

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

Description, Pages

1-138 as originally filed

Sequence listings, SEQ ID NO

1-42 as originally filed

Claims, Numbers

1-14 received on 18-10-2018 with letter of 18-10-2018

Drawings, Sheets

1/34-34/34 as originally filed

The content of the letter dated 18.10. 2018 (L1) and the newly-filed claims have been carefully considered. Not all the objections raised in the previous communications have been overcome. The request for oral proceedings is therefore granted. The subject-matter to be discussed is outlined below.

1 The application

1.1 Chronology of the procedure

15.05.2012	Priority 1, US 61/647,442
15.03.2013	Priority 2, US 61/790,747
13.05.2013	PCT application PCT/US2013/040764
21.11.2013	Publication WO2013/173223
10.12.2014	Entry into regional phase, parent application EP13727687 (deemed to be withdrawn, closed on 07.03.2018)
06.09.2017	Filing of present divisional application (description, drawings, SL)
05.12.2017	Filing of claims of the divisional application
18.10.2018	Amended set of claims

1.2 **Independent claim 1** directed to

an [= any] anti-PD-1 antibody for use in treatment a human subject afflicted to a [= any] cancer in combination with an [= any] anti-CTLA-4 antibody wherein the treatment comprises an

(i) induction dosing schedule of

4 x q3w anti-PD1 and anti-CTLA4,

4 x q3w PD1 alone; followed by

(ii) maintenance dosing schedule of

8 x q(2-12)w; wherein the antibodies are to be administered at dosages of
PD1:CTLA4 = 1:3 or 3:1 mg/kg.

2 **AMENDMENTS** (Art. 76 EPC, Art. 123(2) EPC)

2.1 The set of claims currently on file meets the requirements of Art. 76(1) and 123(2) EPC.

3 **NOVELTY** (Art. 54 EPC)

3.1 The doses regimens according to claim 1 had not been known in the art prior to the application's disclosure. The subject-matter of claim 1 novel and meets the requirements of Art. 54 EPC. The same applies as well to the subject-matter of any claim/s referring back to said claim and/or being dependent thereof.

4 **INVENTIVE STEP** (Art. 56 EPC)

4.1 The attorney's arguments have been carefully considered and the content of description (cf. application: Example 17, p. 127, I. 22 - p. 128, I. 17, Fig. 14, Table 10) revised in detail.

It was stated that '... the specification clearly shows that the dosing regimens recited in claim 1 are associated with a surprising technical effect as they are superior to other dosing regimens that that... disclosed in the specification'. Reference was made to Table 10 that data of which 'clearly show that the dosing regimens of Cohorts 2 and 2a had superior effects as compared to those in cohorts 1 and 3'. Moreover, 'claimed dosing regimens had the highest 80% tumor reduction at 12 weeks, and the treatment of cohort 2 had the highest objective response rate of 53%. . .'. It was concluded that claim 1 was inventive over the alleged disclosure of document D10'.

4.2 The examining division does not share this point of view.

The study disclosed by D10 encompassed experimental cohorts C1 - C7, of which C2 received an induction of with anti-PD1 antibody nivolumab at 1 mg/kg and the anti-CTL-4 antibody ipilimumab at 3 mg/kg, IV 9 x q3w, and a maintenance of the same dosage q12w (cf. D10: p. 2 - 3).

The foremost difference between the teachings of D10 and the subject-matter of claim 1 lies in a variation of the induction regime, namely splitting it between anti-PD1 plus anti-CTLA4 and anti-PD1 alone.

The application did not show any technical effect/s associated with said difference/s over the state of the art over the whole breadth of the claim's scope.

In their letter of reply, in defence of inventive step, the Applicants referred to Table 10, saying that the specific regimen of nivolumab + ipilimumab resulted in a superior effect over the state of the art (D10).

The Division cannot follow this reasoning because:

- It is axiomatic that dosage and regimen depend on the affinity, pharmacokinetics and pharmacodynamics of the antibodies.
What is true for one antibody pair is rarely true for another.
Claim 1 is not limited to the nivolumab + ipilimumab.
- There is no comparison between the regimen of D10 and of claim 1. Specifically, the two variants of the induction phase have not been compared. The fact that cohorts 2 + 2a are better than cohorts 1 + 3 is not really pertinent to the issue in hand.
- Applicants have asserted that the characterization of D10 set out by the Division is not correct – but have not explained in what respect.
- Unless the variation in question is linked to a surprising technical effect, it is considered as arbitrary and therefore not inventive (Art. 56 EPC).

5 **SUFFICIENCY of DISCLOSURE** (Art. 83 EPC) / **CLARITY** / **SUPPORT** (Art. 84 EPC)

- 5.1 In view of the lack of any demonstrated technical effects over the state of the art, i.e. clear evidence of (better) efficacy of generic combinations of anti-PD1 and anti-CTL-4 antibodies for the treatment of any cancer, there is lack of support and sufficiency of disclosure.

The requirements of Art. 83 EPC and Art. 84 EPC are not met.

- 5.2 Moreover, the wording of claim 1 is not in the proper medical use format required by Art. 54(5) EPC, which is 'compound X for use in the treatment of disease Y in subject Z, and not 'compound x for use in treating subject Z with disease Y'.
- 5.3 Claim attempts to define the respective subject-matter by means of a result to be achieved. However, if there is a superior effect - as alleged - all of the technical features essential to achieve it must be included in the independent claim. It is not allowable to let the independent claim 1 deliberately vague and then rely on a result to be achieved in a dependent claim (cf. Guidelines, F-IV 4.10.)

6 **CONCLUSION**

- 6.1 To overcome the above objections:

The claims must be restricted to the indicated regimen of nivolumab and ipilimumab for the treatment off MEL.

Data, or at least a cogent explanation, must be provided to indicate why the variation in the induction phase leads to an improvement over known regimens.

- 6.2 In the circumstances, it is clear that either Applicants can provide these remedies or not. If they can provide the remedies, than things will fall into place. If not, the Division will have to refuse the application.

It is not expedient to continue to exchange communications in writing.

Oral proceedings are indicated and therefore, Applicants are invited to a hearing in accordance with Art. 116 EPC.

- 6.3 If/when making submissions, please be mindful of the rights, limitations, prerogatives and requirements of Rule 137 EPC.