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Datasheet for the decision of 4 July 2024

Case Number: T 1754/22 - 3.3.08

Application Number: 14870360.6

Publication Number: 3079772

IPC: A61P35/00, G01N33/574

Language of the proceedings: EN

Title of invention:
IMMUNOHISTOCHEMICAL PROXIMITY ASSAY FOR PD-1 POSITIVE CELLS AND PD-LIGAND POSITIVE CELLS IN TUMOR TISSUE

Patent Proprietor:
Merck Sharp & Dohme LLC

Opponent:
Pajaro Limited

Headword:
Proximity assay/MERCK SHARP & DOHME

Relevant legal provisions:
EPC Art. 123(2)
RPBA 2020 Art. 13(1), 13(2)

Keyword:
Main request - added matter (yes)
Auxiliary request 1 - amendment to appeal case - admittance (no)

Decisions cited:
G 0003/89, G 0011/91, G 0002/10

Catchword:
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Case Number: T 1754/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 4 July 2024

Appellant: (Opponent)	Pajaro Limited 12 New Fetter Lane London EC4A 1JP (GB)
Representative:	Alt, Michael Bird & Bird LLP Maximiliansplatz 22 80333 München (DE)
Respondent: (Patent Proprietor)	Merck Sharp & Dohme LLC 126 East Lincoln Avenue Rahway, New Jersey 07065 (US)
Representative:	Merck Sharp & Dohme LLC 120 Moorgate London EC2M 6UR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 May 2022 concerning maintenance of the European Patent No. 3079772 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	B. Claes
	A. Bacchin

Summary of Facts and Submissions

I. The appeal lodged by the opponent (appellant) lies from the interlocutory decision of the opposition division that European patent No. 3 079 772 with the set of claims of the main request, and the invention to which it relates, met the requirements of the EPC. The patent was granted based on European patent application No. 14 870 360.6, which was filed as an international application under the PCT and published as WO 2015/088930 (application as filed).

II. With the statement of grounds of appeal the appellant argued, *inter alia*, that claim 1 of the main request did not fulfil the requirements of Article 123(2) EPC.

III. With the reply to the appeal, the patent proprietor (respondent) re-submitted the main request and also submitted an auxiliary request.

IV. The parties were summoned to oral proceedings and the board subsequently issued a communication under Article 15(1) RPBA providing the board's preliminary appreciation of substantive and legal matters concerning the appeal. The board expressed doubts, *inter alia*, on issues of added subject-matter.

V. During the oral proceedings the respondent replaced the auxiliary request filed with the grounds of appeal (see section III.) with a new auxiliary request 1.

VI. The submissions and arguments of the parties to the appeal, in so far as they are relevant to the present decision, are taken into consideration in the reasons for the decision of the board set out below.

VII. The parties' requests in so far as relevant to the present decision were as follows:

The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed (main request), or alternatively, that the decision under appeal be set aside and the patent be maintained with the set of claims of auxiliary request 1, filed at the oral proceedings.

Reasons for the Decision

Main request - claim 1 - added subject-matter

1. Claim 1 of the main request reads:

"A process for testing a tumor sample for the presence or absence of a PD-1:PD-Ligand proximity biomarker that is predictive of an anti-tumor response to treatment with a PD-1 antagonist, which comprises:

(a) obtaining a PD-1:PD-Ligand proximity score for the tumor sample by the process of; obtaining, by imaging, an image of tissue that has been removed from the tumor sample and immunohistochemically stained for PD-1 and PD-Ligand expression in a manner that allows stained PD-1 cells to be distinguished from stained PD-Ligand cells; defining in the image one or more regions of interest (ROIs) that comprises neoplastic cells and associated stroma, wherein substantially all of the neoplastic cells and associated stroma in the image are

contained in the defined ROIs; randomly creating across each defined ROI a plurality of subregions of substantially the same shape and size, wherein each of the subregions defines an area that is large enough to include a spatially proximal pair of a stained PD-1 cell and a stained PD-Ligand cell and small enough to exclude pairs of stained PD-1 and PD-Ligand cells that are not spatially proximal; and calculating the percent of all of the subregions that are positive for both stained PD-1 cells and stained PD-Ligand cells to generate the PD-1:PD-Ligand proximity score for the tumor sample;
(b) comparing the PD-1:PD-Ligand proximity score for the tumor sample with a threshold PD-1:PD-Ligand proximity score;
(c) classifying the tumor as biomarker positive or biomarker negative, wherein if the proximity score for the tumor sample is equal to or greater than the threshold proximity score, then the tumor is classified as positive for the PD-1:PD-Ligand proximity biomarker, and if the obtained score is less than the threshold score, then the tumor is classified as negative for the PD-1:PD-Ligand proximity biomarker; and
(d) using the classification to predict if a subject is likely to respond to a PD-1 antagonist wherein the PD-1 antagonist is a monoclonal antibody that inhibits the binding of PD-L1 to PD-1, or the PD-1 antagonist is a monoclonal antibody that inhibits the binding of PD-L1 and PD-L2 to PD-1, or the PD-1 antagonist is MK-3475 or nivolumab."

2. A process is claimed for testing a tumour sample for the presence or absence of a "PD-1:PD-Ligand proximity biomarker" for the expression of PD-1 (programmed cell death 1 polypeptide) on T-cells and the expression of a PD-1 ligand (PD-L1) on the tumour cells that is

predictive of an anti-tumour response to treatment with a PD-1 antagonist (see section I). The patent discloses in this context that quantifying the number of PD-1-expressing cells that are spatially proximal to PD-L1-expressing cells in tumour samples is useful for predicting which patients are most likely to respond to treatment with a PD-1 antagonist (see paragraph [0007]).

3. The claimed process comprises four steps. In the first one, step (a), a "PD-1:PD-Ligand proximity score" is generated for the tumour sample by a multiparametric immunohistochemical proximity assay generating a "proximity score" for a tumour tissue section that represents the number of tumour-associated pairs of spatially proximal PD-1+ cells and PD-L1+ cells, i.e. cells that are situated within a physiologically relevant distance of each other. In the second step, step (b), this score is compared with a threshold PD-1:PD-Ligand proximity score and, subsequently, in a third step, step (c), the tumour is classified as biomarker-positive or biomarker-negative.

4. The fourth step, step (d), of the claim requires "using the classification [obtained in step (c)] to predict if a subject is likely to respond to a PD-1 antagonist wherein the PD-1 antagonist is a monoclonal antibody that inhibits the binding of PD-L1 to PD-1, or the PD-1 antagonist is a monoclonal antibody that inhibits the binding of PD-L1 and PD-L2 to PD-1, or the PD-1 antagonist is MK-3475 or nivolumab."

5. On appeal the appellant reiterated its view, *inter alia*, that there is no basis in the application as filed for process step (d), i.e. the prediction made on the basis of the classification obtained by

comparing the measured with the threshold proximity score.

6. The gold standard for assessing compliance with Article 123(2) EPC is that any amendment to the parts of a European patent application as filed or a European patent relating to the disclosure is subject to the mandatory prohibition on extension laid down in Article 123(2) EPC. Therefore, irrespective of the context, an amendment can only be made within the limits of what a skilled person would derive directly and unambiguously, explicitly or implicitly, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed. After the amendment, the skilled person must not be presented with new technical information (see decisions G 3/89, OJ EPO 1993, 117; G 11/91, OJ EPO 1993, 125; and G 2/10, OJ EPO 2012, 376; as well as "Case Law of the Boards of Appeal of the EPO", 10th edition 2022, "CLBA", II.E.1.1).

7. For the case in hand, it thus needs to be established whether the skilled person would derive directly and unambiguously from the application as filed a process step using the classification established in step (c), i.e. the tumour being classified as biomarker-positive or bio-marker negative, to predict if a subject is likely to respond to a PD-1 antagonist (step (d)).

8. It is uncontested that there is no *verbatim* disclosure of step (d) in the application as filed. On appeal, however, the respondent has submitted that the disclosure in paragraphs [0001], [0007] and [0024] of the application as filed provided the required basis for the features of step (d).

9. Paragraph [0001] reads: "*The present invention relates generally to the treatment of cancer. In particular, the invention relates to the identification of biomarkers for identifying patients whose tumors are likely to respond to treatment with an antagonist of Programmed Death 1 (PD-1)*." Although this paragraph refers to the identification of biomarkers for identifying patients whose tumours are likely to be responsive to PD-1 antagonists, it fails to directly and unambiguously disclose the use of the biomarker-positive or biomarker-negative classification established in steps (a) to (c) to predict if a subject is likely to respond to a PD-1 antagonist.

10. Paragraph [0007] reads: "*The inventors contemplate that this IHC proximity assay and the proximity scores generated thereby will be useful to identify proximity threshold scores that can serve as biomarkers to predict response of multiple tumor types to treatment with a PD-1 antagonist.*" Similarly to the case of paragraph [0001] discussed above, although paragraph [0007] refers to the identification of biomarkers for predicting the responsiveness of patients with tumours to PD-1 antagonists, it also fails to directly and unambiguously disclose using the *classification* of the tumour established in steps (a) to (c) of the claim to predict if a subject is likely to respond to a PD-1 antagonist.

11. Paragraph [0024] reads: "*In all of the above aspects and embodiments of the invention, the PD-1 antagonist inhibits the binding of PD-L1 to PD-1, and preferably also inhibits the binding of PD-L2 to PD-1. In some preferred embodiments, the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to PD-1 or to PD-L1*

and blocks the binding of PD-L1 to PD-1. In particularly preferred embodiments, the PD-1 antagonist is MK-3475 or nivolumab." The board is also unable to deduce from this paragraph that the skilled person would directly and unambiguously derive a process step using the *classification* of the tumour established in steps (a) to (c) of the claim to predict if a subject is likely to respond to a PD-1 antagonist.

12. For the sake of completeness, the board notes that there is also a reference in claims 18 and 20 (i) and in paragraphs [0224] to [0226] (ii) of the application as filed to the specific PD-1 antagonists referred to in step (d) of claim 1.

13. As regards (i), however, claim 18 as filed is directed to "[T]he composition of claim 16, or the drug product of claim 17" and not to a process for testing a tumour sample for the presence or absence of a "PD-1:PD-Ligand proximity biomarker" for the expression of PD-1 (programmed cell death 1 polypeptide) on T-cells and the expression of a PD-1 ligand (PD-L1) on the tumour cells that is predictive of an anti-tumour response to treatment with a PD-1 antagonist (claim 13 as filed), let alone being directed to such a process including a process step of using the *classification* of the tumour established in steps (a) to (c) of the claim to predict if a subject is likely to respond to a PD-1 antagonist. As regards claim 20 as filed, on the other hand, although it refers back to all previous claims (including claim 13), it is further limited by the feature "wherein the tumour sample is from a human diagnosed with melanoma or NSCLC", a limitation which is not present in claim 1 of the main request.

14. As regards (ii), equally, the embodiments disclosed in the cited paragraphs [0224] to [0226] are of defined compositions or drug products as disclosed in paragraphs [0022] and [0024] and those embodiments do not refer to a process for testing a tumour sample for responsiveness to a PD-1 antagonist including a process step using the *classification* of the tumour established in steps (a) to (c) of the claim to predict if a subject is likely to respond to a PD-1 antagonist.

15. In view of the above considerations, the board holds that the skilled person would not derive directly and unambiguously from the application as filed a process step using the classification established in step (c) to predict if a subject is likely to respond to a PD-1 antagonist. Claim 1 thus fails to meet the requirements of Article 123(2) EPC.

Auxiliary request 1 - admittance (Article 13(2) RPBA)

16. The respondent filed auxiliary request 1 during the oral proceedings before the board (see section V.). Claim 1 of auxiliary request 1 is identical to claim 1 of the main request (see section I.) but for the amendment in step (d) by deletion thus now reading "using the classification to predict if a subject is likely to respond to MK-3475 or nivolumab."

17. It is uncontested that auxiliary request 1 constitutes an amendment to the appellant's case which is subject to the provisions of Article 13(2) RPBA. This article implements the third level of the convergent approach applicable in appeal proceedings and thus imposes the most stringent limitations on a party wishing to amend its appeal case at an advanced stage of the proceedings. It provides that any amendment to a

party's appeal case made at this stage of the proceedings will, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons.

18. The respondent submitted that the amendment in the new auxiliary request 1 constituted a simple mere deletion of an alternative, not a change of the legal and factual framework of the opposition appeal proceedings. Furthermore, the respondent was surprised by the board's preliminary opinion on the question of added subject-matter, which departed from the conclusion reached by the opposition division in its decision and thus amounted to exceptional circumstances.

19. However, no exceptional circumstances are apparent in the present case. The objection of added subject-matter concerning step (d) of the claimed process had already been raised and addressed in the opposition proceedings, and a positive conclusion had been reached in that respect in the decision under appeal (see the appealed decision, point 6.1.2). It was then reiterated by the appellant at the start of the appeal proceedings, namely in the appellant's grounds of appeal (see section II.). The issue was additionally pointed out in the board's communication under Article 15(1) RPBA (see section IV.). The fact that the board, merely agreeing to an objection raised by the then opponent in opposition proceedings, came to a different conclusion from the opposition division on this point does not, as such, constitute exceptional circumstances. Indeed, it is a possible outcome that the respondent could have expected. The respondent also had opportunities to file the new auxiliary request 1 earlier, even in the appeal, without waiting until the

last stage of the appeal proceedings and filing it in the oral proceedings.

20. In addition, at the third level of the convergent approach, the board may also rely on criteria applicable at the second level of the convergent approach, i.e. under Article 13(1) RPBA. According to the latter, the board has to exercise its discretion in view of, *inter alia*, whether the party has demonstrated that the amendment, *prima facie*, overcomes the issues raised and does not give rise to new objections (see the explanatory remarks to the RPBA 2020, Article 13(2), in Supplementary publication 2, OJ EPO 2020, page 60).

21. The board decided that the skilled person would not derive directly and unambiguously from the application as filed a process step using the classification established in step (c) to predict if a subject is likely to respond to a PD-1 antagonist from the application as filed (see point 15.). Although now more stringently formulated (see point 16.), step (d) of claim 1 of auxiliary request 1 is still a process step using the classification established in step (c) to predict if a subject is likely to respond to a PD-1 antagonist, for which no basis exists in the application as filed. The respondent has not argued differently. There is thus no room for the board to conclude that amended claim 1, *prima facie*, overcomes the added subject-matter problem which led the board to conclude that claim 1 of the main request infringed the requirements of Article 123(2) EPC.

22. Accordingly, the board did not admit auxiliary request 1 into the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

A. Vottner T. Sommerfeld

Decision electronically authenticated