

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FUSION PHARMACEUTICALS, INC.,
Petitioner,

v.

UNIVERSITÄT HEIDELBERG AND THE EUROPEAN ATOMIC
ENERGY COMMUNITY (EURATOM), REPRESENTED BY THE
EUROPEAN COMMISSION,
Patent Owner.

IPR2023-00551
Patent 10,980,901 B2

Before ULRIKE W. JENKS, ZHENYU YANG, and
KIMBERLY MCGRAW, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION

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

I. INTRODUCTION

On February 13, 2023, Fusion Pharmaceuticals, Inc. (“Petitioner”) filed a Petition requesting a *inter partes* review of claims 1, 2, and 4–13 (“the challenged claims”) of U.S. Patent No. 10,980,901 B2 (Ex. 1001, “the ’901 patent”). Paper 2 (“Pet.”). On May 17, 2023, Universität Heidelberg (“UH”) and The European Atomic Energy Community (EURATOM), Represented by The European Commission (“EURATOM”) (collectively, “Patent Owner”) filed a Preliminary Response to the Petition. Paper 5 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply to the Preliminary Response (Paper 6, “Reply”) on June 14, 2013 and Patent Owner filed a Preliminary Sur-reply (Paper 7, “Sur-reply”) to Petitioner’s Reply on June 22, 2023.

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon considering the argument and evidence presented in the Petition and Preliminary Response, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1, 2, and 4–13 of the ’901 patent.

A. Real Parties in Interest

Petitioner identifies itself, Fusion Pharmaceuticals, Inc., as the real party-in-interest. Pet. 3. Patent Owner, identifies itself, Universität

Heidelberg and EURATOM, Represented by The European Commission, as real parties-in-interest. Paper 4, 1.

B. Related Matters

The parties state that they are not aware of any related matters. Pet. 3; Paper 4, 1.

C. The '901 Patent (Ex. 1001)

The '901 patent is titled "Treatment of PMSA Expressing Cancers." Ex. 1001, code (54). The '901 patent issued from Application No. 16/470,104 ("the '104 application"), filed June 14, 2019. *Id.* at codes (21), (86).

The '901 patent relates to a method of treating prostate specific membrane antigen ("PSMA") expressing cancers. *Id.* at code (57), 1:66–67. The method includes administering an effective amount of one or more ²²⁵Ac radiopharmaceuticals in a dosage of from 25 kBq to 400kBq/kg of body weight of a patient or as a unitary dosage of from 3 MBq to 30 MBq to the patient. *Id.* at code (57).

According to the '901 patent, radiopharmaceuticals are useful as tracers, imaging agents, and the treatment of various cancers. *Id.* at 1:21–22. The '901 patent states that radiopharmaceuticals generally include a targeting moiety (a ligand) and a chelating moiety. *Id.* at 1:23–24. The targeting moiety is specific to certain target markers expressed by target cells and the chelating moiety binds a radionuclide. *Id.* at 1:24–51. As a result, the radiopharmaceutical is able to target and bind to a desired site of cells. *Id.* at 1:51–52. The radiopharmaceutical may be used for imaging or destroy the cell to which it is bound or nearby cells. *Id.* at 1:52–55. The '901

patent further explains that PSMA expressing cancers, specifically prostate and breast, are among the most frequent cancers but lack reliable and efficient therapies. *Id.* at 1:66–2:5.

The '901 patent states that radiopharmaceuticals including ^{225}Ac provide significantly better therapeutic results than corresponding radiopharmaceuticals with other radionuclides. *Id.* at 11:36–39. The '901 patent explains that ^{225}Ac is an alpha particle emitter having a short range, which provides good results for the destruction of cancer cells without notable damage to non-target tissues. *Id.* at 12:19–24.

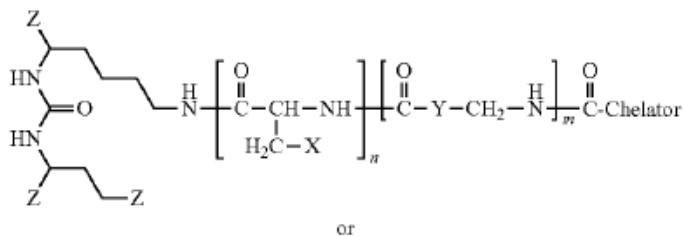
D. Illustrative Claim

Claim 1 is the sole independent claim challenged by Petitioner in this proceeding. Independent claim 1, reproduced below is illustrative of the subject matter:

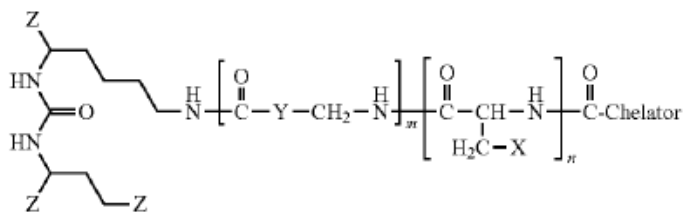
1. A method for treating PSMA^[1] expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

¹ Prostate-specific membrane antigen (PSMA) is found on prostate cancer and breast cancer cells. *See* Ex. 1001, 1:66–2:1.

Formula (A)



Formula (B)



with:

n: 0, 1

m: 1, 2, 3, 4

Z: $\text{---CO}_2\text{H}$, $\text{---SO}_2\text{H}$, $\text{---SO}_3\text{H}$, $\text{---SO}_4\text{H}$, $\text{---PO}_2\text{H}$,
 ---POSH , $\text{---PO}_4\text{H}_2$

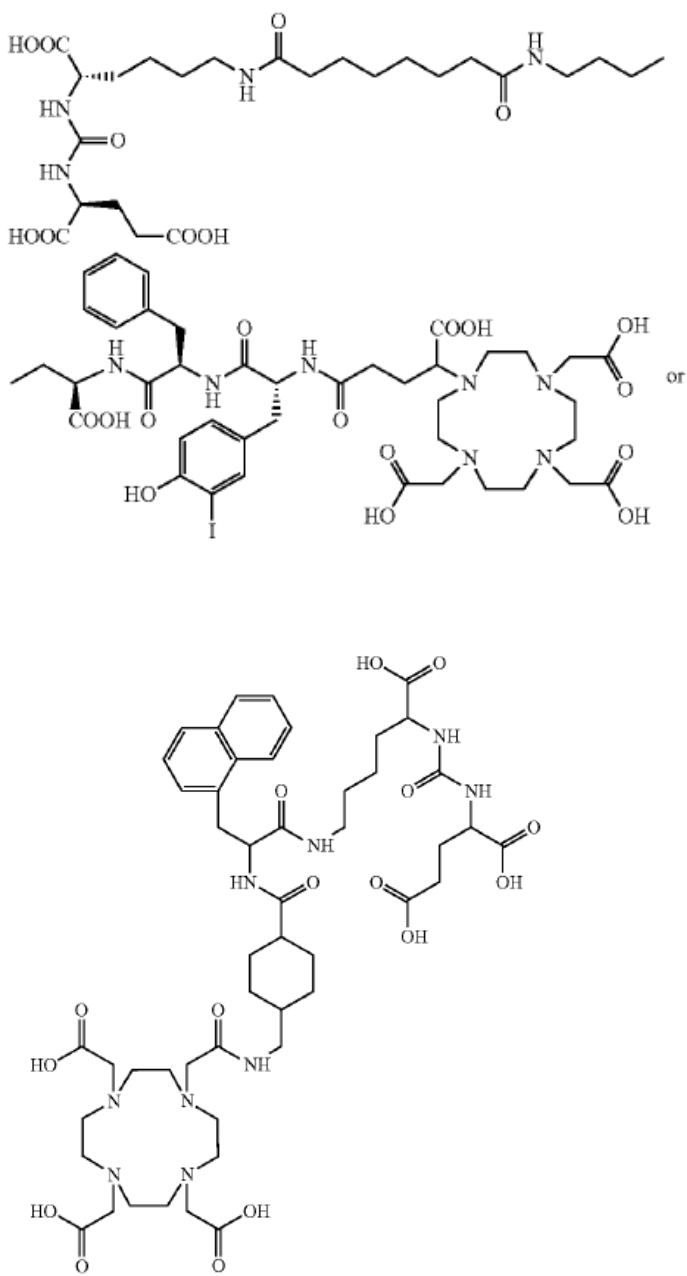
X: naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl

Y: aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl

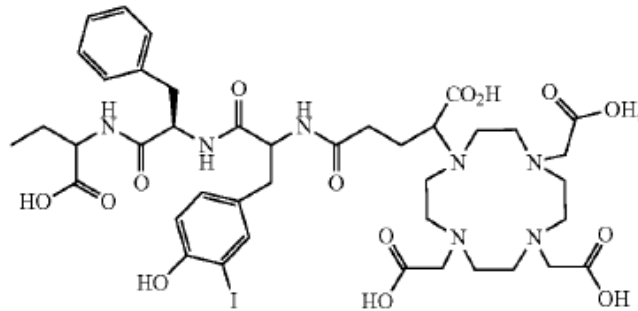
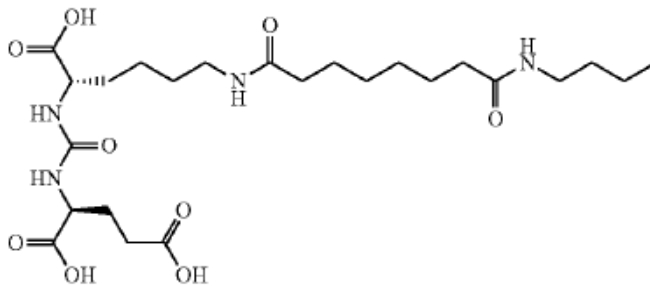
Chelator: 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''tetraacetic acid (DOTA), N,N''-bis [2-hydroxy-5-(carboxyethyl)benzyl]ethyl-enediamine-N,N''-diacetic acid (HBED-CC), 1,4, 7-triazacyclononane-1,4,7-triacetic acid (=NOTA), 2-(4,7-bis(carboxymethyl)-1,4,7-triazonan-1-yl) pentanedioic acid (NODAGA), 2-(4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanedioic acid (DOTAGA), 1,4,7-triazacyclononane phosphinic acid (TRAP), 1,4,7-triazacyclononane-1-[methyl(2-carboxyethyl) phosphinic acid]-4,7-bis[methyl(2-hydroxymethyl) phosphinic acid] (NOPO), 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15), 11,13-triene-3,6,9-triacetic acid (PCTA), N'-{5-[Acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)-(hydroxy)amino]-4-oxo butanoyl}amino)pentyl]-N-hydroxysuccinamide (DFO), diethylenetriaminepentaacetic acid (DTPA), Trans-cyclohexyl-diethylenetriaminepentaacetic acid

(CHX-DTPA), 1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid (oxo-Do3A) p-isothiocyantobenzyl-DTPA (SCN-Bz-DTPA), 1-(p-isothiocyantobenzyl)-3-methyl-DTPA (1B3M), 2-(p-isothiocyantobenzyl)-4-methyl-DTPA (1M3B), or 1-(2-methyl-4-isocyantobenzyl)-DTPA (MXDTPA)
 or

Formula (C)



Formula (D)



Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.
Ex. 1001, 18:14–20:37.

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1, 2, and 4–13 of the '901 patent are unpatentable based on the following grounds. Pet. 5.

Claims challenged	35 U.S.C. §	References/Basis
1, 2, 4–8, 10–13	103	Weineisen 2015 ² , Kratochwil ³
9	103	Weineisen 2015, Kratochwil, Jurcic ⁴

Petitioner also relies upon the declaration of Rebecca Abergel, Ph.D. (Ex. 1002) to support its contentions.

II. ANALYSIS

A. Discretionary Denial Under 35 U.S.C. § 325(d)

As a preliminary issue, Patent Owner urges the Board to exercise discretion to deny institution of *inter partes* review under 35 U.S.C. § 325(d). Prelim. Resp. 11–38.

We have discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.⁵ *Advanced Bionics, LLC v. Med-*

² Martina Wineisen et al., *⁶⁸Ga- and ¹⁷⁷Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies*, 56 J. Nuclear Med. 1169–1176 (2015). Ex. 1028.

³ Clemens Kratochwil et al., *Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter base radionuclide therapy of neuroendocrine tumors*, 56 J. Nuclear Medicine 1232 (2015). Ex. 1031.

⁴ Joseph G. Jurcic et al., *Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML)*, 128 Blood 4050 (2016). Ex. 1011.

⁵ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a);

El Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics* at 8.

In applying the two-part framework, we consider several nonexclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Advanced Bionics, Paper 6 at 7 n.7.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”). Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* “[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9.

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8.

Petitioner contends that the asserted prior art is not the same or substantially the same as that considered during prosecution. Pet. 51 (citing Ex. 1002 ¶¶ 41–42). Specifically, Petitioner argues that Kratochwil is the only asserted reference that was before the Examiner. *Id.* at 52. Kratochwil was cited on an Information Disclosure Statement (IDS) but not otherwise discussed by Examiner. *See* Ex. 1004, 402–410, 426. Petitioner asserts that “[t]he Board has stated on many occasions that a reference merely cited in an IDS is not sufficient to support denial under § 325(d).” Reply 5.

Petitioner relies on Weisen 2015 for disclosing the use of a particular chelating ligand termed “PSMA I&T” with beta-emitting

radionuclides (^{68}Ga and ^{177}Lu) and for teaching that PSMA I&T is a safe and effective ligand for treating cancer. Pet. 30 (citing Ex. 1002 ¶¶ 77–79). Petitioner asserts, and Patent Owner does not dispute, that PSMA I&T is the same compound as that shown in claim 1, Formula C of the '901 patent. Pet. 17. Petitioner and Patent Owner agree that neither Weineisen 2015 nor the specific PSMA I&T ligand disclosed in Weineisen 2015 was before the Office or considered by the Examiner. Pet. 21; Reply 7; Prelim. Resp. 16 (“The PSMA I&T ligand [disclosed in Weineisen 2015 was] not specifically disclosed in the references previously before the Office”). Petitioner contends that the “Examiner only considered disclosures focused on a different compound—PSMA-617” not encompassed in the Petition. Reply 2 (citing Ex. 1004, 32–34); *see* Pet. 52. Because PSMA I&T was not disclosed in any of the references considered by the Examiner, Petitioner reasons that “[t]he arguments presented in this petition are[, therefore,] also not substantially the same as those considered during prosecution.” Pet. 52. Petitioner contends that the Petition cites prior art that was not before the Examiner and “relies on expert testimony that explains how a POSA [(person of ordinary skill in the art)] would have understood the prior art.” Reply 6.

Patent Owner argues that the Petition’s references were either considered by, or are cumulative of, references considered by the Examiner. Prelim. Resp. 12–21. Specifically, Patent Owner contends that Kratochwil was considered by the Examiner during examination, as Petitioner admits. *Id.* at 13 (citing Pet. 52).

Patent Owner asserts that Weineisen 2015 is cumulative of the claims recited in Eder '791 and Eder '160, which were before the Office and which

recited nearly all of the other members of the claimed Markush group recited in the '901 patent. *See* Prelim. Resp. 15–18; Sur-reply 3–4. Specifically, Patent Owner contends that Petitioner “relies on Weineisen 2015 as disclosing PSMA I&T as a PSMA targeting ligand that can be chelated to a radionuclide to produce a radiopharmaceutical.” Prelim. Resp. 15 (citing Pet. 21–23, 29–30). According to Patent Owner, “[t]he challenged claims each recite a Markush group covering the general structure of a number of PSMA-targeting ligands” but Petitioner “fails to mention that several other PSMA-targeting ligands covered by the challenged claims . . . were disclosed in the prior art considered by the Examiner.” *Id.* at 15–16.

Patent Owner argues that “[t]hough they may not have specifically recited PSMA I&T, the Eder claims did specifically recite nearly all other members of the recited Markush group.” Sur-reply 3 (citing Ex. 1001, claims 1, 3). Therefore, Patent Owner contends that “Weineisen 2015 simply does not provide any new information to the examination, and is ‘the same in all material respects’ to the Eder claims.” *Id.* at 4 (citing *R.J. Reynolds Vapor Co. v. Fontem Holdings I B.V.*, IPR2017-01642, Paper 10, 11 (PTAB Jan. 16, 2018)) (emphasis omitted).

There can be no dispute that Kratochwil was before the Office. Kratochwil was listed in an IDS and appears on the face of the '901 patent. Ex. 1004, 426; Ex. 1001, code (56). The Examiner also certified that all references listed in the IDS “except where lined through” were considered, and Kratochwil is not lined through. Ex. 1004, 426. Accordingly, Kratochwil is “[p]reviously presented art.” *See Advanced Bionics*, 7–8 (indicating that “previously presented art” includes “art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS)”).

On the other hand, Weineisen 2015 was not before the Office during examination of the application leading to the '901 patent and therefore is not the “same art” previously presented to the Office. *Advanced Bionics*, 13–14; *see also* Prelim. Resp. 16 (“The PSMA I&T ligand [disclosed in Weineisen 2015 was] not specifically disclosed in the references previously before the Office”). But, Patent Owner argues, art substantially similar to this reference was before the Office during examination.

Having considered the record, we disagree with Patent Owner that Weineisen 2015 is substantially similar or cumulative. Just because the Eder '160 patent claims disclose many of the members of the Markush group recited in the '901 patent claims does not mean that *all* the members of the Markush group are represented or encompassed by the Eder '160 claims. Sur-reply 3 (“Though they may not have specifically recited PSMA I&T, the Eder claims did specifically recite nearly all other members of the recited Markush group. Ex. 1001, claims 1, 3”). Here, the species disclosed in the Weineisen 2015 reference is not present in the Eder '160 patent claims. Accordingly, we determine that the Weineisen 2015 not substantially similar or cumulative to the art previously presented to the Office.

For these reasons, we determine that the Weineisen 2015 reference that Petitioner advances in the Petition is not the same or substantially the same art that was previously presented to the Office. Accordingly, we determine that the first part of the *Advanced Bionics* framework is not satisfied. Because we determine that the first part of the *Advanced Bionics* framework is not satisfied, we do not reach the second part of the *Advanced Bionics* framework to determine whether Petitioner has demonstrated a material error. *See Advanced Bionics*, Paper 6 at 10 (explaining that “*If . . . it*

is determined that the same or substantially the same art or arguments were previously presented,” the other factors are assessed) (emphasis added). Accordingly, we decline to exercise our discretion to deny the Petition under § 325(d).

B. Level of Ordinary Skill in the Art

Petitioner contends:

A POSA [person of ordinary skill in the art] as of December 2016 would have been a scientist or clinician, having a Ph.D. or M.D., or a team of such individuals, who alone or in combination had experience with (i) the concept of radioimmunoconjugation, (ii) the chemical behavior of radiometals from the d- and f-blocks of the Periodic Table such as ¹¹¹In, ¹⁷⁷Lu, and ²²⁵Ac, (iii) the design, synthesis, and use of chelators that form kinetically and thermodynamically stable complexes with the radiometals, and (iv) the clinical use of radiotherapeutic agents.

Pet. 28 (citing Ex. 1002 ¶ 18). Petitioner further argues that one of ordinary skill in the art “would have easily understood the prior art references referred to herein and would have had the capability to draw reasonable inferences from them.” *Id.*

Patent Owner does not dispute Petitioner’s definition of a POSA at this stage of the proceeding. Prelim. Resp. 3.

Based on the present record, we adopt Petitioner’s definition of a POSA. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown”) (quoting *Litton*

Indus. Prods., Inc. v. Solid State Sys. Corp., 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

Petitioner “asserts that the claim terms should be given their plain and ordinary meaning” but does not argue any constructions for any claim terms. Pet. 17–18. Patent Owner contends that “it is not necessary to construe any claim term at this stage.” Prelim. Resp. 6.

For purposes of this decision on institution, at this stage of the proceeding, we need not construe any claim terms. *See, e.g., Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Obviousness over Weineisen 2015 and Kratochwil

Petitioner contends that claims 1, 2, 4–8, and 10–13 are unpatentable as obvious over Weineisen 2015 and Kratochwil. Pet. 29–49. Patent Owner opposes. Prelim. Resp. 38–70.

1. Overview of Weineisen 2015 (Ex. 1028)

Weineisen 2015 is titled “⁶⁸Ga- and ¹⁷⁷Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies” and relates to an “investigation of a PSMA [prostate specific membrane antigen] inhibitor for imaging and therapy (PSMA I&T) for ⁶⁸Ga-based PET and ¹⁷⁷Lu-based endoradiotherapeutic treatment in patients with metastatic and castration-resistant disease. Ex. 1028, 1. The cell surface enzyme prostate-specific membrane antigen

(PSMA) is found on prostate cancer. Weineisen 2015 teaches the use of two PSMA inhibitors, reproduced below:

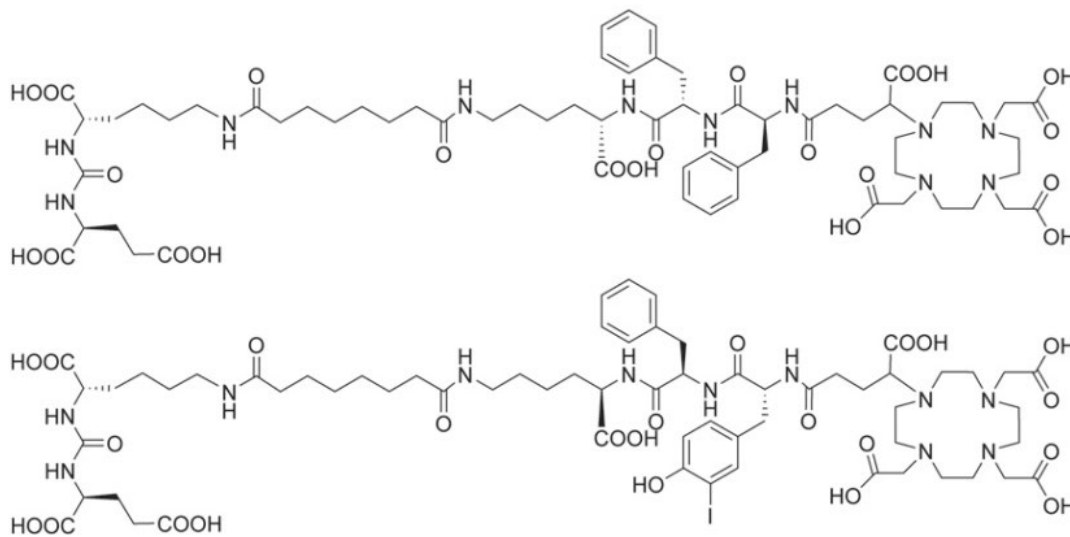


Figure 1, reproduced above, shows the chemical structures of DOTAGA-FFK(Sub-KuE), a first-generation tracer (upper structure), and PSMA I&T, a third-generation tracer (lower structure). *Id.* at 2.

In the study, PSMA I&T was synthesized and biodistribution studies were performed. *Id.* at 1, 3. Based on the study, Weineisen 2015 describes ^{68}Ga -PSMA I&T as a PET tracer of high potential for the detection of metastatic prostate cancer that “may be useful for stratification and follow-up of patients undergoing radioligand therapy with ^{177}Lu -PSMA I&T.” *Id.* at 8. According to Weineisen 2015, “ ^{177}Lu -PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic [prostate cancer].” *Id.*

2. Overview of Kratochwil (Ex. 1031)

Kratochwil is titled “Ac-225-DOTATOC – an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors” and relates to a study for finding the maximum tolerable dose (“MTD”) “of single cycle and fractionation concepts for Ac-225-

DOTATOC radionuclide therapy.” Ex. 1031, 1. Kratochwil’s study involved forty-six treatment cycles in thirty-four patients with progressive neuroendocrine tumors and evaluating acute toxicity after each cycle. *Id.* According to Kratochwil, the maximum tolerable dose (MTD) “of a single cycle of a Ac-225-DOTATOC was considered to be 40 MBq,” “[m]ultiple fractions were tolerated with 25MBq every 4 months or 18.5 MBq every 2 months,” and “[c]umulative activities of 75 MBq were found tolerable in regard to delayed toxicity.” *Id.* at 2.

3. Claim 1

Petitioner contends that the combination of Weineisen 2015 and Kratochwil teaches all the limitations of claim 1. Pet. 41–44. Patent Owner opposes. Prelim. Resp. 38–70.

a. A method for treating PSMA expressing cancers

Petitioner relies on Weineisen 2015 for teaching ¹⁷⁷Lu-PSMA I&T therapy. *See* Pet. 29–30, 41–44. Weineisen 2015 teaches that prostate specific membrane antigen (PSMA) is a target for radioligand therapy. Ex. 1028, 1. Weineisen 2015 treated two patients with ¹⁷⁷Lu-PSMA I&T and shows that “3 mo after ¹⁷⁷Lu-PSMA I&T therapy revealed partial remission.” *Id.* at 6.

At this stage of the proceeding, Petitioner has shown a reasonable likelihood that Weineisen 2015 teaches a “a method for treating PSMA expressing cancers.”

- b. wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals*

Petitioner acknowledges that Weineisen 2015 does not use ^{225}Ac as a radionuclide but relies on Kratochwil for using alpha emitting particle Ac-225-DOTATOC radionuclide therapy. *See* Pet. 30–31, 41–44. According to Petitioner, a “POSA would have appreciated that alpha emitters were known to be superior to beta emitters in that they were more potent and caused fewer side effects.” *Id.* at 42 (citing Ex. 1002 ¶¶ 29, 78, 81–86; Ex. 1006, 1–2; Ex. 1014, 1; Ex. 1015, 1–2, 6; Ex. 1022, 1; Ex. 1027, 11).

Dr. Abergel, Petitioner’s declarant cites references to support the position that a POSA at the time the invention was made would have known that ^{225}Ac can be substituted for another radionuclide with reasonable expectation of success, and that there are advantages to using the alpha emitter ^{225}Ac .

For example, Miederer, cited by Dr. Abergel suggests that radionuclide ^{225}Ac , ^{213}Bi , and ^{177}Lu chelated complexes work similarly.

Just like ^{225}Ac -DOTATOC, ^{213}Bi -DOTATOC compared favorably with ^{177}Lu -DOTATOC *in vitro* and displayed a higher therapeutic efficacy at the same absorbed dose [], supporting the idea that α -emitting isotopes may help to improve the efficacy of PRRT in neuroendocrine tumors. . . . In spite of the potential toxicity of therapies with α -emitting isotopes, a therapeutic window of ^{225}Ac -DOTATOC was shown in a tumor model. As expected from the physical properties of the α -generator nuclide, the beneficial effect(s) of ^{225}Ac -DOTATOC over ^{177}Lu -DOTATOC was shown.

Ex. 1015, 6.

Scheinberg, cited by Dr. Abergel suggests that there are certain advantages to using the alpha emitter ^{225}Ac instead of the alpha emitter ^{213}Bi as a radionuclide. *See generally* Ex. 1022. The decay scheme of ^{225}Ac is shown in the figure below:

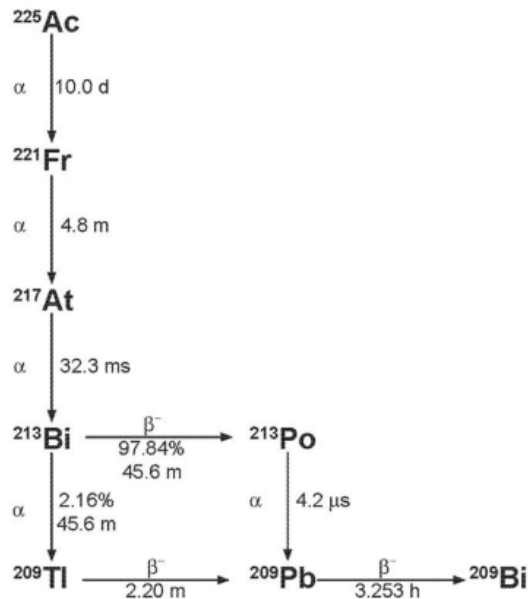


Figure 1, reproduced above, shows ^{225}Ac decay yields six principal radionuclide progeny in the decay cascade to stable ^{209}Bi . Ex. 1022, 25. Scheinberg explains:

^{213}Bi is generator-produced and has a very short half-life. The clinical use of ^{213}Bi presents the logistical dilemma of eluting the generator, radiolabeling the targeting molecule, administering a dose, and allowing sufficient time for targeting. All of these steps consume valuable time that decreases the effective dose administered. An innovative alternative to ^{213}Bi was the use of its parent nuclide, ^{225}Ac , which has a ten-day half-life and 4 net alpha particle-emissions per decay. In vitro cytotoxicity data using the same antibodies labeled with either ^{213}Bi or ^{225}Ac demonstrated that several logs less ^{225}Ac radioactivity was necessary to reach LD50, presumably because

of the multiple alpha emissions and the 300-fold longer half-life.

Ex. 1022, 2.

Dr. Abergel explained that a POSA would have appreciated that “ ^{225}Ac , and its resultant decay chain, produces more alpha emissions than ^{213}Bi and has a substantially longer half-life of about 10 days. . . . Further, studies that directly compare ^{225}Ac to ^{213}Bi in the same antibody constructs have shown that ^{225}Ac is substantially more potent than the ^{213}Bi analog.” Ex. 1002 ¶ 83 (citing Ex. 1022, 4; Ex. 1013, 4). “Alpha emission is higher in energy than beta emission, therefore alpha particles can do more damage to cells within the body than beta particles. . . . By directly comparing [^{177}Lu]-DOTATOC with [^{225}Ac]-DOTATOC, Miederer showcases the increased efficacy of an alpha emitter (^{225}Ac) compared to a beta emitter (^{177}Lu).” Ex. 1002 ¶ 85 (citing Ex. 1015, 1).

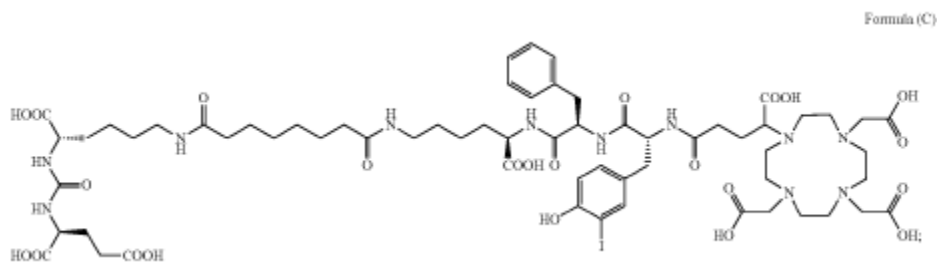
Accordingly, we agree with Petitioner, based on the present record, that at the time the invention was made a POSA would have appreciated that ^{213}Bi or ^{177}Lu are interchangeable with ^{225}Ac in a chelation complexed compound. *See* Ex. 1002 ¶¶ 26, 80–86; Ex. 1013; Ex. 1015; Ex. 1022. At this stage of the proceeding, Petitioner has shown a reasonable likelihood that the combination of Weineisen 2015 and Kratochwil teaches a method for treating cancer using the alpha emitter ^{225}Ac .

c. said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E)

Petitioner contends that Weineisen 2015 teaches Formula C complexed with the beta emitter ^{177}Lu . Pet. 41–42 (citing Ex. 1028, 2; Ex. 1002 ¶¶ 95–98). Petitioner reasons that “[i]t would also have been

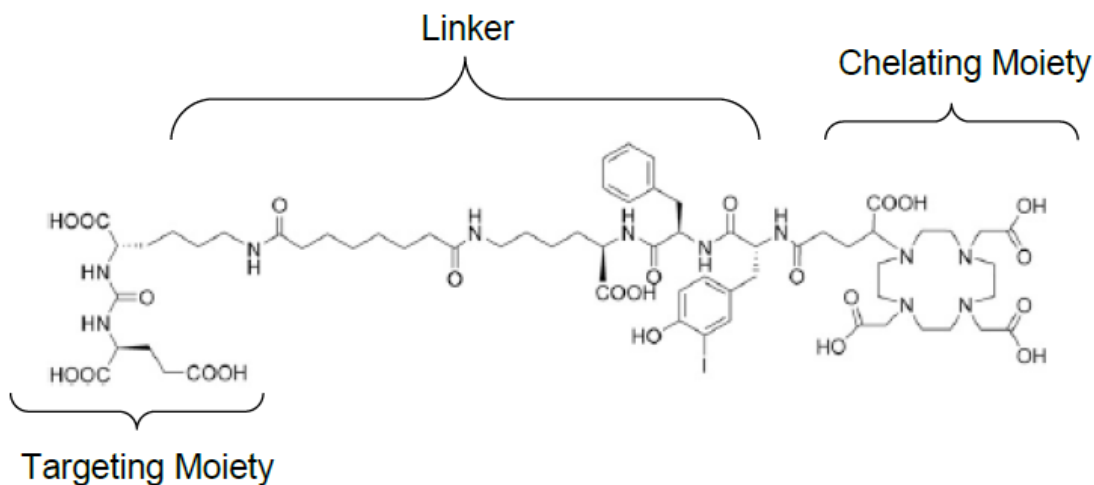
obvious to a POSA to complex the alpha emitter ^{225}Ac with PSMA I&T.” *Id.* at 42 (citing Ex. 1002 ¶ 98). According to Petitioner, a POSA would have known that ^{177}Lu and ^{225}Ac can be used interchangeably in a chelator targeting molecule. *Id.* Petitioner finds support for this position in Miederer that “shows that ^{177}Lu and ^{225}Ac can be used interchangeably in an chelator targeting molecule. . . . When used in the same targeting compound, ^{225}Ac and ^{177}Lu showed similar stability profiles, but ^{225}Ac exhibited increased efficacy compared to the ^{177}Lu analog.” *Id.* (citing Ex. 1015, 5–6; Ex. 1002 ¶ 98).

Formula C of the '901 patent is reproduced below:



The above figure shows Formula C of the '901 patent. Ex. 1001, 19:20–39.

Weineisen 2015’s structural formula for PSMA I&T, as annotated by Petitioner’s declarant, is reproduced below:



The PSMA I&T formula shows the targeting moiety, the linker, and the chelating moiety DOTAGA. Ex. 1002 ¶¶ 59–60, *see also id.* ¶ 26 (“dodecane tetraacetic acid (‘DOTA’) . . . , is a well-known chelator, capable of forming complexes with many different types of radionuclides, such as ^{177}Lu , ^{90}Y , and ^{225}Ac , upon deprotonation” (citing Ex. 1014, 1–2; Ex. 1027, 11; Ex. 1035, 4, 14, 16)). Weineisen 2015 describes the above formula PSMA I&T as a third-generation tracer. Ex. 1028, 6, *see also id.* at 2 (Figure 1 (lower formula)).

Formula C of the '901 patent and the PSMA I&T compound from Weineisen 2015 is reproduced above, a comparison of these two compounds shows that they are identical when no radionuclide is chelated with DOTA the chelating moiety. Although Weineisen 2015 uses ^{68}Ga - and ^{177}Lu -labeled PSMA I&T, we agree with Petitioner that it would have been obvious to use ^{225}Ac based on the teaching of Miederer that suggests that the radionuclides ^{225}Ac , ^{213}Bi , and ^{177}Lu are interchangeable. Pet. 42 (citing Ex. 1002 ¶ 98; Ex. 1015, 5–6).

At this stage of the proceeding, Petitioner has shown a reasonable likelihood that the combination of Weineisen 2015 and Kratochwil in conjunction with the knowledge of the POSA suggests substituting ^{177}Lu with the alpha emitter ^{225}Ac in PSMA I&T.

- d. wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.*

Petitioner contends that “[t]he POSA seeking to use ^{225}Ac -PSMA I&T for treating cancer would have been motivated to use doses within the claimed ranges.” Pet. 43 (citing Ex. 1002 ¶ 99). In the declaration, Dr. Abergel shows how to convert a unit dose to a body weight dose. Ex. 1002 ¶ 99. Kratochwil “ ^{225}Ac -DOTATOC is a targeted radiopharmaceutical which comprises the targeting agent octreotide linked to a ^{225}Ac -chelated DOTA.” Ex. 1002 ¶ 70 (citing Ex. 1031, 1). Dr. Abergel states that Kratochwil’s ^{225}Ac -DOTATOC teaches a different linker and targeting moiety but acknowledges that the chelating moiety, DOTA, is the same as the chelating moiety in Formula C of the ’901 patent. *See* Ex. 1002 ¶¶ 25, 26 (“Chelation is a unique kind of molecular interaction, in which a charged metal atom (a metal ion) interacts with heteroatoms (N, S, O, etc.) of the chelator. For example, dodecane tetraacetic acid (“DOTA”) . . . is a well-known chelator.”), 70.

Patent Owner disagrees. *See* Prelim. Resp. 38–70. Specifically, Patent Owner contends that in arriving at the presently claimed methods from the disclosure of Weineisen 2015 would require several steps such as a motivation to use an alpha-emitter instead of a beta emitter, the specific selection of ^{225}Ac as the alpha emitter, the recited ^{225}Ac doses, applying the treatment to PSMA expressing cancers, and showing a reasonable expectation of success. *Id.* at 42.

On the current record, we find Patent Owner's arguments unavailing.

Weineisen 2015 teaches that PSMA I&T has “an enhanced internalization efficiency of ^{68}Ga -/ ^{177}Lu -PSMA I&T into PSMA-expressing LNCaP cells. . . . It also shows a nearly 2-fold-higher accumulation in lung, spleen, and kidney, all of which are tissues with documented PSMA expression.” Ex. 1028, 7. Although Wineisen 2015 acknowledges that further studies are needed, their “proof-of-concept study [shows that using the beta emitter] ^{177}Lu -PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC.” *Id.* at 8. Thus, Wineisen 2015 reasonably suggests using PSMA I&T compound in radiotherapy.

Kratochwil performed a dose escalation study with the alpha emitter Ac-225-DOTATOC to find the maximum tolerable dose (MDT) for a single cycle of targeted alpha emitter-therapy. Ex. 1031, 1. According to Kratochwil, the maximum tolerable dose was 40 MBq. *Id.* at 2. Kratochwil also taught administration of 25 MBq Ac-225-DOTATOC every 4 months or 18.5 MBq Ac-225-DOTATOC every 2 months. *Id.* Supplying the Ac-225-DOTATOC in multiple fractions allowed for a lower dose with each administration. Kratochwil, therefore, reasonably suggests that the alpha emitter ^{225}Ac may be administered at doses of 40 MBq, 25 MBq, or 18.5 MBq. We, therefore, agree with Petitioner that the ^{225}Ac doses applied in the dose escalation studies of Kratochwil overlap with the claimed “unitary dosage of from 3 MBq to 30 MBq.” Pet. 43 (citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)). Kratochwil, therefore, suggests using the alpha emitter ^{225}Ac for administration to patients within the dosage range claimed in the '901 patent.

Weineisen 2015 and Kratochwil both use the same DOTA chelating structure. Specifically, Dr. Abergel explains that “DOTATOC is a radiotherapy ligand made up of a DOTA, a linker, and a peptide targeting moiety. Because of the DOTA’s ability to chelate a variety of radionuclides including ^{225}Ac , Miederer proposed swapping ^{225}Ac for ^{177}Lu .” Ex. 1002 ¶ 65 (citing Ex. 1015, 1). Dr. Abergel explains that coupling PSMA I&T to an alpha emitter is not new. *Id.* at ¶ 80 (“PSMA I&T was not limited to use with beta emitters, disclosing PSMA I&T complexed with alpha emitter ^{213}Bi as a potential lead in preclinical studies” *Id.* ¶ 80 (citing Ex. 1006, 1–2)). Dr. Abergel further explains that the draw back with using ^{213}Bi as an alpha emitter is its short half-life (*id.* at 82), therefore, providing motivation to look for an alpha-emitter with a longer half-life.

“[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007), citing *United States v. Adams*, 383 U.S. 39, 50-51 (1966); *see also In re Newton*, 111 F.2d 907, 908 (CCPA 1940) (“This appears to be merely a simple case of substituting one reagent for another in analogous equivalent relation and without inventive results.”). It is obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) (“[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another.”).

Both Wineisen 2015 and Kratochwil employ the DOTA chelating structure to bind their respective radionuclides. Here, the art (e.g., Miederer)

supports the position that chelating structure – DOTA – the structure that holds the radionuclide within the therapeutic compound can accept many different radionuclides including ^{225}Ac . Specifically, Miederer explains that “[j]ust like ^{225}Ac -DOTATOC, ^{213}Bi -DOTATOC compared favorably with ^{177}Lu -DOTATOC *in vitro* and displayed a higher therapeutic efficacy at the same absorbed dose [], supporting the idea that α -emitting isotopes may help to improve the efficacy of PRRT in neuroendocrine tumors.” Ex. 1015, 6. The art, therefore, suggests that there is a reasonable expectation of success that substituting one radionuclide for another produces a compound that retains its function. In this case, substituting ^{177}Lu in PSMA I&T taught in Weineisen 2015 with the alpha emitter ^{225}Ac taught in Kratochwil would similarly result in a radionuclide compound that is reasonably expected to work. Indeed, the art even suggests that the use of alpha emitting isotopes may help to improve the efficacy of the compound providing the POSA further motivation to substitute a beta emitter ^{177}Lu with an alpha emitter ^{225}Ac . *Id.*

At this stage of the proceeding, Petitioner has shown a reasonable likelihood that the combination of Weineisen 2015 and Kratochwil suggests substituting the beta emitter ^{177}Lu with alpha emitter ^{225}Ac in PSMA I&T.

e. Summary

Based upon our review of the parties’ arguments and supporting evidence in the current record, we determine that Petitioner has shown a reasonable likelihood that claim 1 would have been obvious over Weineisen 2015 and Kratochwil.

4. Claims 2, 4–8, and 10–13

Claims 2, 4–8, and 10–13 depend directly or indirectly from claim 1. Ex. 1001, 20:38–26:42. Petitioner points out where each of the limitations of dependent claims 2, 4–8, and 10–13 are disclosed by the references. Pet. 45–49. Petitioner supports its assertions with the testimony of Dr. Abergel. *Id.* Patent Owner argues the claims as a group and does not provide arguments for claims 2, 4–8, and 10–13 separate from those discussed above for claim 1. Prelim. Resp. 38–70.

We are persuaded, for the reasons stated in the Petition, which findings we adopt as our own for the purpose of institution, that Petitioner’s arguments and evidence have established a reasonable likelihood that each limitation of claims 2, 4–8, and 10–13 would have been obvious over the teachings of *Weineisen 2015* and *Kratochwil*. *See* Pet. 45–49.

*E. Obviousness over *Weineisen 2015*, *Kratochwil*, and *Jurcic**

Petitioner contends that claim 9 is unpatentable as obvious over *Weineisen 2015*, *Kratochwil*, and *Jurcic*. Pet. 49–50. Patent Owner opposes. Prelim. Resp. 38–70.

*1. Overview of *Jurcic* (Ex. 1011)*

Jurcic is titled “Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML).” Ex. 1011, 1. *Jurcic* describes a study in which patients with relapsed / refractory AML were administered a dose of ²²⁵Ac-lintuzumab. *Id.* *Jurcic* concluded that ²²⁵Ac-lintuzumab could be safely combined with LDAC to induce remission in order patients with untreated AML. *Id.* at 3. *Jurcic* stated

that “[a] phase II trial of ²²⁵Ac-lintuzumab monotherapy at 2 µCi/kg/fraction using hydroxyurea, if needed, to lower peripheral blast counts prior to administration [sic] will be undertaken to determine response rate, PFS, and OS in this patient population.” *Id.*

2. Claim 9

Petitioner argues that claim 9 would have been obvious over the combined teachings of Weineisen 2015, Kratochwil, and Jurcic. Pet. 49–50. Patent Owner does not advance specific arguments with respect to claim 9.

We are persuaded, for the reasons stated in the Petition, which findings we adopt as our own for the purpose of institution, that Petitioner’s arguments and evidence have established a reasonable likelihood that the limitations of claim 9 would have been rendered obvious over the teachings of Weineisen 2015, Kratochwil, and Jurcic. *See* Pet. 49–50.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one challenged claim of the ’901 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review “require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition.”); 37 C.F.R. § 42.108. At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1, 2, and 4–13 of the '901 patent is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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For PETITIONER:

Linnea Cipriano
Olivia Uitto
Grace Truong
Christopher Haley
GOODWIN PROCTER LLP
lcipriano@goodwinlaw.com
ouitto@goodwinlaw.com
gtruong@goodwinlaw.com
christopherhaley@goodwinlaw.com

For PATENT OWNER:

S. Art Hasan
Lauren E. Schneider
LEWIS ROCA ROTHGERBER CHRISTIE LLP
AHasan@LewisRoca.com
LSchneider@LewisRoca.com