

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: KORMAN *et al.*

Confirmation No.: 2347

Applicant: BRISTOL-MYERS SQUIBB
COMPANY

Art Unit: 1644

Application No.: 15/021,102

Examiner: Ilia I. Ouspenski

371(c) Date: March 10, 2016

Atty. Docket: 3338.0750002

Title: **COMBINATION OF ANTI-LAG-3 ANTIBODIES AND ANTI-PD-1 ANTIBODIES
TO TREAT TUMORS**

Amendment and Reply Under 37 C.F.R. § 1.111

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In reply to the Office Action dated January 8, 2018, Applicant submits the following
Amendment and Remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of
this paper.

Remarks and Arguments begin on page 6 of this paper.

It is not believed that extensions of time are required beyond those that may otherwise be
provided for in documents accompanying this paper. However, if additional extensions of time are
necessary to prevent abandonment of this application, then such extensions of time are hereby
petitioned under 37 C.F.R. § 1.136(a), and any additional fees required to continue prosecution or
appeal of this application (including issue fee, fees for net addition of claims or forwarding to
appeal) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

- 1-23. (Canceled)
24. (Currently amended) A method of treating melanoma in a human patient, the method comprising administering to the patient an effective amount of each of:
- (a) an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:5,
 - (b) an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO: 19, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:21,
- wherein the method comprises at least one administration cycle, wherein the cycle is a period of two weeks, wherein for each of the at least one cycle, one dose of the anti-LAG-3 antibody is administered at a dose of 80 mg and one dose of the anti-PD-1 antibody is administered at a dose of 240 mg, and
- wherein the patient has been previously treated with anti-PD-1 or ~~and~~ anti-PD-L1 antibody therapy.
25. (Previously presented) The method of claim 24, further comprising the administration of an anti-CTLA-4 antibody.
26. (Previously presented) The method of claim 24, wherein the anti-PD-1 and anti-LAG-3 antibodies are formulated for intravenous administration.
27. (Previously presented) The method of claim 24, wherein the anti-PD-1 and anti-LAG-3 antibodies are formulated together.
28. (Previously presented) The method of claim 24, wherein the anti-PD-1 and anti-LAG-3 antibodies are formulated separately.

Atty. Dkt. No. 3338.0750002

29. (Previously presented) The method of claim 24, wherein the treatment consists of up to 12 cycles.
30. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody is administered prior to administration of the anti-LAG-3 antibody.
31. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody is administered after administration of the anti-LAG-3 antibody.
32. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody is administered concurrently with the anti-LAG-3 antibody.
33. (Previously presented) The method of claim 24, wherein the anti-LAG-3 antibody comprises
 - (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:7;
 - (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:8;
 - (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:9;
 - (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:10;
 - (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:11; and
 - (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:12.
34. (Previously presented) The method of claim 24, wherein the anti-LAG-3 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs:3 and 5, respectively.
35. (Previously presented) The method of claim 24, wherein the anti-LAG-3 antibody comprises heavy and light chains comprising the sequences set forth in SEQ ID NOs: 1 and 2, respectively.
36. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody comprises

- (a) a heavy chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:23;
 - (b) a heavy chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:24;
 - (c) a heavy chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:25;
 - (d) a light chain variable region CDR1 comprising the sequence set forth in SEQ ID NO:26;
 - (e) a light chain variable region CDR2 comprising the sequence set forth in SEQ ID NO:27; and
 - (f) a light chain variable region CDR3 comprising the sequence set forth in SEQ ID NO:28.
37. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody comprises heavy and light chain variable regions comprising the sequences set forth in SEQ ID NOs: 19 and 21, respectively.
38. (Previously presented) The method of claim 24, wherein the anti-PD-1 antibody comprises heavy and light chains comprising the sequences as set forth in SEQ ID NOs: 17 and 18, respectively.
39. (Previously presented) The method of claim 24, wherein the anti-LAG-3 antibody and/or anti-PD-1 antibody is a full-length antibody.
40. (Previously presented) A kit for treating melanoma in a human patient, the kit comprising:
- (a) a dose of an anti-LAG-3 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO:3, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:5;
 - (b) a dose of an anti-PD-1 antibody comprising CDR1, CDR2 and CDR3 domains of the heavy chain variable region having the sequence set forth in SEQ ID NO: 19, and CDR1, CDR2 and CDR3 domains of the light chain variable region having the sequence set forth in SEQ ID NO:21; and

- (c) instructions for using the anti-LAG-3 antibody and anti-PD-1 antibody in the method of claim 24.
41. (Previously presented) The method of claim 25, wherein the anti-CTLA-4 antibody is ipilimumab.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 24-41 are pending in the application, with claim 24 being the independent claim. Claim 24 is sought to be amended to correct a clerical error. Support for the amendment is found throughout the specification and claims as originally filed, for example, in the specification at pages 40 and 46. Claims 1-21 and 23 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim 24

Applicant thanks the Examiner for the courtesy of bringing to our attention an apparent clerical error in claim 24. Claim 24 has been amended to correct the error by replacing "anti-PD-1 and anti-PD-L1" with "anti-PD-1 or anti-PD-L1."

Rejection under 35 U.S.C. § 102

Claims 1-21 and 23 have been rejected under 35 U.S.C. § 102(a)(2) as allegedly being anticipated by U.S. Patent Appl. Pub. No. 2014/0093511, as evidenced by the instant specification. Applicant traverses the rejection. Not in acquiescence to the propriety of the rejection, but rather solely to advance prosecution claims 1-21 and 23 have been canceled rendering the rejection moot. Accordingly, Applicant requests the rejection of claims 1-21 and 23 under 35 U.S.C. § 102(a)(2) be withdrawn.

Atty. Dkt. No. 3338.0750002

Rejection under 35 U.S.C. § 102/103

Claims 24-41 have been rejected under 35 U.S.C. § 102(a)(2) as allegedly being anticipated by U.S. Patent Appl. Pub. No. 2014/0093511 to Lonberg et al., as evidenced by Drake et al., *Nature Reviews Clinical Oncology* 11(1): 24-37 (2014), or in the alternative under 35 U.S.C. § 103 as allegedly obvious over the '511 publication in view of Drake. Applicant traverses the rejection.

Applicant respectfully submits that the rejection under 35 U.S.C. § 102/103 must fail because the '511 publication is not prior art to the claimed invention under 35 U.S.C. § 102(a)(2). 35 U.S.C. § 102(b)(2)(C). As stated in the accompanying "Statement in Support of Prior Art Exception under 35 U.S.C. 102(b)(2)(C)," the '511 publication is not prior art to the claimed invention because the instant application and the application published as the '511 publication were, not later than the effective filing date of the instant application, owned by, or subject to an obligation for assignment to the Bristol-Myers Squibb Company.

With regards to the alternative rejection under 35 U.S.C. § 103, Applicant further respectfully submits that Drake is not available as prior art against the claimed invention either. According to the publisher's web site, Drake was published on November 19, 2013, which is after the filing date of U.S. Provisional Appl. 61/880,606, whose benefit of priority is claimed by the pending application.^{1, 2}

¹ See, <https://www.nature.com/articles/nrclinonc.2013.208>, accessed on March 23, 2018. A hard copy of the site is attached as Exhibit A.

² Support for claims 24-41 can be found throughout the specification and claims of U.S. Provisional Appl. 61/880,606, for example, in the specification at pages 3-5, 39, 43-4, Figure 2, and in claims 1-22, as originally filed.

Accordingly, Applicant requests that the rejection of claims 24-41 under 35 U.S.C. § 102/103 be reconsidered and withdrawn.

Non-statutory Double Patenting

Claims 1-21 and 23-41 have been provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 5-14, 16-19, 24-28 and 39 of copending Application U.S. Appl. No. 15/296,290, published as U.S. Patent Appl. Pub. No. 2017/0137514. Claims 1-21 and 23 have been canceled rendering moot the rejection with regards to the canceled claims. Applicant traverses the rejection.

An obviousness-type nonstatutory double patenting (ODP) rejection is "analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. 103 except that the patent disclosure principally underlying the double patenting rejection is not considered prior art." M.P.E.P. § 804 II.B.2 (internal citation omitted). Therefore, an ODP rejection should make clear (a) the "differences between the inventions defined by the conflicting claims — a claim in the patent compared to a claim in the application," and (b) the "reasons why a person of ordinary skill in the art [POSA] would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent." *Id.* (emphasis added). While the factual enquires for an ODP analysis and an analysis under 35 U.S.C. §103 are similar, a crucial difference is that "[w]hen considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent or copending application, the disclosure of the patent may not be used as prior art." M.P.E.P. § 804 II.B.2(a) (citing *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279 (Fed. Cir. 1992)) (emphasis added).

Atty. Dkt. No. 3338.0750002

Applicant respectfully submits that the Office has not met its burden of establishing a *prima facie* case of ODP. The Office has not determined the differences between the reference claims and the claim at issue, and the Office's analysis improperly relied on the disclosure of the '290 specification.

Applicant further respectfully submits that the method according to claim 24-41 is patentably distinct from the subject matter of the reference claims, *i.e.*, claims 5-14, 16-19, 24-28 and 39 of the '290 application. The reference claims do not anticipate claims 24-41 because they do not disclose, either expressly or inherently, each and every element of claims 24-41. And the reference claims do not render obvious claims 24-41 because they do not disclose or suggest each and every element of the claimed method, and a person of ordinary skill in the art (POSA) would not have been motivated to modify the teachings of the reference claims to arrive at the claimed method.

No *prima facie* case of ODP has been established

The Office has not determined the differences between claims 24-41, *i.e.*, the claims at issue and claims 5-14, 16-19, 24-28 and 39 of the '290 application, *i.e.*, the reference claims. While the Office Action includes a brief summary of the subject matter of claims 5-14, 16-19, 24-28 and 39 of the '290 application, it does not include any comparison with the claimed method. Office Action, p. 9.

Furthermore, the Office improperly relied on disclosures in the '290 application's specification to support the ODP rejection. The entirety of the analysis supporting the ODP rejection consists of a single sentence reference to the analysis supporting the rejections under 35 U.S.C. §§ 102(a)(2) and 103 in view of the '511 publication, which is the publication of the '290

Atty. Dkt. No. 3338.0750002

application's parent. Office Action, p. 9 ("Accordingly, the instant claims are anticipated and/or made obvious by the claims of the '290 application for the same reasons as presented in sections 5 and 7 above."). The referenced analysis cannot support an ODP rejection. While the factual enquires for an ODP analysis are similar to the ones in an analysis under 35 U.S.C. §103, a crucial difference is that the disclosure of the reference application may not be used as prior art. M.P.E.P. § 804 II.B.2(a) (citing *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279 (Fed. Cir. 1992)). Here, the analysis under 35 U.S.C. §§ 102(a)(2) and 103 focus exclusively on alleged teachings in the specification of the '511 publication, and consequently cannot be used to support the ODP rejection. *See, e.g.*, Office Action, p. 4 (reference to dosage regimens disclosed in paragraphs [0159] and [0160] of the '511 publication), p. 5 (reference to cancer types disclosed in paragraphs [0175]-[0176] of the '511 publication).

Claims 24-41 are patentably distinct from claims 5-14, 16-19, 24-28 and 39 of the '290 application

The reference claims of the '290 application

are directed to a method of stimulating an immune response in a subject, comprising administering to the subject and anti-LAG-3 antibody comprising the same amino acid sequences as the anti-LAG-3 antibody recited in the instant claims (e.g. claims 5, 6 and 13; see sequence alignment in SCORE), wherein the subject is a tumor-bearing subject and an immune response against the tumor is stimulated (claim 14). Claims 19, 24, 25 and 39 are directed the method of claim 5, further comprising administering anti-PD-1 antibody nivolumab, which is the same anti-PD-1 antibody as recited in the instant claims.

Office Action, p. 9.

Claims 24-41 are directed to method of treating melanoma comprising administering an anti-LAG-3 antibody comprising the 6 CDRs of BMS-986016 and an anti-PD-1 antibody comprising the 6 CDRs of nivolumab, wherein the method comprises at least one administration

Atty. Dkt. No. 3338.0750002

cycle, wherein the cycle is a period of two weeks, wherein for each of the at least one cycle, one dose of the anti-LAG-3 antibody is administered at a dose of 80 mg and one dose of the anti-PD-1 antibody is administered at a dose of 240 mg, and wherein the patient has been previously treated with anti-PD-1 or and anti-PD-L1 antibody therapy.

The reference claims do not anticipate claim 24-41 because they do not disclose, *inter alia*, a method of treating melanoma, that the melanoma patient has been previously treated with anti-PD-1 or and anti-PD-L1 antibody therapy, or the dosage of the anti-LAG-3 and anti-PD-1 antibodies recited in the claims.

The reference claims also do not render obvious claims 24-41 because a POSA would not have had a reason to modify the method of stimulating an immune response according to the reference claims to arrive at the claimed method of treating melanoma in a patient who has been previously treated with anti-PD-1 or and anti-PD-L1 antibody therapy by administering at least one administration cycle of an anti-LAG-3 antibody comprising the 6 CDRs of BMS-986016 and an anti-PD-1 antibody comprising the 6 CDRs of nivolumab, wherein the cycle is a period of two weeks, wherein for each of the at least one cycle, one dose of the anti-LAG-3 antibody is administered at a dose of 80 mg and one dose of the anti-PD-1 antibody is administered at a dose of 240 mg.

Accordingly, Applicant requests that the provisional rejection of claims 24-41 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 5-14, 16-19, 24-28 and 39 of the '290 application be reconsidered and withdrawn.

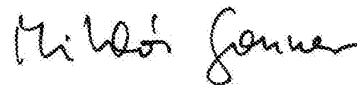
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Miklos Gaszner
Attorney for Applicant
Registration No. 61,314

Date: 4/9/2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

9165745_1.docx

Atty. Dkt. No. 3338.0750002