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Datasheet for the decision of 15 May 2020

Case Number: T 3196/19 - 3.3.08

Application Number: 10075561.0

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Language of the proceedings: EN

Title of invention:

Assays for screening anti-pd-1 antibodies and uses thereof

Applicant:

Dana-Farber Cancer Institute, Inc.
Genetics Institute, LLC

Headword:

Anti-PD-1 antibody/DANA-FARBER GENETICS INSTITUTE

Relevant legal provisions:

EPC Art. 76(1), 111(1), 112a(2)(c), 113, 123(2)
EPC R. 106, 137(3)
RPBA Art. 12(4)
RPBA 2020 Art. 13(1)

Keyword:
Main request and auxiliary requests 1 to 7 - added subject-matter (yes);
Auxiliary requests 8 to 14 - admitted into the appeal proceedings (no);
Appellant's right to be heard - violation (no);

Decisions cited:
G 0002/10, T 0054/82

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 3196/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 15 May 2020

Appellant: (Applicant 1)	Dana-Farber Cancer Institute, Inc. 450 Brookline Avenue Boston, MA 02215 (US)
Appellant: (Applicant 2)	Genetics Institute, LLC 87 Cambridge Park Drive Cambridge, MA 02140 (US)
Representative:	Jolink, Mark EP&C P.O. Box 3241 2280 GE Rijswijk (NL)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 12 November 2019 refusing European patent application No. 10075561.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	J. Geschwind

Summary of Facts and Submissions

I. European patent application no. 10 075 561.0 (published as EP 2 360 254; hereinafter "the patent application") is a divisional application of the earlier European patent application no. 00 959 394.8 (published as EP 1 210 428) which is based on the international patent application PCT/US00/23347 published under the PCT as WO 01/14557 (hereinafter "the earlier patent application").

II. An examining division considered the main request and auxiliary requests 1 to 7 to contravene Articles 76(1) and 123(2) EPC. Auxiliary requests 8 to 10 were not admitted into the proceedings (Rule 137(3) EPC) and, accordingly, the patent application was refused.

III. The applicant (appellant) lodged an appeal, filed new documentary evidence, a main request and auxiliary requests 1 to 14. The appellant requested to accelerate the appeal proceedings and, as an auxiliary measure, oral proceedings. In further submissions, the appellant withdrew the main request and renumbered previous auxiliary requests 1 to 14 as main request and auxiliary requests 1 to 13, respectively.

IV. Appellant's request for acceleration of the appeal proceedings was granted by the board and oral proceedings were scheduled for 15 May 2020.

V. In a communication pursuant to Article 17 of the Rules of Procedure of the Boards of Appeal (RPBA 2020) (OJ EPO Supplement to Official Journal 1/2020, 42), the appellant was informed of the board's provisional opinion on the issues of the case, in particular, that:

i) the board was minded not to admit auxiliary requests 8 to 13 into the proceedings; ii) the main request and auxiliary requests 1 to 7 formed part of the appeal proceedings but appeared to contravene Articles 76(1) and 123(2) EPC; and iii) if any of auxiliary requests 11 to 13 were admitted into the proceedings, none of them appeared to fulfil the requirements of Articles 54 and 56 EPC. The board introduced new documentary evidence and, in view of these considerations, informed the appellant that the appeal was likely to be dismissed.

VI. Oral proceedings were held by video conference on 15 May 2020. During these proceedings, the appellant filed *via* e-mail an auxiliary request 14 and raised an objection under Rule 106 EPC with respect to a procedural defect under Article 112a, par. 2(c) EPC.

VII. Claim 1 of the **main request** reads as follows:

"1. An anti-human PD-1 antibody that inhibits signaling via PD-1 by inhibiting the interaction of human PD-1 and human B7-4, which is a human protein comprising the amino acid sequence shown in figure 3 or 4, for use in the treatment of a condition that would benefit from upregulation of an immune response, wherein the said condition is a tumour."

VIII. Claim 1 of **auxiliary request 1** reads as claim 1 of the main request, except that the antibody is defined as "a non-activating anti-human PD-1 antibody that inhibits signaling via ..." (underlined by the board).

IX. Claim 1 of **auxiliary request 2** is identical to claim 1 of the main request.

X. Claim 1 of **auxiliary request 3** reads as claim 1 of the main request, except that the antibody is defined as "a blocking antibody that recognizes human PD-1 and that inhibits signaling via ..." (underlined by the board).

XI. Claim 1 of **auxiliary request 4** reads as claim 1 of the main request, except that the antibody is defined as "a anti-human PD-1 antibody that inhibits signaling via PD-1 in an immune cell by inhibiting the interaction ..." (underlined by the board).

XII. Claim 1 of **auxiliary request 5** (mark-up copy) is identical to claim 1 of auxiliary request 1, while claim 1 of **auxiliary request 6** combines the amendments of auxiliary requests 1 and 4 (as claim 1 of the clean copy of auxiliary request 5).

XIII. Claim 1 of **auxiliary request 7** reads as follows:

"1. A non-activating anti- PD-1 antibody that inhibits signaling via PD-1 in an immune cell by inhibiting the interaction of PD-1 and B7-4, for use in the treatment of a condition that would benefit from upregulation of an immune response, wherein the said condition is a tumour."

XIV. Claim 1 of **auxiliary request 8** reads as claim 1 of the main request except for the deletion of the feature "wherein the said condition is a tumour".

XV. Claim 1 of **auxiliary request 9** reads as claim 1 of the main request, except that the feature "wherein the said condition is a tumour" is replaced by the feature "wherein the condition is chosen from the group consisting of a tumour, a neurological disease, or an immunosuppressive disease".

XVI. Claim 1 of **auxiliary request 10** reads as follows:

"1. A non-activating anti- PD-1 antibody that inhibits signaling via PD-1 in an immune cell, for use in the treatment of a condition that would benefit from upregulation of an immune response, wherein the said condition is a tumour."

XVII. Claim 1 of **auxiliary request 11** reads as follows:

"1. A non-activating anti- PD-1 antibody that inhibits the inhibitory activity of PD-1, for use in the treatment of a medical condition, wherein the use is for inducing immune responses against a tumor specific antigen."

XVIII. Claim 1 of **auxiliary request 12** reads as claim 1 of auxiliary request 11, except for the antibody being defined as "a blocking antibody that recognizes PD-1 and that inhibits the inhibitory activity of PD-1 ...".

XIX. Claim 1 of **auxiliary request 13** reads as follows:

"1. A non-activating anti- PD-1 antibody against PD-1 that prevents an inhibitory signal of PD-1 in immune cells, for use in the treatment of a medical condition, wherein the use is for upmodulation of an immune response".

XX. Claim 1 of **auxiliary request 14** reads as claim 1 of auxiliary request 7 except for the deletion of the feature "by inhibiting the interaction of PD-1 and B7-4".

XXI. The description, claims and Figures of the patent application are identical to those of the earlier patent application. References given in the appellant's submissions below and in the board's reasoning of this decision are only to the earlier patent application. Any deficiency identified in the earlier patent application (Article 76(1) EPC) is also relevant for the patent application (Article 123(2) EPC).

XXII. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request and auxiliary requests 1 to 7

Although the gold standard set out in the decision G 2/10 (OJ 2012, 376) had to be applied for assessing the compliance of the claimed subject-matter with Articles 76(1) and 123(2) EPC, the case law established also that the common general knowledge of the skilled person and the state of the art could also be taken into account when carrying out such assessment (T 54/82, OJ 1983, 446).

The functional similarity between CTLA4 and PD-1, as inhibitory receptors critical in the negative regulation of T cell responses, was identified in the earlier patent application (*inter alia*, page 3, lines 15 to 18, and page 9, lines 22 and 23). Based on this similarity, a skilled person would have applied the knowledge in the art about the CTLA4 receptor to the PD-1 receptor. Since, as shown by the prior art cited in the earlier patent application and by the evidence submitted in the statement of grounds of appeal, the blockage of the CTLA4 receptor by anti-CTLA4 antibodies was known in the art to result in the removal of an inhibitory signal and in upregulation of

the T cell immune responses, the skilled person would have applied this information to the PD-1 receptor and, indeed, to the interaction of the PD-1 receptor with the specific PD-1 ligands B7-4 shown in figures 3 and 4 of the earlier patent application.

A method for treating a subject - having a condition that would benefit from upregulation of an immune response - comprising the administration of an agent that inhibited signaling *via* PD-1 in an immune cell was disclosed on page 4, lines 28 to 32 of the earlier patent application. On the same page, the agent and the conditions were identified as being, *inter alia,* a blocking antibody and a tumour, respectively (page 4, lines 4 and 5 and lines 36 and 37). On page 9, line 29 to page 10, line 2, reference was made to the prevention of an inhibitory signal *via* PD-1 by using a non-activating anti-PD-1 antibody in immune cells and to the resulting upmodulation of the immune cell responses.

Methods for upregulating the immune responses were also described on page 82 of the earlier patent application. In lines 19 to 24 on this page, a non-activating anti-PD-1 antibody was defined as an agent that inhibited the interaction of B7-4 with an inhibitory receptor or an agent that inhibited transduction of an inhibitory signal *via* PD-1, that was therapeutically useful in situations where upregulation of antibody and cell mediated responses were beneficial. On page 85, lines 9 to 12, it was stated that immune responses could be stimulated by inhibiting signaling *via* the PD-1 receptor binding to B7-4 and, in lines 12 to 15, further reference was made to the induction of an immune response against a tumour specific antigen in a subject by administration of an agent that inhibited

the inhibitory activity of the PD-1 receptor. This agent was thus defined in the same terms as those found on pages 4 and 82 for defining a blocking anti-PD-1 antibody and a non-activating anti-PD-1 antibody, respectively. In light thereof and of the references to the functional similarity of the PD-1 receptor with the CTLA4 receptor, a skilled person - with a mind willing to understand - would have understood that these anti-PD-1 antibodies could be used in the treatment of a condition that would benefit from upregulation of an immune response, wherein said condition was a tumour, i.e. the subject-matter of claim 1 of the main request and of auxiliary requests 1 to 7.

Other features present in claim 1 of these requests were also disclosed in the earlier patent application, such as the features: human, the amino acid sequences of the human B7-4 ligand shown in figures 3 or 4, etc. Standard techniques known in the art for generating (human) antibodies were also disclosed in the earlier patent application. Example 9 (page 122) described the generation of human antibodies against B7-4 or PD-1. Example 13 (page 126) showed that the interaction of PD-1 with B7-4 inhibited T cell proliferation and cytokine secretion. Example 17 (page 131) disclosed the ability of anti-B7-4 and anti-PD-1 antibodies to inhibit the interaction of human B7-4 and human PD-1. There was also post-published evidence on file showing that anti-PD-1 antibodies such as those claimed in the main request and in auxiliary requests 1 to 7 were suitable for the treatment of tumours.

Admission of auxiliary requests 8 to 10

The feature "inhibiting the interaction of human PD-1 and human B7-4, which is a human protein comprising the

amino acid sequence shown in figure 3 or 4" was not present in auxiliary request 10. This auxiliary request had been filed at the oral proceedings at first instance but had not been admitted into the proceedings by the examining division.

The objection under Articles 76(1) and 123(2) EPC concerning the use of an anti-PD-1 antibody in the treatment of a tumour, had been raised by the examining division only in the Summons to attend the oral proceedings. There had been a limited time and opportunity for the appellant to react to this objection and to file auxiliary requests that took into account this objection. Moreover, there had been no discussion at first instance of the relevant disclosures on pages 4, 82 and 85 of the earlier patent application, wherein the "agent" used in the treatment of a tumour referred to on page 85 was defined in the same terms as those found on pages 4 and 82 of the earlier patent application, and wherein the "agent" was identified as "a blocking antibody" and "a non-activating antibody" that recognised PD-1, respectively. There was no reference in the decision under appeal to such a discussion and/or to these disclosures in the reasons given by the examining division for not admitting auxiliary request 10 into the proceedings.

In view of the board's comments in appeal proceedings, the examining division should have admitted auxiliary request 10 into the proceedings. Auxiliary request 10, filed at the oral proceedings at first instance, had not been properly examined by the examining division at the oral proceedings and thus, the examining division did not act reasonably by not admitting it into the proceedings. The examining division failed to exercise

a proper balance between procedural efficiency or economy and the appellant's right to have a reasonable opportunity to defend its arguments. The reasons given in the decision under appeal for not admitting auxiliary request 10 were neither detailed nor correct. Both auxiliary requests 9 and 10 were treated together, and there was only a general reference to the use of an anti-PD-1 antibody that inhibited signaling *via* PD-1 to treat a tumour. In light of the board's decision on the main request and auxiliary requests 1 to 7, this was not correct and auxiliary request 10 should have been admitted into the proceedings at first instance.

Objection under Article 112a(2)(c) EPC and Rule 106 EPC

The board decided not to admit auxiliary request 10 into the appeal proceedings and based its decision on point 6 of the Minutes of the oral proceedings at first instance. With respect to auxiliary request 10, point 6 of the Minutes merely stated that "recite again the treatment of tumor, re-introduce the same objections under Art. 76(1)/123(2) EPC which had been already discussed for the higher ranking claim requests". As established by the board in the appeal proceedings, this statement, with respect to the treatment of a tumour, was incorrect. The objection in point 6 of the Minutes to the reintroduction of objections that had already been overcome at earlier stages of the examination, was made only with respect to auxiliary request 8 but not auxiliary request 10. The fact that the board did not admit auxiliary request 10 into the appeal proceedings showed that the board had not properly considered this argument and therefore, appellant's right to be heard had been violated.

Admission of auxiliary requests 11 to 13

Auxiliary requests 11 to 13 were filed with the statement of grounds of appeal and thus, at the earliest stage of the appeal proceedings. They could not have been filed earlier because the objection under Articles 76(1) and 123(2) EPC was raised by the examining division at a late stage of the proceedings. The filing of these auxiliary requests was a direct response to the late explanation and reasoning given by the examining division for this objection at the oral proceedings and in the decision under appeal. The reasoning given by the examining division on page 5, last full paragraph of the decision under appeal was based on a wrong interpretation of the disclosures found under the heading "Upregulation of Immune Responses" on pages 82 to 86 of the earlier patent application. This wrong interpretation created a new situation that triggered the filing of auxiliary requests 11 to 13 by the appellant. These auxiliary requests took into account this reasoning and overcame the objection raised under Articles 76(1) and 123(2) EPC. The late reasoning given by the examining division was based on a wrong interpretation and fell short of a procedural defect.

The admission of auxiliary requests 11 to 13 into the appeal proceedings did not require to re-run or reopen the examination proceedings because they were based on the same definitions and context as those of the main request and auxiliary requests 1 to 7 which already formed part of the appeal proceedings. Indeed, they were not different alternative requests because a skilled person - with a mind willing to understand - would have understood, in light of the whole disclosure of the earlier patent application, that the terms

"inhibits signalling via PD-1" and "inhibits the interaction of PD-1 and B7-4" to be interchangeable. Moreover, since the claims of auxiliary requests 11 to 13 were drafted as second medical use claims, there was no need to limit them to "human" embodiments, a limitation introduced into other requests for overcoming a (first medical use) novelty objection over document (1). Thus, there was no need to reopen the discussion on the disclosure of document (1) and the objection of lack of novelty based thereupon raised at earlier stages of the proceedings.

Admission of auxiliary request 14 (amended auxiliary request 7)

Auxiliary request 14 was based on auxiliary request 7, an auxiliary request considered by the examining division and thus, already forming part of the appeal proceedings. The feature "inhibiting the interaction of PD-1 and B7-4" present in auxiliary request 7 was deleted in auxiliary request 14. This feature had not been properly discussed by the examining division but only in the appeal proceedings. Since claims 1 of both, auxiliary requests 7 and 14, were second medical use claims, there was no need to limit them to "human" embodiments. This limitation was introduced in other requests only for overcoming a (first medical use) novelty objection over document (1). Thus, both auxiliary requests 7 and 14 comprised the use of non-activating anti-PD-1 antibodies in animals for "the treatment of a condition that would benefit from upregulation of an immune response, wherein the said condition is a tumour". The scope of claim 1 of auxiliary request 14 was justified in light of the contribution of the earlier patent application to the prior art.

XXIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of any of the auxiliary requests 1 to 14 filed on 25 November 2019 with the statement of grounds of appeal, and renumbered as main request and auxiliary requests 1 to 13, respectively, in its submissions of 17 December 2019, or in the alternative, on the basis of auxiliary request 14 filed during the oral proceedings before the board on 15 May 2020.

Reasons for the Decision

Admission of the main request and auxiliary requests 1 to 7

1. The main request and auxiliary requests 1 to 6 are identical to the main request and auxiliary request 1 to 6 underlying the decision under appeal. They were originally filed on 25 July 2019 (main request), 20 September 2019 (auxiliary requests 1 and 2), and 10 October 2019 (auxiliary requests 3 to 6). Auxiliary request 7 is identical to the amended auxiliary request 7 filed on 22 October 2019 at the oral proceedings before the examining division. All these requests were considered by the examining division and a decision was taken thereupon; they underlie the decision under appeal. Thus, the main request and auxiliary requests 1 to 7 already form part of the appeal proceedings.

Main request
Articles 76(1) and 123(2) EPC

2. The board agrees with both, the examining division and the appellant, on the relevance of the gold standard set out in decision G 2/10 (*supra*) for assessing the

compliance with Articles 76(1) and 123(2) EPC. It is also acknowledged in the case law that the common general knowledge and the state of the art may be taken into account for assessing whether a subject-matter is directly and unambiguously derivable from the (earlier) patent application (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, II.E.1.3.1, 436). However, a distinction must also be made between subject-matter directly and unambiguously derivable from the (earlier) patent application and subject-matter rendered obvious by the (earlier) patent application in light of the common general knowledge and the state of the art (cf. "Case Law", *supra*, II.E. 1.3.3, 438, and II.E.1.3.4, 439).

3. Claim 1 of the main request is a product-claim directed to an anti-human PD-1 antibody characterised by inhibiting the signaling *via* PD-1, wherein said inhibition is achieved by inhibiting the interaction of human PD-1 and human B7-4, and wherein human B7-4 is further defined as a human protein comprising the amino acid sequence shown in figure 3 or 4 of the earlier patent application. The claimed anti-human PD-1 antibody must also be suitable for use in the treatment of a condition that would benefit from upregulation of an immune response, wherein said condition is a tumour. Thus, it is this specifically defined subject-matter that, according to the gold standard set out in decision G 2/10 (*supra*), has to be directly and unambiguously derivable from the earlier patent application.

4. In the decision under appeal, the examining division considered that, although there were several passages in the earlier patent application outlining the similar properties of the CTLA4 and PD-1 receptors, there were

also other passages throughout the earlier patent application wherein the differences between these two receptors were elaborated on. The examining division considered that the finding that PD-1 was an inhibitory receptor like the CTLA4 inhibitory receptor, was not enough to provide a basis for an implicit disclosure of the claimed subject-matter and, after considering the disclosures in the earlier patent application of both, the anti-PD-1 antibodies and the treatment of a tumour, the examining division decided that the use of an anti-PD-1 antibody for the treatment of a tumour was not directly and unambiguously derivable from the (earlier) patent application.

5. As regards the disclosure in the earlier patent application and the passages referred to by both, the appellant and the examining division, the board observes that:

6. Under the heading "Summary of the Invention" on page 3 of the earlier patent application, PD-1 is described as "a receptor for B7-4 molecules expressed on antigen presenting cells" which "transmits a negative signal to immune cells, similar to CTLA4". It is further stated that the "modulation of PD-1, B7-4, and/or the interaction between B7-4 and PD-1 results in modulation of the immune response". According thereto, a method is disclosed "for modulating an immune response" using "an agent that modulates signaling *via* PD-1 to thereby modulate the immune response" (cf. page 3, lines 15 to 25). Embodiments of the invention are then described in which the immune response is either downregulated or upregulated and "agents" are identified for each type of modulation (cf. page 3, line 26 to page 4, line 8). In particular, for upregulation of the immune response, reference is made to the inhibition of the signaling

via PD-1 using an agent selected from "the group consisting of: a blocking antibody that recognizes PD-1, a non-activating form of B7-4, an antibody that recognizes B7-4, and a soluble form of PD-1" (cf. page 4, lines 4 to 6).

6.1 There is then a disclosure of "a method for modulating the interaction of B7-4 with an inhibitory receptor on an immune cell" using "an agent selected from the group consisting of: a form of B7-4, a form of PD-1, or an agent that modulates the interaction of B7-4 and PD-1 such that the interaction of B7-4 with an inhibitory receptor on an immune cell is modulated" (cf. page 4, lines 9 to 14). There is no reference in this group of agents to any anti-PD-1 antibody.

6.2 Methods are further disclosed "for treating a subject having a condition that would benefit from" either upregulation or downregulation of an immune response "comprising administering an agent that" either inhibits or stimulates "signaling *via* PD-1 in an immune cell of the subject" (cf. page 4, line 28 to page 5, line 5). For both methods, agents and conditions are disclosed, in particular for upregulation of an immune response, the agent is described as comprising "a soluble form of PD-1 or B7-4" and the condition as being "selected from the group consisting of: a tumor, a neurological disease or an immunosuppressive disease" (cf. page 4, lines 33 to 37). There is no reference in this group of agents to any anti-PD-1 antibody.

6.3 In the section with the heading "Detailed Description of the Invention" of the earlier patent application, it is stated that the "instant discovery that PD-1 binds to B7-4 places PD-1 in a family of inhibitory receptors

with CTLA4" (cf. page 9, lines 22 and 23), and that "the prevention of an inhibitory signal (*e.g.*, by using a non-activating antibody against PD-1) in immune cells leads to upmodulation of immune cell responses (and a resulting upmodulation of an immune response)" (cf. page 9, line 29 to page 10, line 2). In this disclosure, there is neither a reference to any specific condition that would benefit from upregulation of the immune response, let alone a tumour, nor to any modulation of the interaction of B7-4 with the PD-1 receptor.

6.4 The board observes that the group of agents disclosed on page 4 for upregulating the immune response by inhibiting the signaling *via* PD-1 is much larger and, except for one agent (a soluble form of PD-1), different from the agents described for use in the treatment of a subject having the specific conditions cited further down on the same page including a tumour. There is neither an indication that each agent of the larger group must be necessarily suitable for every condition cited on the same page, nor a suggestion that a blocking anti-PD-1 antibody could be selected from the larger group of agents for being a suitable agent for the treatment of one of the specific conditions cited on that page, namely a tumour. Moreover, although the blocking anti-PD-1 antibody is defined as inhibiting the signaling *via* PD-1, there is neither a hint nor an indication of the mechanism underlying said inhibition. This mechanism could involve modulation of the interaction between PD-1 and B7-4 and, more particularly, inhibition of said interaction, but is not necessarily limited thereto. Likewise, there is no indication that the non-activating anti-PD-1 antibody disclosed on page 9 modulates the interaction of PD-1 and B7-4, let alone inhibits said interaction. It may

be so, but there are also many other possible mechanisms that may result in non-activation or inhibition of the signaling *via* PD-1. Moreover, there is no reference in the disclosure on page 9 to the treatment of any specific condition, let alone of a tumour. Thus, none of the paragraphs on pages 4 and 9 of the earlier patent application provides a basis for the subject-matter of claim 1 of the main request.

7. Under the heading "Methods of Treatment" on page 72 of the earlier patent application, methods are described for "Downregulation of Immune Responses by Modulation of B7-4 or PD-1" and for "Upregulation of Immune Responses" (cf. page 75, line 20 to page 82, line 7; and page 82, line 10 to page 86, line 10, respectively). For these latter methods, it is stated that "[u]pregulation of B7-4 costimulatory activity or inhibit [sic] an inhibitory activity of PD-1 or B7-4 as a means of upregulating immune responses is also useful in therapy", and "infections with microbes, e.g. bacteria, viruses, or parasites" are disclosed as a first example (cf. page 82, lines 11 to 17).

7.1 In this context of microbial infections, reference is made to "a form of B7-4 that promotes a costimulatory signal in an immune cell (*e.g.*, a B7-4 peptide ...) or an agent that inhibits the interaction of B7-4 with an inhibitory receptor or an agent that inhibits transduction of an inhibitory signal *via* PD-1, *e.g.*, a non-activating antibody against PD-1" as being therapeutically useful (underlined by the board) (cf. page 82, lines 17 to 24). This form of B7-4 and the two agents are further cited for specific therapeutic and prophylactic uses against microbial infections, such as for administration to an infected patient and for the production of vaccines (cf. page 83, lines 1 to 20).

7.2 The induction of tumour immunity is described as a further example of a useful method of treatment. On page 85 of the earlier patent application, it is stated that "immune responses against antigens to which a subject cannot mount a significant immune response, *e.g.*, to an autologous antigen, such as a tumor specific antigens can be induced by administering an agent that inhibits the inhibitory activity of PD-1 or the ability of B7-4 to bind to an inhibitory ligand. For example, in one embodiment, soluble PD-1 or soluble B7-4 can be used ... to enhance an immune response, *e.g.*, to a tumor cell" (underlined by the board) (cf. page 85, lines 12 to 17). Contrary to the methods for microbial infections, there is no reference to any anti-PD-1 antibody in these passages concerned with tumour immunity.

7.3 It is however argued by the appellant that, since the agent is characterised by the same properties ("an agent that inhibits the inhibitory activity of PD-1") as the blocking anti-PD-1 antibody on page 4 and the non-activating anti-PD-1 antibody on pages 9 and 82, a skilled person with a mind willing to understand would directly and unambiguously understand these antibodies to be useful as agents for enhancing tumour immunity.

7.4 The board observes that the functional definition on page 85 characterises a generic group of agents and that the sole example of specific agents disclosed in this context are the soluble forms of PD-1 or B7-4, but not any anti-PD-1 antibody. Although a non-activating anti-PD-1 antibody is disclosed on page 82 as a possible example of an agent falling within the definition given on page 85, the disclosure on page 82 is made only in the context of microbial infections and

not of tumour immunity. Moreover, in all disclosures of microbial infections and tumour immunity, and in particular for the disclosures on both pages 82 and 85, reference is always made to several different classes of agents, such as those that inhibit "the interaction of B7-4 with an inhibitory receptor" (such as PD-1) or those that inhibit "the inhibitory activity of PD-1" (i.e. "the transduction of an inhibitory signal via PD-1"). Whilst a non-activating anti-PD-1 antibody falls within this latter class of agents, it does not necessarily fall within the former class of agents as explained in point 6.4 above for the disclosures of blocking and non-activating anti-PD-1 antibodies on pages 4 and 9, respectively. Indeed, for the same reasons as given in point 6.4 above, appellant's argument based on the identity of the functional definitions given on pages 4, 9 and 85, is not convincing. Thus, the disclosure on page 85, either alone or in combination with those on page 82, page 4 and/or page 9 of the earlier patent application, does not provide a basis for the subject-matter of claim 1 of the main request.

8. The relevance of the Examples of the earlier patent application is acknowledged by the board. In particular, the generation of human anti-B7-4 and anti-PD-1 antibodies by using standard methods known in the art like those described in Example 9 as well as the demonstration in Example 13 that the interaction of PD-1 with its ligand B7-4 in (murine and human) T cells results in the inhibition of both proliferation and cytokine (interferon-γ and IL-10) secretion. Example 17 refers to the production of the extracellular regions of human PD-1 or human B7-4 fused to the hinge-CH2-CH3 domains of murine Igγ2a (PD-1Fc, B7-4Fc) in transfected (COS and CHO) cell lines and the ability of antibodies

to B7-4 or PD-1 to inhibit the interaction of human B7-4Fc and human PD-1Fc. Although this example discloses the degree of (IC50) inhibition achieved by the exemplified antibodies, there is no information on the efficiency of these specific antibodies for inhibiting the inhibitory signal *via* PD-1 or on their suitability for therapeutic uses (microbial infections, neurological diseases, etc.), let alone for enhancing tumour immunity. Therefore, in the board's view, Example 17 does not provide a basis for the subject-matter of claim 1 of the main request.

9. The board fails also to find a basis for this subject-matter in the claims of the earlier patent application.

9.1 Independent claim 1 of the earlier patent application is directed to a "method for modulating an immune response comprising contacting a cell expressing B7-4 or an immune cell expressing PD-1 with an agent that modulates the interaction of B7-4 with PD-1 to thereby modulate the immune response". Claim 8, dependent on claim 1, further requires the signaling *via* PD-1 to be inhibited using an agent selected from a group of agents that includes a blocking antibody that recognizes PD-1. Thus, the blocking anti-PD-1 antibody modulates the interaction of B7-4 with PD-1 and inhibits the (inhibitory) signaling *via* PD-1. However, neither is the inhibition required to be necessarily achieved through said modulation nor is the modulation required to necessarily result in an inhibition of the interaction of B7-4 with PD-1 as it is required for the subject-matter of claim 1 of the main request. It is also worth noting here that none of the claims dependent on claim 1 refers to the treatment of any specific (therapeutic) condition, let alone a tumour.

9.2 Indeed, it is in the "method for treating a subject having a condition that would benefit from upregulation of an immune response" of independent claim 18 of the earlier patent application, that the agent used for administering to this subject is defined as being "an agent that inhibits the interaction of PD-1 and B7-4" and, in dependent claim 21, mention is made of the (therapeutic) conditions, namely "a tumor, a neurological disease or an immunosuppressive disease". However, this agent is defined in dependent claim 19 as comprising "a soluble form of PD-1 or B7-4", but there is no mention of any anti-PD-1 antibody. Thus, the subject-matter of these claims corresponds to the disclosure on page 4 of the earlier patent application and thus, for the same reasons as those explained above for the disclosure on page 4, they do not provide a basis for the subject-matter of claim 1 of the main request.

10. As regards appellant's argument based on the similarity of the CTLA4 inhibitory receptor known from the prior art and the PD-1 inhibitory receptor disclosed in the earlier patent application, the board, leaving aside the differences between these two receptors mentioned in the earlier patent application and in the decision under appeal, sees no indication in the general references to the CTLA4 receptor of the earlier patent application that could lead a skilled person - in a direct and unambiguous manner - to identify and select anti-CTLA4 antibodies with properties corresponding to those characterising the subject-matter of claim 1 of the main request.

11. It may be that the claimed anti-PD-1 antibodies are rendered obvious by the disclosure of the earlier patent application, either alone or in combination with

the whole knowledge on the CTLA4 inhibitory receptor available from the prior art and the common general knowledge of the skilled person. However, as stated above, this is not the criterion set out in the established case law for assessing whether or not the claimed subject-matter contravenes Articles 76(1) and 123(2) EPC. The relevant criterion is set out in decision G 2/10 (*supra*), namely the gold standard, and in the present case, this standard is not met by the claimed subject-matter, as shown by all considerations made above.

12. Therefore, the main request contravenes Articles 76(1) and 123(2) EPC.

Auxiliary requests 1 to 7

13. These auxiliary requests are directed to "an anti-human PD-1 antibody" (auxiliary request 2 and 4), "a non-activating (anti-human) PD-1 antibody" (auxiliary requests 1, 5, 6 and 7) and "a blocking antibody that recognises human PD-1" (auxiliary request 3) which are all characterised by the combination of the features: (i) inhibits signaling *via* PD-1 (in an immune cell) by inhibiting the interaction of human PD-1 and human B7-4, and (ii) for use in the treatment of a condition that would benefit from upregulation of an immune response, wherein the said condition is a tumour.

14. As stated in points 5 to 12 above for the main request, there is no basis in the earlier patent application for anti-PD-1 antibodies defined by the combination of all these features. Therefore, auxiliary requests 1 to 7 contravene Articles 76(1) and 123(2) EPC.

The decision of the examining division not to admit auxiliary request 8 to 10 into the proceedings

15. Auxiliary requests 8 to 10 filed in appeal are identical to auxiliary requests 8 to 10 underlying the decision under appeal. They were originally filed at the oral proceedings before the examining division and not admitted into the proceedings.

15.1 As regards auxiliary request 8, the examining division stated in the decision under appeal that the wording of claim 1 "entails at least one new objection under Art. 84 EPC as the disease to be treated is undefined ... the claims of the AR8 are not in the proper second medical use format. In addition, the amendment made in claim 1 is not deemed appropriate to overcome the outstanding objection under Art. 83 EPC, if at all the objection under Art. 76(1)/123(2) EPC".

15.2 The examining division further stated in the decision under appeal that "[t]he same applies to AR9 and AR10 as these claims still relate to the use of an anti-PD-1 antibody that inhibits signaling via PD-1 to treat tumour. Thus, the claims of these requests are not deemed purposeful to overcome the objection under Art. 76(1)/123(2) EPC raised with respect to the claims of the MR and AR1-AR7" (underlined by the board).

15.3 According to the Minutes of the oral proceedings, the examining division, "in exercising its discretion under Rule 137(3) EPC, decided not to admit any of the requests AR8 to AR10, because the introduction of these claims re-introduces prima facie objections which had already been overcome during the procedure and/or introduces new objections. In particular, it was obvious that AR8 introduces at least objections under

Art. 83 and 84 EPC and that AR9 and AR10, each of which recite again the treatment of tumor, re-introduce the same objections under Art. 76(1)/123(2) EPC which had been already discussed for the higher ranking claim requests" (underlined by the board) (cf. page 2, point 6 of the Minutes of the oral proceedings).

16. According to the case law, a board should only overrule the way in which a department of first instance has exercised its discretion if it comes to the conclusion either that the department of first instance, in its decision, has not exercised its discretion in accordance with the right principles or that it has exercised its discretion in an unreasonable way (cf. "Case Law", *supra*, V.A.4.11.4.a), 1240). It is not for the board to review all the facts and circumstances of the case as if it were the department of first instance and decide whether or not it would have exercised discretion in the same way (cf. "Case Law", *supra*, V.A.3.5.1.b), 1198).

17. In the statement setting out its grounds of appeal, the appellant argued that the examining division applied its discretion incorrectly because auxiliary request 8 fulfilled the requirements of Articles 84 and 83 EPC and, like auxiliary requests 9 and 10, it did not contravene Articles 76(1) and 123(2) EPC. At the oral proceedings before the board, the appellant argued that the anti-PD-1 antibody claimed in auxiliary request 10 was not characterised by the feature "by inhibiting the interaction of human PD-1 and human B7-4, which is a human protein comprising the amino acid sequence shown in figure 3 or 4". Thus, this subject-matter had a basis in the earlier patent application and the amendment overcame the objection raised under Articles 76(1) and 123(2) EPC. Therefore, the examining

division should have admitted auxiliary request 10 into the proceedings.

18. In the board's view, it is doubtful whether the deletion of that feature in auxiliary request 10 was enough for the examining division to consider the objection raised under Articles 76(1) and 123(2) EPC to be overcome. In light of the reasoning given in the decision under appeal, the board considers that the examining division was convinced that the combination of an anti-PD-1 antibody - regardless of its properties (blocking, non-activating, inhibiting the interaction of human PD-1 and human B7-4, etc.) - with its use in the treatment of a tumour had no basis in the earlier patent application. Moreover, in the board's view, the examining division was also convinced that the admission of auxiliary request 10 could introduce new objections or re-introduce other objections "which had already been overcome during the procedure".

19. The board does not agree with the appellant that the examining division considered the (re)introduction of such objections to apply only to auxiliary request 8. In the board's view, the use of the terms "same" and "in particular" in the decision under appeal and in the Minutes of the oral proceedings, respectively, indicate that the findings for auxiliary request 8 apply to, or at least do not clearly exclude that they apply to, auxiliary requests 9 and 10 as well.

20. In line with the case law referred to above, it is not relevant whether the board agrees with the examining division's reasoning on these issues or whether the board would have exercised its discretion differently, but whether the examining division exercised its discretion in an unreasonable way. In the board's view,

the reasoning provided by the examining division in the decision under appeal and in the Minutes of the oral proceedings shows that this was not the case.

21. Therefore, the board sees no reason to overrule the decision of the examining division not to admit auxiliary requests 8 to 10 into the proceedings.

Admission of auxiliary request 10 into the appeal proceedings

22. In its pleading for the admission of auxiliary request 10 into the appeal proceedings, the appellant did not only argue on the basis of the examining division having exercised its discretion in an unreasonable way and thus, the board having to overturn the examining division's decision on this issue for this reason. The appellant argued also on the basis of the board's findings on the main request and auxiliary requests 1 to 7. Based on these findings, the subject-matter of claim 1 of auxiliary request 10 - which does not comprise the feature concerning the interaction of human PD-1 and human B7-4 - had to have a basis in the earlier patent application. Consequently, the objection raised under Articles 76(1) and 123(2) EPC was moot and auxiliary request 10 should be admitted into the appeal proceedings by the board exercising its own discretion (Article 111(1) EPC).

23. Leaving aside the question whether the examining division was right to consider the deletion of the feature referred to above not to be sufficient for overcoming the objection raised under Articles 76(1) and 123(2) EPC, the board considers that auxiliary request 10 cannot be admitted into the appeal proceedings.

23.1 The subject-matter of auxiliary request 10 is much broader than that of all other requests of higher ranking already forming part of the appeal proceedings, i.e. the main request and auxiliary requests 1 to 7, as well as auxiliary requests 8 and 9. The non-activating anti-PD-1 antibody claimed in auxiliary request 10 is limited neither by the feature "human" nor by any mechanism for inhibiting the signaling *via* PD-1. Therefore, auxiliary request 10 does not converge with all other requests of higher ranking (cf. "Case Law", *supra*, V.4.12.4, 1248).

23.2 The board agrees with the examining division that the admission of auxiliary request 10 would lead to the (re)introduction of objections that had been already dealt with, or should have been dealt with, at earlier stages of the examination procedure (*supra*). The claimed non-activating anti-PD-1 antibody comprises murine antibodies as well as antibodies that have no effect on, or do not even modulate, the interaction of human PD-1 with human B7-4, allegedly the relevant contribution of the earlier patent application to the prior art. Thus, documents on file concerned with anti-murine PD-1 antibodies, such as document (1), may become again relevant prior art, if not under Article 54 EPC, certainly under Article 56 EPC. Moreover, in light of the relevant similarities between the inhibitory receptors, CTLA4 and PD-1, as disclosed in the earlier patent application and emphasised by the appellant itself in the statement setting out its grounds of appeal, the board is also convinced that other prior art on anti-CTLA4 antibodies may also be relevant for assessing the requirements of Article 56 EPC.

23.3 Thus, in the board's view, the admission of auxiliary request 10 into the appeal proceedings would result in an opportunity for the appellant to re-open or restart the examination proceedings and, indeed, at an earlier stage than that already arrived at by the examining division when taking the decision under appeal. This is not in line with the function of an appeal as defined in the established case law (cf. "Case Law", *supra*, V.A.1, 1133).

24. Therefore, the board, in the exercise of its discretion (Article 111(1) EPC; Rule 137(3) EPC), does not admit auxiliary request 10 into the appeal proceedings.

Appellant's objection under Article 112a(2)(c) EPC and Rule 106 EPC - Violation of the appellant's right to be heard (Article 113 EPC)

25. Appellant's objection under Article 112a(2)(c) EPC arises from the board's decision not to admit auxiliary request 10 into the appeal proceedings which, according to the appellant, showed that it was taken without proper consideration of appellant's argument in favour of admitting auxiliary request 10. Therefore, according to the appellant, its right to be heard had been violated (Article 113 EPC).

26. In view of the reasoning provided in point 23 *et seq.* above, which the board summarily explained to the appellant at the oral proceedings, appellant's objection raised under Article 112a(2)(c) EPC is not considered to arise from the board not having properly considered appellant's arguments but rather from the board not deciding in appellant's favour. Appellant's arguments have been properly considered by the board but have not been found convincing. Therefore, the

board has decided, in the exercise of its discretion (Article 111(1) EPC; Rule 137(3) EPC), not to admit auxiliary request 10 into the appeal proceedings.

27. The board cannot recognize any violation of appellant's right to be heard and therefore dismisses the objection.

Admission of auxiliary requests 11 to 13 into the appeal proceedings

28. Auxiliary requests 11 to 13 were filed by the appellant with the statement setting out its grounds of appeal, i.e. at the earliest stage of the appeal proceedings, and thus, according to Article 12(3) RPBA 2020, they are part of the appellant's complete appeal case and should be part of the appeal proceedings. However, Articles 12(2) and 12(4) RPBA 2020 state that any part of a party's appeal case which is not directed to, *inter alia*, requests which the decision under appeal is based, are to be regarded as an amendment and that any such amendment may be admitted only at the board's discretion. Since the statement of grounds of appeal was submitted before the date of the entry into force of the RPBA 2020, in the present case according to Article 25(2) RPBA 2020, the board's discretion is ruled by Article 12(4) RPBA 2007. Thus, since auxiliary requests 11 to 13 were not filed at first instance and the decision under appeal is not based thereupon, their admission into the appeal proceedings is only at the discretion of the board (Article 12(4) RPBA 2007).

29. In view of the subject-matter of auxiliary requests 11 to 13 and the reasons given by the appellant for the admission of these requests into the appeal proceedings, the following issues are relevant:

29.1 In the Summons to attend oral proceedings issued by the examining division, the main objection raised against the set of claims then under consideration was an objection under Articles 76(1) and 123(2) EPC. In reply thereto and in preparation of the oral proceedings, the appellant filed a new main request and auxiliary requests 1 to 7 which were all admitted into the proceedings by the examining division. According to the Minutes of the oral proceedings, the appellant was given the opportunity to file new requests after the examining division decided that all claim requests then on file contravened Articles 76(1) and 123(2) EPC. The appellant replaced its previous auxiliary request 7 by a new auxiliary request 7 and filed auxiliary requests 8 to 10, these latter auxiliary requests were not admitted into the proceedings by the examining division. This main request and auxiliary requests 1 to 10 are those underlying the decision under appeal. According to the Minutes, the oral proceedings were closed at 11:30 hours. The Minutes have not been contested by the appellant. There is no evidence on file that the examining division denied the appellant the opportunity to file new requests or that the appellant requested such opportunity.

29.2 Whilst auxiliary requests 11 and 12 define the medical condition for which the claimed anti-PD-1 antibody is used as being "for inducing immune responses against a tumor specific antigen", the medical condition in auxiliary request 13 is defined as "upmodulation of an immune response" in general. In auxiliary request 13, the signal of PD-1 in immune cells is not required to be "inhibited" as in all other requests on file but to be "prevented". In auxiliary requests 11 and 12, there is no reference to an inhibition of the "signaling *via*

PD-1" - present in all other requests on file - but to an inhibition of the "inhibitory activity of PD-1". Regardless of the possible differences or similarities between the actual meaning of all these terms and the resulting amendments, there is no doubt, as observed by the board in its communication pursuant to Article 17 RPBA 2020, that the wording of auxiliary requests 11 to 13 is different from the wording of the claims of the auxiliary requests underlying the decision under appeal.

29.3 Moreover, in the board's view, auxiliary requests 11 to 13 have the same problems as indicated above for auxiliary request 10, namely that the claimed anti-PD-1 antibody is limited neither to "human" nor to any mechanism for inhibiting the (inhibitory) signaling *via* PD-1. Therefore, the reasons provided in point 23 *et seq.* above for not admitting auxiliary request 10 into the appeal proceedings apply also *mutatis mutandis* to auxiliary requests 11 to 13.

30. Therefore, the board, in the exercise of its discretion (Article 12(4) RPBA 2007), does not admit auxiliary requests 11 to 13 into the appeal proceedings.

Admission of auxiliary request 14 (amended auxiliary request 7)

31. Auxiliary request 14 was filed at the oral proceedings before the board and thus, represents an amendment to the appellant's case and its admission into the appeal proceedings is at the board's discretion (Article 13(1) RPBA 2020). The appellant argues that auxiliary request 14 is based on an auxiliary request that already forms part of the appeal proceedings, namely auxiliary request 7, and results from a mere deletion of a feature present in said auxiliary

request. The deleted feature of auxiliary request 7 is "by inhibiting the interaction of PD-1 and B7-4".

32. The board observes that the deletion of the feature referred to by the appellant results in the subject-matter of auxiliary request 14 being identical to that of auxiliary request 10. Therefore, appellant's request to admit auxiliary request 14 into the appeal proceedings amounts to nothing more than to request reconsideration of the board's decision to not admit auxiliary request 10 into the appeal proceedings.

33. Since the board, in the exercise of its discretion (Article 12(4) RPBA 2007) and for the reasons provided above, has already decided that auxiliary request 10 is not to be admitted into the appeal proceedings, the board does not see any reason to overturn this decision on the sole fact that auxiliary request 10, or for the case of the identical auxiliary request 14, may be derived from an auxiliary request (auxiliary request 7) that already forms part of the appeal proceedings.

34. Therefore, the board, in the exercise of its discretion (Article 13(1) RPBA 2020) and for the reasons given for auxiliary request 10, does not admit auxiliary request 14 into the appeal proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated