.* Also, the Examiner finds, "instant SEQ ID Nos: 62, 64, 66 comprise the CDRs of SEQ ID Nos: 13, 81, 15-18 such that the prior art also contains these sequences." *Id.* The Examiner finds that Park teaches "the hu38SB19 antibody which is effective in treating mouse models of lymphoma and multiple myeloma," and also teaches that the described "anti-CD38 antibodies can be combined with chemotherapeutic agents." *Id.* at 3–4; *see also id.* at 17 ("Notably, as evidenced by Park . . . in 2 lymphoma mouse models and 2 multiple myeloma models the hu38SB19 antibody extended the survival of mice, prevented tumor growth, and/or led to tumor regression.").

The Examiner cites to Romaguera and Piccaluga as evidencing combinations of antibodies or ADCs (antibody-drug conjugates) with known chemotherapeutic agents, including cytarabine. *Id.* at 4. According to the Examiner, such combinations are commonly known in the art for use in treating hematological cancers. *Id.*; *see also id.* at 17.

The Examiner concludes it would have been obvious to produce a combination of the anti-CD38 humanized antibody of Park (hu38SB19) and cytarabine as claimed. *Id.* The Examiner reasons that the skilled artisan would have been motivated to make this combination, *inter alia*, "to test the effectiveness of the combination in treating leukemia, multiple myeloma or lymphoma cancers . . . in order to determine if such a combination might be effectively used to treat the disease in humans in a clinical setting." *Id.* Also, the Examiner reasons, given the known effectiveness of Park's antibody in killing cancer cells, it would have been obvious to use that antibody in combination with other known anti-cancer agents. *Id.* at 4–5. According to the Examiner, the skilled person would have been motivated to make a pharmaceutical combination of known antibodies (hu38SB19) and chemotherapeutic agents (e.g., cytarabine) that were taught for use in treating multiple myeloma and other hematological cancers. *Id.* at 14; *see also id.* at 13–14 ("One would have been motivated to do so with a reasonable expectation of success because [Weers] teaches that a chemotherapeutic agent including cytarabine can be administered with an anti-CD38 antibody and antibody and cytarabine combinations were known in the art."), 17 ("a combination of the hu38SB19 antibody with cytarabine merely combines prior art elements according to known methods to yield predictable results.").

Appellants argue "that there is still no motivation to combine the teachings of Weers *et al.* and Park *et al.* in light of the teachings of Romaguera *et al.* and Piccaluga *et al.*" App. Br. 12; *see also id.* at 8–9. According to Appellants, Weers "does not teach that the combination of cytarabine with an anti-CD38 antibody would be a particularly suitable or effective agent" and, instead, Weers simply recited "cytarabine in a boilerplate list of hundreds of potential conjugates and compositions with no teaching that cytarabine was preferred." *Id.* at 9. As for Park, Appellants contend it "makes no mention of cytarabine" or combinations with cytarabine specifically. *Id.* According to the Appellants, "the Examiner is using an improper obvious to try rationale." *Id.* at 9, 12.

Appellants' arguments are unpersuasive. Obviousness does not require that a particular combination be identified in the art as the "preferred" or best option.[13] In any event, here Park exemplifies an especially effective anti-CD38 antibody (hu38SB19) for the treatment of, *inter alia*, multiple myeloma — providing the skilled artisan a clear and specific reason for using that antibody as an alternative to the anti-CD38 antibodies identified in Weers, which are also described as useful for treating multiple myeloma. FF 1–2, 7; Ans. 17, 19. Although Park does not expressly disclose combinations of hu38SB19 with cytarabine, Park teaches

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[13] *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("[I]n a section 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.") (internal quotation marks omitted); *see also In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.").

generally that its antibodies may be combined with chemotherapeutic agents. FF 6. Also, Weers explicitly identifies cytarabine and suggests its use in combinations with anti-CD38 antibodies for treating multiple myeloma and other cancers. FF 4. The Examiner's rejection does not rest merely on "obvious to try" reasoning when the art itself teaches or suggests the combination claimed. *Merck*, 874 F.2d at 807 ("[D]isclos[ing] a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art."). And the Examiner's findings and conclusion are buttressed further by Romaguera and Piccaluga, which show that cytarabine is a well-known chemotherapeutic agent, commonly used in combination therapy with antibody and/or antibody drug conjugates for the treatment of hematological cancers, providing an even further evidentiary basis for the skilled artisan's motivation to have used cytarabine in combination with Park's antibody. FF 8–9.

Appellants next argue that unexpected synergism with the claimed combination rebuts any *prima facie* case of obviousness. App. Br. 14. More specifically, citing the Specification's Table 1 (*see* FF 10), Appellants argue that the "results demonstrate that an anti-CD38 antibody (hu38SB19) and cytarabine act synergistically to decrease tumor growth, giving much better results in combination than would be expected from the results obtained with either agent alone." *Id.* at 16. For example, Appellants cite results comparing (i) intravenous administration of 40.0 mg/kg (160.0 mg/kg total after four doses) of the hu38SB19 antibody alone, (ii) subcutaneous administration of 36.0 mg/kg (144 mg/kg total after four doses) of a formulation of a cytarabine derivative (Palmo-Ara-C) alone, and (iii)

combination therapy with both formulations. App. Br. 14–16. In this example, the number of tumor-free survivors (TFS) following administration of the hu38SB19 formulation alone was 0/6 and the $\log_{10}$ cell kill was determined to be 0.5 (inactive).[14] *Id.* at 14–15. With administration of 36.0 mg/kg (144 mg/kg total) of the Palmo-Ara-C formulation, TFS was 0/6 and $\log_{10}$ cell kill was 4.3 (highly active). App. Br. 14–15. But with combination therapy at those dosages, TFS was 3/6 and $\log_{10}$ cell kill increased to 8.1 (highly active). *Id.*; *see* Spec. 11:4–5 (defining "Therapeutic Synergism" as follows: "a combination has therapeutic synergism if it is more active than the best single agent of the study (by at least 1 log cell kill)").

We have considered Appellants' arguments related to alleged unexpected synergism along with the Specification's test results. App. Br. 14–23; Reply Br. 8–12. But when those arguments and results are balanced against the remainder of the record, the preponderance of the evidence remains in the Examiner's favor, supporting the Examiner's conclusion that claim 1 would have been obvious. We explain further below.

The Examiner finds that Appellants' test results are not commensurate with the broad scope of the combination claimed. We agree. For example, the Examiner points out that Appellants' own testing shows that certain combinations display synergism, but others do not. Ans. 19, 23. Indeed, as noted by the Examiner, "based on the [Specification's] definition it does not

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[14] As explained in the Specification, "TFS" corresponds to complete regression below the limit of tumor palpation for the entire duration of the study (>100 days after the last treatment), and log cell kill is measure of antitumor efficacy. Spec. 10:25–11:3.

appear the combination with Ara-C at the lowest or highest dose [when combined with the antibody formulation] displays therapeutic synergism." Ans. 19; *see also* Adv. Act. (Feb. 25, 2016) ("It was further noted that the claims were not commensurate because they cover all combinations yet it appears that specific doses are required based on table 1."). As Table 1 makes clear, the combination of 40 mg/kg (160 mg/kg total) of the antibody formulation with 22.3 mg/kg (89.2 mg/kg total) of Palmo Ara-C — a combination encompassed by claim 1 — provided no improvement in tumor-free survival and only a marginal increase in $\log_{10}$ cell kill that falls below the threshold of therapeutic synergism set in the Specification. FF 10; Spec. 11:4–5. Some of the combinations using higher overall doses of the cytarabine derivative do display synergism as noted above. But claim 1 is wholly silent on dosages of either the antibody or cytarabine that are required. And Appellants' assertion that "the skilled artisan would conclude that the synergistic effect is . . . independent of the particular total doses indicated in Table 1" is contradicted by the data itself. App. Br. 19; Reply Br. 12. As already explained, some embodiments falling within the scope of claim 1 do not provide synergism, much less unexpected synergism.[15]

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[15] "It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims." *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972). Claim 1 recites a "combination," not a method of treatment, much less a treatment for particular cancers. *See* Adv. Act. (May 18, 2016) ("[W]hile the results may be applicable to method claims they were not sufficient for the pending product claims."). Further to this point, the results in the Specification purporting to show synergism are for one type of cancer (T-cell acute lymphoblastic leukemia), the treatment involved specific routes of administration (IV for the antibody formulation and subcutaneously for the cytarabine formulation), and a particular dosing

The Examiner also points out that attorney argument is generally insufficient to show that results observed are surprising or unexpected. *See, e.g.*, Ans. 20. According to the Examiner, "nowhere in the specification or other evidence of record does it state or suggest that therapeutic synergism is surprising or unexpected as *argued* by Appellant's counsel." *Id.* at 19–20 (emphasis by Examiner).[16] Appellants submitted no affidavit or other persuasive evidence to demonstrate that the skilled artisan would have considered the results in the Specification to be unexpected. *Id.* To the contrary, Appellants respond that they have "stated through counsel that the results are unexpected." Reply Br. 9. But such statements from counsel fall short in rebutting the rejection here, particularly where the evidence of obviousness is reasonably strong. *De Blauwe*, 736 F.2d at 705; *Lindner*, 457 F.2d at 508.[17] Synergism, standing alone, does not demonstrate nonobviousness, and Appellant bears the burden of making a sufficient

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schedule (one administration on each of days 18, 21, 24, and 27). Spec. 10–12; *compare* Park, 85 (providing effective treatment of multiple myeloma by administering 40 mg/kg intravenously, twice per week over three weeks (for a total of six doses), with administration starting four days after inoculation).

[16] We note that, for one of the results shown in Table 1, the Specification characterizes the result (TFS of 5 of the 6 mice) as "[r]emarkabl[e]." Spec. 11:24–25. We agree with the Examiner, however, that the evidence on this record is wanting to establish unexpected or surprising results for the broad combination claimed.

[17] *Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("[E]ven if Pfizer showed . . . unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.").

evidentiary showing that any synergism is, in fact, unexpected. *Huellmantel*, 324 F.2d at 1003; *Klosak*, 455 F.2d at 1080.

Appellants argue that other prior art references support a finding that the alleged synergism was unexpected. App. Br. 16–19, 20–21. More specifically, pointing to references that the Examiner cited to show that synergy with cytarabine combinations would have been expected, Appellants argue these references show the opposite — that such synergism is unpredictable and unexpected. *Id.* For example, with respect to the Johnson[18] reference, Appellants contend synergy was observed with a combination of cytarabine and a radiolabeled anti-CD20 antibody but not when combined with a naked antibody. *Id.* at 17; *see also* Remarks (April 25, 2016) 11, 13. Regarding the Roth[19] reference, Appellants acknowledge that synergy was shown for cytarabine in combination with a CD95 ligand in malignant glioma cells, but Appellants contend Roth suggests this synergism is attributable to specific mechanistic activities of the target cells. App. Br. 18; *see also* Remarks (April 25, 2016) 12–13. To the extent synergy is shown with cytarabine combinations in these other references, Appellants argue "the synergy observed . . . is limited to the specific compounds studied," and that none of the references studied a combination of cytarabine and an anti-CD38 antibody. *Id.* at 17–18.

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[18] Timothy A. Johnson et al., *Synergistic cytotoxicity of Iodine-131-Anti-CD20 Monoclonal Antibodies and Chemotherapy for Treatment of B-Cell Lymphomas*, 85 INT. J. CANCER 104–112 (2000).
[19] Wilfried Roth et al., *Immunochemotherapy of malignant glioma: synergistic activity of CD95 ligand and chemotherapeutics*, 44 CANCER IMMUNOL. IMMUNOTHER. 55–63 (1997).

On the record before us, we are unpersuaded these other references demonstrate that synergism with the claimed combination would have been unexpected. On the one hand, the references show that combinations of cytarabine with several different agents (e.g., CD95 ligands, anti-FAS IgM antibodies, radiolabeled-anti-CD20 antibodies) provide synergy. *See* App. Br. 17–18 (table summarizing references). Consistent with the Examiner's position, this provides some evidentiary support for the notion that synergy with cytarabine combinations like claimed would have been reasonably expected. *See*, *e.g.*, Ans. 21–22.[20] On the other hand, as Appellants argue, the references also demonstrate that synergism was not universally observed with all cytarabine combinations. *Id.*; *see also* Remarks (April 25, 2016) 9–13. As to these other references, we find the argument and evidence is in equipoise. But when we consider the entire record here, the preponderance of the evidence still tilts in favor of the conclusion of obviousness for all the reasons explained above.

Claims 2, 11, and 30–32

Appellants address dependent claims 2, 11, and 30–32 under separate headings, yet Appellants' argument again relies on alleged unexpected

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[20] The Examiner also cites to disclosure in Weers as generally indicating that the identified therapeutic agents (which includes cytarabine) can act synergistically with anti-CD38 antibodies. Ans. 22; FF 3. Hence, the Examiner finds, "as the prior art recognized that synergy could occur, it is unclear on what basis the synergy might be considered 'unexpected' especially in the absence of other evidence." Ans. 22. The Examiner also finds that, if synergistic effects cannot be generalized (as Appellants argue), this would further illustrate why the results in the Specification are not commensurate with the claims "because the claims are not limited to a specific combination that has synergistic effect." Ans. 23.

synergism with the claimed combination. App. Br. 23–25. For reasons discussed above, based on the record before us, we are unpersuaded Appellants have provided evidence of unexpected synergism that outweighs the evidence of obviousness. Ans. 24–25. We otherwise adopt as our own the Examiner's findings of fact, reasoning, and conclusion of obviousness with respect to these dependent claims. Ans. 3–11, 16–25.

*Conclusion of Law*

The preponderance of the evidence on this record supports the Examiner's conclusion that claims 1, 2, 11, and 30–32 would have been obvious over Weers, Park, Romaguera, and Piccaluga.

II – DOUBLE PATENTING

The Examiner rejected the pending claims for obviousness-type double patenting over the claims of the '765 patent, the claims of the '406 patent, and the claims of the '301 patent. Ans. 12. The Examiner finds that the patented claims recite anti-CD38 antibodies with the CDRs/sequences encompassed by pending claim 1, and that the patented claims further disclose combinations of those antibodies with other therapeutic or chemotherapeutic agents (e.g., vincristine). *Id.* at 12–13; *see*, *e.g.*, the '765 patent (claim 22), the '406 patent (claim 1), the '301 patent (claim 1). Because the patented claims do not identify cytarabine, the Examiner makes the rejections in further view of Weers, Romaguera, and Piccaluga, which (as discussed above) teach the use of combinations with the known chemotherapeutic agent cytarabine for treating multiple myeloma and other hematological cancers. *Id.* at 12–13; FF 4, 8–9. The Examiner provides substantially the same rationale for using cytarabine in combination with an

anti-CD38 antibody to kill cancer cells to that discussed above related to the § 103 rejection. Ans. 13–14.

Appellants argue the obviousness-type double patenting rejections as a group. App. Br. 25. Appellants contend that none of the patented claims are directed to a pharmaceutical combination comprising cytarabine and, like argued above, Appellants contend the combination of the antibodies and cytarabine as recited in pending claim 1 provides "unexpected properties." App. Br. 25–26; Reply Br. 12–14.

Whether the patented claims recite cytarabine is not dispositive. The teaching of combinations with cytarabine is provided in the secondary references (e.g., Weers (FF 4)), and Appellants' argument, thus, fails to grapple with the rejections as framed and what the art as a whole teaches.

Although we agree with Appellants that evidence of unexpected properties should, when such evidence is presented, be considered in an obviousness-type double patenting inquiry,[21] the evidence here is insufficient to rebut the Examiner's prima facie case. First, the alleged unexpected synergism suffers from the same shortcomings discussed above, including that the results in the Specification are not commensurate in scope with the broad combination recited in pending claim 1. Second, as the Examiner points out, "the instant combination has not been established to display unexpected results as compared to the results obtained with combinations of the claims in the recited patents," such as the anti-CD38 antibody/melphalan combination (in claim 1 of the '406 patent) or the anti-

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[21] *See Eli Lilly and Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012) (holding a "[t]he district court's categorical repudiation of Lilly's evidence [on unexpected results] was . . . erroneous.").

CD38 antibody/vincristine combination (as recited in claim 1 of the '301 patent). Ans. 26. Without such comparisons, Appellants fail to show unexpected synergism with the anti-CD38 antibody/cytarabine combination versus the combination of anti-CD38 antibodies and other chemotherapeutic agents as in the patented claims.

Appellants' contentions regarding the double-patenting rejections of the dependent claims, which again rely on alleged unexpected properties, fall for substantially the same reasons. App. Br. 26–27.

## SUMMARY

We affirm the rejections for obviousness and obviousness-type double patenting on appeal.

## TIME PERIOD FOR RESPONSE

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

## AFFIRMED