The examination is being carried out on the **following application documents**

Description, Pages

1-55	as published	

Sequence listings, SEQ ID NO

1-8	as published	

Claims, Numbers

1-15	filed in electronic form on	18-06-2018

Drawings, Sheets

1/6-6/6	as published	

1 Amended claims 1-15 appear to comply with the requirements of Art. 123(2) EPC. The limitation to a flat dose of 80 mg establishes novelty over the cited documents. However the following objections apply.

2 Claims 1 and 2 have been drafted as separate independent claims. Under Article 84 in combination with Rule 43(2) EPC, an application may contain more than one independent claim in a particular category only if the subject-matter claimed falls within one or more of the exceptional situations set out in paragraph (a), (b) or (c) of Rule 43(2) EPC. This is not the case in the present application since present claims 1 and 2 both relate to further medical use claims characterised by the use of an anti-PD-1 antibody, administered at a flat dose of 80 mg, in combination with an anti-CTLA-4 antibody, for treating melanoma.

2.1 In the further prosecution of the application, failure to file an amended set of claims which complies with Rule 43(2) EPC, or to submit convincing arguments as to why the current set of claims does in fact comply with these provisions, may lead to refusal of the application under Article 97(2) EPC.

Amgen Exhibit 1059
Amgen v. BMS
IPR2025-00602

2.2 The feature "identifying the patient having a PD-L1 negative melanoma tumor" is present in claim 1 but not in claim 2, which raises doubt as to whether this feature is essential or not (Rule 43(1) and (3) EPC together with Art. 84 EPC). Furthermore the difficulties and lack of reliability associated with detecting PD-L1 have been identified, see the cited prior art documents D1 (page 5306, l.h.c., para. 2 to r.h.c., para. 1), D2 (page 44, r.h.c - page45, l.h.c., §2) and D3 (page 771, l.h.c., §2 - . page 774, r.h.c., §1), D4, (page 128, r.h.c., last § - page 130, r.h.c, §2).

2.3 Therefore without defining how this identification is carried out (methods and conditions), step (i) of claim 1 is not defining a sub-category of patients and is not further distinguishing the claimed treatment over the prior art. Present claim 1 thus lacks clarity and seems redundant with claim 2.

2.4 When defining a specific dosage regimen, the specific compound(s) to be used at the claimed dosage should be identified. Therefore present claims 1 and 2 should be limited to nivolumab and ipilimumab, both being essential technical features of the present application (page 38, [0128]).

3 Reference is made to the following documents:

D1 P. A. OTT ET AL: "CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients", 2013, XP055200528

D2 G. K. PHILIPS ET AL: "Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies", 2014, XP55217958

D3 MAHONEY KATHLEEN M ET AL: "The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma.", 2015, XP055285031

D4 JEDD D. WOLCHOK ET AL: "Nivolumab plus Ipilimumab in Advanced Melanoma", 2013, XP55182024

D5 MARZUKA ALEXANDER ET AL: "Melanoma Treatments: Advances and Mechanisms.", 2015,XP002759396

D6 PAOLO A ASCIERTO ET AL: "The additional facet of immunoscore: immunoprofiling as a possible predictive tool for cancer treatment", 2013, XP021142097

D7 US 2013/309250 A1 (COGSWELL JOHN [US] ET AL) 21 November 2013

3.1 Document D1 identifies PD-L1 as a biomarker suitable to discriminate the patients suffering from melanoma that would respond to the therapy with anti PD-1 antibody from the others. A passage identifies issues that could limit its use as a clear-cut predictive biomarker (page 5306, l.h.c.,§2 to r.h.c., §1). The authors of D1 refer to combined therapy with anti PD-1 and anti CTLA-4 antibodies as a way to overcome the lack of response observed in some patients with either monotherapy (page 5307, l.h.c., para.2 to r.h.c., para. 3).

3.2 Document D2 reviews different clinical trials based upon the use of nivolumab (1 mg/kg or 3 mg/kg) in combination with ipilimumab (3 mg/kg or 1 mg/kg) in patients with advanced melanoma and metastatic RCC (page 43, r.h.c., §4). Another study of patients with NSCLC started with higher doses (3 mg/kg for each mAb, page 44, l.h.c., §1).

3.3 Document D3 reviews the clinical studies of PD-1/PD-L1-targeted therapies in melanoma. The synergistic antitumour activity of the combination of nivolumab and ipilimumab in the preclinical B16 mouse model has prompted clinical trials and the outcome is discussed together with their side-effects (page 774, r.h.c., §2 - page 778, r.h.c., §1).

3.4 Document D4 discloses the combined therapy of patients with melanoma based upon ipilimumab (anti-CTLA-4 antibody) and nivolimumab (anti PD-1 antibody) as well as the immunohistochemical assessment of PD-L1 (page 124, r.h.c., § 2 and page 128, r.h.c., last § to page 130, r.h.c., para. 3).

3.5 Document D5 discloses the advances on understanding mechanisms in melanoma treatments and focuses on the clinical studies of PD-1/PD-L1-targeted therapies in melanoma. The correlation between the expression of PD-L1 and the objective rate response to nivolumab is reported (page 2631, l.h.c., § 2 to r.h.c.,§ 3).

3.6 Document D6 discloses the concept of immunoprofiling patients suffering from cancer as "using an individual's immune system signature (or profile) to predict that patient's response to therapy" and refers to PD-L1 as a possible predictive biomarker of therapeutic response to anti PD-1 treatment (abstract and page 3/4, lines 10-17).

3.7 Document D7 discloses the treatment of melanoma with anti-PD-1 antibody following the determination of PD-L1 levels (claims 1-17).

4 Document D2 is considered as the closest prior art for assessing the inventive step of claims 1 and 2 since it refers to the combined use of nivolumab (1 or 3 mg/kg) and ipilimumab (1 or 3 mg/kg) for treating melanoma (page 43, r.h.c., §4 - page 44, l.h.c., §1). The rational for selecting patients with PD-L1 positive tumor before treating them with anti PD-1 antibody is disclosed (page 44, r.h.c., para.2) in spite of some limitation and drawback associated with this restriction due to the method and products used to determine the level of PD-L1 (page 44, r.h.c., para. 3 - page 45, l.h.c., para. 2).

4.1 Present claims 1 and 2 thus differ from this disclosure in that a flat dose of nivolumab at 80 mg is used. No particular effect has been shown to be associated with the difference : in the experimental section dosage of nivolumab is reported to be of 1 mg/kg every 2 weeks or 3 mg/kg every 2 weeks (page 38, [0128]). Furthermore 80 mg corresponds to 1 mg/ml for a patient of 80 kg, thus the claimed flat dose is within the range of the known dosage disclosed in D2.

4.2 The technical problem is therefore the provision of an alternative dosage regimen for the treatment of melanoma with nivolumab and ipilimumab as combination therapy.

4.3 The claimed solutions are solving the problem posed. However in the absence of any technical effect associated with the claimed differences, the solutions are obvious in the light of the prior art, thereby not involving an inventive step.

4.4 The same applies to dependent claims 2-15 since none of the features has been associated with a particular effect.

5 It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 43(1) EPC. The applicant should also indicate the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

5.1 The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC).

5.2 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments carried out, and indicate the passages of the application as filed on which these amendments are based (Guidelines H-III, 2.2).

5.3 At the present stage it is considered that refusal of the application under Article 97(2) EPC is to be expected.

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Application No.	Ref.	Date
16 725 959.7 - 1111	M/58241-EP	08.10.2018
Applicant: Bristol-Myers Squibb Company		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11 (b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter

Le Flao, Katell
Primary Examiner
For the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

Registered letter
EPO Form 2001 11.16TRI