

1 Application documents

- 1.1 As published : Description pages 1-55, Sequence listings, SEQ ID NO 1-8 and Drawing Sheets 1/6-6/6.
- 1.2 As filed in electronic form on 29-07-2019 : Claims 1-11.

2 Amendments and lack of compliance with Art. 123(2) EPC

- 2.1 Claim 1 reads: A composition comprising an effective amount of nivolumab for use in treating a melanoma tumor in a human patient having a PD-L1-negative melanoma tumor in combination with an effective amount of ipilimumab, wherein the effective amount of nivolumab is a flat dose of 80 mg, and wherein the patient is identified as having a PD-L1-negative tumor by measuring a PD-L1 expression on the melanoma tumor.
- 2.2 Basis for a flat dose of nivolumab of 80 mg is to be found in original claim 44, where it was furthermore defined that the dose of ipilimumab was 240 mg. The same is to be found in paragraphs 39, 40 and 114. Extracting one feature from its context defining the doses of both antibodies, is an intermediate generalisation which goes beyond the application as originally filed. The only passage disclosing a flat dose of 80 mg for nivolumab, without defining the dose of ipilimumab is in paragraph 114, last line. However this passage is not singling out this dose as a preferred embodiment. Present claim 1 is thus considered as introducing an amendment not complying with the requirements of Art. 123(2) EPC.

3 Patentability

- 3.1 The following documents are cited by the Examiner. A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure.
 - D9 LONG G V ET AL: "Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer.", ANNALS OF ONCOLOGY, vol. 29, no. 11, 1 November 2018, pages 2208-2213, XP55651364

- D10 POLLACK M H ET AL: "Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma.", ANNALS OF ONCOLOGY, vol. 29, no. 1, 1 January 2018, pages 250-255, XP55651368
- D11 ZHAO X ET AL: "Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors.", ANNALS OF ONCOLOGY, vol. 28, no. 8, 1 August 2017, pages 2002-2008, XP2789767

- 3.2 Document D2 is considered as the closest prior art for assessing the inventive step of claim 1 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).
- 3.3 Claim 1 differs in that a flat dose of nivolumab at 80 mg is used or treating melanoma in patients having a PD-L1-negative melanoma tumor.
- 3.4 No particular effect has been shown to be associated with the difference(s) : 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.
- 3.5 The technical problem is therefore the provision of an alternative dosage regimen for the treatment of melanoma with nivolumab and ipilimumab as combination therapy.
- 3.6 Although it is known that flat doses offer advantages compared to body-weight-based doses, there is no experimental evidence, either in the patent application or in post-published documents D9, D10 or D11, that an advantage in terms of treatment will be achieved by selecting this specific dose. Without a technical effect associated with the claimed difference(s), the solution represents an arbitrary solution to the problem posed, thereby not involving an inventive step.
- 3.7 The same applies to dependent claims 2-11.

- 4 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.
- 4.1 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).
- 4.2 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).
- 4.3 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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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).

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



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For the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)
XP055651364, XP055651368, XP002789767