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BY E-FILING

European (EP) Patent Application No: 22196038.8
Applicant(s): Bristol-Myers Squibb Company
Mewburn Ref: 008325144

I write in response to the communication under Rules 69 and 70a(1) EPC dated 24 April 2023.

The examination and designation fees are being paid using the form 1038E accompanying this letter, which authorises the EPO to debit the fees from our deposit account.

In the event that the EPO believes that a fee amount in the 1038E is incorrect and/or that additional fees are due, the EPO is authorised to debit the shortfall from deposit account no. 2805.0013 under reference "SHORTFALL".

The remainder of this letter addresses the objections set out in the European search opinion.

Amendments

Amended claims 1 to 7 are filed now, to replace all claims on file. A marked-up copy of the claims showing the amendments is attached for the examiner's reference.

Claim 1 is amended to specify the anti-CTLA-4 antibody as "*ipilimumab*". The feature is taken from previous claim 4.

Claim 2 remains unchanged.

In **claim 3**, a typographical error in "*one of more*" is rectified.

In the **remaining claims**, adjustments are made to the claim numbering and dependencies.

For conciseness reasons, the wording throughout the claims is simplified by substituting "*anti-PD-1 antibody*" with "*nivolumab*".

To avoid unnecessary duplication of effort I request that amendment of the description be deferred until an allowable claim set is agreed upon with the examiner.

Novelty and Inventive Step

The examiner acknowledges that the subject matter of the previous claims is novel over the cited prior art. However, they assert that it is not based on an inventive step in view of the Clinical Trial NCT01024231 announcement dated April 30, 2012 (**D10**). Briefly, the Examiner objects that the claims are “*not limited to the combination of nivolumab and ipilimumab*” and asserts that the variation in the dosing regimen compared to **D10** is arbitrary, unless the applicant provides “*a cogent explanation, and indicate[s] why the variation in the induction phase leads to an improvement over known regimens*”.

We respectfully disagree with the examiner’s objections. However, solely to advance prosecution, claim 1 is amended to specify that the anti-CTLA-4 antibody is ipilimumab, rendering the examiner’s objection in this regard moot.

Furthermore, the dosing regimen recited in present claim 1, including the variation in the induction phase, provides superior results that would not have been expected in view of the references cited by the examiner, e.g., **D10**. In particular, Table 10 of the specification shows the effects of four different dosing regimens on patients, with cohort 2 corresponding to the dosing regimen recited in amended claim 1. Cohorts 1, 2a, and 3 are three different regimens that were tested. The data in Table 10 clearly show that the dosing regimen of Cohort 2 has superior effects as compared to those of cohorts 1, 2a, and 3. The claimed dosing regimen had the highest rate of 80% tumor reduction at 12 weeks (41%) and the highest objective response rate (53%) of any of the dosing regimens tested. These results clearly show that not all dosing regimens of nivolumab and ipilimumab will have an equal impact on the efficacy of the therapy. And, the dosing regimen recited in claim 1 is superior to the other regimens tested in the specification. This outcome would not have been expected by the person of ordinary skill in the art. The skilled person would therefore not have been led to arrive at the claimed invention in an obvious manner.

Therefore, the subject matter of present claim 1 is inventive over the alleged teaching of **D10**. The same applies to claims 2-7 which depend directly or indirectly from claim 1 and thus include every element of claim 1.

Final Remarks

I believe the claims are now in order for allowance. If any minor points remain outstanding, then I invite the examiner to telephone me in order that they may be resolved efficiently.

Precautionary Statements

I ask the examiner to discuss with me any amendments that the Examining Division intends to make to the claims before issuing the Rule 71(3) EPC communication. I refer to the Guidelines at C-V 1.1, which suggest that the Examining Division should only make amendments which the

applicant can reasonably be expected to accept. Amendments that affect the scope of the claims are unlikely to be acceptable.

As a routine precaution, I request oral proceedings under Art 116 EPC, to take place only in the event that the Examining Division forms the intention to refuse this application. For compliance with Art 113(1) EPC I request that, before any summons to oral proceedings is issued, the applicant be given a proper opportunity to reply in writing to any objection raised by the Examining Division, especially any objection based on prior art not previously referred to in the examination.

Amendments made during the prosecution of this application are not to be interpreted as acknowledgement of the validity of any objection, nor as acknowledgement that any citation against the application is material to the patentability of the application.

In this application, unless expressly stated otherwise, the cancellation, abandonment or amendment of any claim or any amendment of the description does not amount to abandonment of any subject matter in the application, and the applicant reserves the right to pursue some or all of such subject matter in this application, any resulting patent, or in one or more divisional applications. Additionally, the applicant reserves the right to file divisional applications in respect of any subject matter in the application as filed.

Yours faithfully

/ Thomas Wolter /

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Encl: Amended claims 1 to 7
Copy claims marked up to show amendments

TXW/APK/dxk