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Title of invention:
DETERMINANTS OF CANCER RESPONSE TO IMMUNOTHERAPY BY PD-1 BLOCKADE

Applicant:
Memorial Sloan Kettering Cancer Center

Headword:
Determinants of cancer response to immunotherapy/MEMORIAL SLOAN KETTERING CANCER CENTER

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Main request and auxiliary requests 1 to 5 - added subject-matter (yes)

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Catchword:

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Case Number: T 1776/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 February 2024

Appellant: (Applicant)	Memorial Sloan Kettering Cancer Center 1275 York Avenue New York, NY 10065 (US)
Representative:	Truscott, Glyn Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 16 April 2021 refusing European patent application No. 15861224.2 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	T. Sommerfeld
Members:	D. Pilat
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent application 15 861 224.2 was filed as international application and published as WO 2016/081947.

II. The examining division found that the subject matter of claim 1 of the main request and of auxiliary requests 1 to 4 before it contravened Article 123(2) EPC. The application was refused.

III. The applicant (appellant) lodged an appeal and requests that the decision under appeal be set aside and amended such that a patent be granted on the basis of the claims of the main request or of auxiliary requests 1 to 4, all filed during examination and re-submitted with the grounds of appeal, or on the basis of new auxiliary request 5, filed with the grounds of appeal.

IV. The arguments of the appellant, insofar as relevant to the decision, may be summarised as follows:

The patent application was directed to determinants of cancer response to immunotherapy, aimed at predicting the likelihood of a favourable response to cancer immunotherapy by using the mutational load in patients, thereby determining whether patients undergoing a known immunotherapy would benefit from an appropriate treatment or not (paragraph [3]). The number of mutations, especially a high number of nonsynonymous mutations, identified patients who were candidates for treatment with an immune checkpoint modulator (paragraph [8]). A link between pembrolizumab, lung cancer and mutational characteristics was disclosed in paragraphs [156] and [176]. The three features lung

cancer, pembrolizumab, and the ≥178 nonsynonymous mutation marker were linked and disclosed together in paragraph [160]. The detection of "≥178 nonsynonymous mutations" in a lung cancer sample was explicitly described in paragraphs [31], [160] and [161]. Lung cancer and pembrolizumab were disclosed as preferred indication and treatment (claims 64, 68, 85 and 88). The mere reformulation of methods of treatment disclosed in the patent application (paragraph [132]) to comply with the wording of the second medical type claim format could not offend the requirements of Article 123(2) EPC.

Reasons for the Decision

Main Request
Article 123(2) EPC - claim 1

1. Claim 1 of the main request is identical to claim 1 of of the main request dealt with in the decision under appeal. The examining division found that claim 1 did not meet the requirements of Article 123(2) EPC.

The board agrees with the conclusions of the examining division (Article 15(8) RPBA).

2. Claim 1 of the main request reads as follows:

"1. An anti-PD-1 antibody for use in a method of treating lung cancer in a human subject, wherein the anti-PD-1 antibody is pembrolizumab,

wherein the subject is identified for treatment by a method comprising:

detecting ≥178 nonsynonymous mutations in a lung cancer sample from the subject and

identifying the subject as a candidate for treatment."

3. The appellant indicates a large number of passages in the application as filed as basis for this claim, namely:

- paragraphs [31], [160] and [161] for the feature "detecting ≥178 nonsynonymous mutations";
- the title of the application and paragraph [3] teaching that it is possible to predict the response of a cancer patient to immunotherapy, in particular immunotherapy by PD-1 blockade;
- paragraphs [17], [19], [102], [118], [126], [143] and claims 85, 88 95 and 103, as well as the Examples starting at paragraph [152] for the use of the anti-PD1 antibody pembrolizumab;
- paragraphs [15], [21], [24], [106], [107], [115], [117] and claims 13, 14, 26, 27, 40, 41, 55, 56, 61, 62, 81, 91, 99 and 109, as well as the examples starting at paragraph [152] for lung cancers;
- paragraphs [3], [8] and claim 68 teaching that a high number of nonsynonymous mutations identifies the subject as a candidate for treatment;
- paragraph [156] disclosing that lung cancer patients treated with pembrolizumab are defined by exemplary mutational characteristics, followed by paragraph [160] defining those mutational characteristics.

4. However, while these passages may provide basis for each of the features of the claim, there is no basis in the application as filed for the claimed combination of features.

5. None of the originally filed claims indicates detection of ≥178 nonsynonymous mutations in a lung cancer sample from the subject, so they cannot serve as a basis on their own. The only passages in the application as filed referring to the "≥178 nonsynonymous mutations" threshold are indeed paragraphs [31], [160] and [161]. Paragraph [31] states in its first sentence that "Figures 1A-1G shows Nonsynonymous mutation burden predicts clinical benefit with anti-PD-1 therapy". It then goes on describing Figures 1A to 1G and indicating the median values for nonsynonymous mutation burden in tumors with "durable clinical benefit" (DCB) compared to those with "no durable benefit" (NDB). In the middle of the paragraph it is stated, in relation to Figure 1E, that "Cut-off of ≥178 nonsynonymous mutations is designated by triangle". Figures 1A to 1B are further discussed in Example 1, which includes paragraphs [160] and [161] and thus the other two references to the "≥178 nonsynonymous mutations" threshold. However, none of these passages teach treatment of a subgroup of patients which is characterised by having ≥178 nonsynonymous mutations. Contrary to the appellant's arguments, Example 1 does not provide all features of claim 1 in combination. The passages disclosing the "≥178 nonsynonymous mutations" threshold may render obvious that such a patient group is particularly suitable for treatment with pembrolizumab, but the standard for Article 123(2) EPC is direct and unambiguous disclosure and not potential obviousness.

6. None of the many passages indicated by the appellant can be combined with any of the above passages to provide a basis for the claimed subject-matter. First, most of them also only relate to methods of diagnostic prediction of therapeutic response and not to methods

of treatment. This is apparent, for example, from the first sentence of the Summary of the Invention at paragraph [3] "The present invention encompasses the discovery that the likelihood of a favorable response to cancer immunotherapy can be predicted". The anti-PD1 antibody pembrolizumab is disclosed at paragraphs [17], [19], [102], [118], [126], [143] and claims 85, 88, 95 and 103 of the application as filed, and in the Examples starting at paragraph [152]. However, with the exception of paragraph [19] and claims 88 and 103 (see below), all these passages are in the context of identifying a candidate subject for treatment or of characterising/predicting treatment responsiveness, not of methods of treatment, and none of them indicates the value of ≥178 for the tumor burden of nonsynonymous mutations. As to the passages disclosing lung cancers, again, with the exception of paragraph [24] and claims 61, 62, 99 and 109 (see below), none of them is related to treatment: paragraphs [15], [21], [24], [106], [107], [115], [117] and claims 13, 14, 26, 27, 40, 41, 55, 56, 61, 62, 81, 91, 99 and 109 of the application as filed, and examples starting at paragraph [152].

7. Finally, none of the passages which are directed to methods of treatment disclose treatment of lung cancer with pembrolizumab; in particular, claim 103, which discloses treatment with pembrolizumab, does not refer back to claim 99, defining the cancer as "comprising lung carcinoma" (which is not necessarily identical to "lung cancer" as in the claim); claim 88, which also discloses treatment with pembrolizumab, refers back (directly or indirectly) to claims 64, and 83 to 85, none of them disclosing lung cancer. On the other hand, the claims that are directed to lung cancer (claims 61, 62, 99 and 109) either do not encompass the diagnostic part of the claim (claims 61 and 62) or do not disclose

the specific mutation profile of the claim (claims 99 and 109). The same considerations apply to paragraphs [19] and [24].

8. Accordingly, there is no teaching of all the features of claim 1 in combination in the application as filed. In view of this finding it is not necessary to discuss whether "marker(s) of high mutations", "high number of nonsynonymous mutations", "high neoantigen burden", "high nonsynonymous burden", "high numbers of neoepitopes", "high (somatic) mutation load", "high number(s) of mutations", "high neoepitope/mutational load(s)" or "high marker of mutations" can be considered necessarily and unequivocally identical to "≥178 nonsynonymous mutations".

9. The appellant also argues that the entire application is directed to determining response to immunotherapy with the aim of identifying patients that can be treated and that it would therefore be bizarre to identify such patients but then not treat them.

While the board agrees, this is again a question of obviousness but what counts for Article 123(2) EPC is what is directly and unambiguously disclosed in the application as filed. As argued by the appellant, it is true that several passages in the application as filed are also directed to treatment, e.g. paragraphs [17], [19], [143] and [176] and Example 1. However, as explained above, they do not teach the combination of all features of claim 1. For example, while paragraph [176], which is part of Example 4, discloses treatment of lung cancer patients with pembrolizumab, it does not teach the "≥178 nonsynonymous mutations" threshold or any other threshold at all.

10. Contrary to the appellant, there is also no link between the use of pembrolizumab for the treatment of lung cancer patients and any one of the particular mutational characteristics set out in paragraphs [156] and [160] of Example 1, and paragraph [176] of Example 4 of the patent application.

11. Example 1 relates to an analysis of the mutational landscape of tumors from patients with diverse clinical outcomes to pembrolizumab (Title), which concludes that a higher somatic nonsynonymous mutation burden was found to be predictive of the clinical efficacy of anti-PD1 therapy (e.g. pembrolizumab), in terms of durable clinical benefit (DCB), objective response rate (ORR), progression free survival, in both the discovery and validation cohorts in lung cancer patients (paragraphs [158], [159], Fig 1F). One of the hallmarks of patients responding favourably or poorly to an immune checkpoint modulator, for predicting clinical efficacy of anti-PD1 therapy, was an overall higher somatic nonsynonymous mutation burden. A median of either 200 nonsynonymous mutations per sample or a median number of 302 and 244 nonsynonymous mutations in patients with DCB in the discovery and validation cohorts, respectively, supported this view (paragraphs [158] and [159]). Another hallmark was the cut-off point of ≥178 nonsynonymous mutation burden in patients, derived from an area under the receiver characteristic curve (AUC) of 87% (paragraph [160], Fig. 1E) between the number of nonsynonymous mutations and the DCB in the discovery cohort, which combined the maximum sensitivity and best specificity of 100% and 67%, respectively, with a likelihood ratio for DCB of 3.0. Using the same cut-off for all patients in the validation cohort allowed the identification of 75% of patients with DCB, albeit with lower sensitivity and

higher specificity than in the discovery cohort (86% and 75%, respectively). However, there were exceptions (paragraph [161]). Five of 18 tumour patients harbouring ≥178 non-synonymous mutations had no durable benefit (NDB) and one tumour patient harbouring 56 non-synonymous mutations had a partial response to pembrolizumab. The rate of DCB in patients with tumors harbouring less than 178 nonsynonymous mutations was 14% (paragraph [160], Fig. 1E).

12. In the light of this teaching, first, the skilled person can only directly and unambiguously derive from Example 1 that lung cancer patients treated with pembrolizumab in the discovery and validation cohorts with DCB or in cohorts independent of the observed patient's clinical outcome have different median values of nonsynonymous mutations and that the cut-off point of ≥178 nonsynonymous mutation burden identified as optimal cut-off value in patients could be applied to the validation cohort, albeit with an altered sensitivity and specificity rate for identifying patients with DCB. The skilled person is also taught that there are exceptions to this correlation. Second, the identification of a subject likely to respond to treatment with an immune checkpoint modulator, comprising detecting a marker of high mutations in a cancer sample from a subject, does not, however, disclose a method of treating the identified candidate subjects. Thus, there is no implicit disclosure of a method of treating only a selected subset of lung cancer patients harbouring ≥178 nonsynonymous mutations with pembrolizumab in the patent application as filed. Identifying patients who are likely to respond to pembrolizumab with DCB as candidates for pembrolizumab treatment is not the same as using the predictive cut-off of ≥178 nonsynonymous mutations to select lung

cancer patients who are then treated with pembrolizumab. Hence, the subject-matter of claim 1 cannot be directly and unambiguously derived from Example 1 or any other passage of the application as filed.

13. Accordingly, although, as argued by the appellant, the invention provides methods for identifying cancer patients that are likely to respond favourably to treatment with an immune checkpoint modulator (patent application, paragraphs [132], [133], [143]) and that high mutation load can predict clinical efficacy of immunotherapy treatment for certain cancers (patent application, paragraph [109]), none of these passages constitute a direct and unambiguous disclosure of a method of treating lung cancer in a human subject with pembrolizumab who had been selected to have ≥178 nonsynonymous mutations in a lung cancer sample in accordance with claim 1.

14. Consequently, none of the above paragraphs or claims explicitly or implicitly disclose an anti-PD1 antibody pembrolizumab for use in a method of treating lung cancer in patients who have been selected to have ≥178 nonsynonymous mutations in a lung cancer sample.

15. Claim 1 of the main request therefore contravenes Article 123(2) EPC.

Auxiliary requests
Article 123(2) EPC - claim 1

16. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the antibody dosage and regimen is further specified: "wherein the method comprises administering the pembrolizumab to the

subject at 10mg/kg every 2-3 weeks or 2mg/kg every 3 weeks".

17. Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that the step of detecting ≥178 nonsynonymous mutations occurs "in one or more exomes".

18. Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 2 in that "lung cancer" has been replaced by "lung carcinoma".

19. Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 3 in that "lung carcinoma" has been further specified as "non-small cell lung carcinoma".

20. Claim 1 of auxiliary request 5 differs from claim 1 of auxiliary request 4 in that "non-small cell lung carcinoma" has been further defined as "stage IV non-small cell lung carcinoma".

21. Hence, in claim 1 of auxiliary requests 1 to 5, further features have been introduced such as administration regimen and dosage (in all requests), and further characterisation of the cancer and of the mutations. None of these amendments solves the issue of added subject-matter of the main request.

22. Consequently and in conclusion, neither the main request nor any of auxiliary requests 1 to 5 meet the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated