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Datasheet for the decision of 28 October 2021

Case Number: T 0975/16 - 3.3.04

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Language of the proceedings: EN

Title of invention:
T cell regulation

Patent Proprietors:
The Johns Hopkins University
St. Jude Children's Research Hospital Inc.

Opponent:
4-ANTIBODY AG

Headword:
LAG-3 on regulatory T cells/JOHNS HOPKINS

Relevant legal provisions:
EPC Art. 123(2), 54, 56, 83
RPBA 2020 Art. 13(2)
RPBA Art. 12(4)

Keyword:
Amendments - allowable (yes)
Novelty - main request (no)
Novelty - auxiliary request 1 (no)
Novelty - auxiliary request 2 (yes)
Inventive step - auxiliary request 2 (yes)
Sufficiency of disclosure - auxiliary request 2 (yes)

Decisions cited:
G 0003/89, G 0011/91, G 0002/10, T 0197/10, T 2221/10

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Case Number: T 0975/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 October 2021

Appellants: (Patent Proprietor 1)	The Johns Hopkins University 3400 N. Charles Street Baltimore, MD 21218 (US)
(Patent Proprietor 2)	St. Jude Children's Research Hospital Inc. 332 North Lauderdale Memphis, Tennessee 38105-2794 (US)
Representative:	Tombling, Adrian George Withers & Rogers LLP 2 London Bridge London SE1 9RA (GB)
Respondent: (Opponent)	4-ANTIBODY AG Hochbergerstrasse 60C 4057 Basel (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 23 February 2016 revoking European patent No. 1897548 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	R. Morawetz
Members:	O. Lechner
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the patent proprietors ("appellants") lies against the opposition division's interlocutory decision to revoke European patent No. 1 897 548 ("the patent").

II. The patent is based on European patent application No. 07 021 595.9 ("application as filed" or "application"), a divisional application of European patent application 04 716 126.0 ("parent application"), filed on 1 March 2004 and claiming priority from US 451039 P (filed on 28 February 2003), US 482143 P (filed on 24 June 2003) and US 531704 P (filed on 22 December 2003), respectively. The patent is entitled "*T cell regulation*".

III. An opposition had been filed invoking the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), under Article 100(a) EPC, as well as the grounds under Article 100(b) and (c) EPC.

IV. The decision under appeal dealt with sets of claims of auxiliary requests 1 to 4. The opposition division held, *inter alia*, that:

- the subject-matter of claims 1, 4, 7, 8, 10 and 11 of auxiliary request 1 did not extend beyond the content of the application as filed (Article 123(2) EPC);
- the subject-matter of claims 1, 4, 7, 8 and 10 was novel over the disclosure in document D3, D6 and D7 (Article 54 EPC) but not inventive starting from document D6 as the closest prior art and the technical problem of providing further means for cancer immunotherapy (Article 56 EPC);

- auxiliary requests 2 to 4 lacked an inventive step (Article 56 EPC) starting from document D2 as the closest prior art and the technical problem of providing a vaccine that potentially has better efficacy or better coverage in a population.

V. With their statement of grounds of appeal, the appellants filed arguments under Article 56 EPC and a new main request (identical to auxiliary request 1 underlying the decision under appeal). They also filed auxiliary requests 1 to 5 and six new documents (D24 to D29, see below).

VI. In reply, the opponent ("respondent") raised objections under:

- Article 123(2) EPC against claims 1, 4, 7, 8 and 10 of the main request;
- Article 54 EPC in view of document D3 against the claims of the main request and in view of document D7 against claims 1, 4 and 10 of the main request;
- Article 56 EPC against claim 7 of the main request when starting from document D6 as the closest prior art and the technical problem of providing an alternative means for cancer immunotherapy. The subject-matter of claim 1 was merely an arbitrary combination of known features and, thus, obvious. The arguments also applied to the claims of the auxiliary requests;
- Article 83 EPC against the second medical use claims in all claim requests.

The respondent also submitted four new documents (D30 to D33, see below).

VII. The board issued a summons for oral proceedings, followed by a communication pursuant to Article 15(1) RPBA providing the board's preliminary appreciation of the appeal as follows.

- The board provided its analysis on claim construction;
- the claims of the main request were considered to not add subject-matter (Articles 76(1) and 123(2) EPC);
- claims 1, 4, 7, 8 and 10 of the main request were considered to lack novelty in view of the teaching of document D3;
- for assessing inventive step (Article 56 EPC), document D6 was considered to represent the closest prior art. The board indicated that it intended to hear the parties on whether a "*patient with regulatory T-cells which suppress an immune response in response to an anti-cancer vaccine*" disclosed a subset of cancer patients which was sufficiently disclosed and on which specific effects were provided, evident and/or (non-)obvious in light of the disclosure in the patent *vis a vis* document D6 alone or in combination with the other cited prior art.

VIII. By letter dated 27 August 2021, the appellants provided arguments in response to issues raised in the board's preliminary opinion and filed three new documents (D34 to D36, see below).

IX. By letter dated 21 September 2021, the appellants requested that the oral proceedings be conducted as a video conference.

X. By letter dated 28 September 2021, the respondent withdrew its request for oral proceedings and announced

that it would not attend the oral proceedings and withdrew its request for oral proceedings. No submissions on the board's communication or the appellants' letter of 27 August 2021 and the newly cited documents D34 to D36 were made.

XI. The oral proceedings before the board took place as a video conference in the absence of the duly summoned respondent pursuant to Rule 115(2) EPC and Article 15(3) RPBA.

XII. At the end of the oral proceedings, the Chair announced the board's decision.

XIII. The following documents are referred to in this decision:

D3: WO 98/23748 A1

D6: F. Triebel, Trends in Immunology, vol. 24(12), 2003, 619-22

D7: WO 95/30750 A2

D13: G.Q. Phan et al., PNAS, vol. 100(14), 2003, 8372-7

D24: CV and declaration of Professor Dario Vignali

D25: CV and declaration of Dr Nils Lonberg

D26: CV and declaration of Professor Christophe Benoist

D27: CV and declaration of Professor Diane Mathis

D28: R.P.M. Sutmuller et al., J. Exp. Med., vol. 194(6), 2001, 823-32

D29: L. Ramarathinam et al., J. Exp. Med., vol. 179(4), 1994, 1205-14

D30: K. Hung et al., J. Exp. Med., vol. 188(12), 1998, 2357-68

D31: O. Murillo et al., Clinical Cancer Research, vol. 9, 2003, 5454-64

D32: J. Duraiswamy et al., Blood, vol. 101(8), 2003, 3150-6

D33: Declaration of Dr Nicholas Wilson of 17 November 2016

D34: Declaration of Drew M. Pardoll of 26 August 2021

D35: M.Y. Mapara et al., Journal of Clinical Oncology, vol. 22(6), 2004, 1136-51

D36: S. Sakaguchi et al., Immunological Reviews, vol. 182, 2001, 18–32

XIV. Claims 1, 4, 7, 8 and 10 of the main request read as follows:

"1. A composition, comprising:
antibodies which specifically bind to CD223 and block its ability to function; and
an anti-cancer vaccine comprising isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumor antigens.

4. A kit comprising: antibodies which specifically bind to CD223 and block its ability to function; and an anti-cancer vaccine comprising isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumor antigens.

7. An antibody which specifically binds to CD223 and blocks its ability to function and an anti-cancer vaccine comprising isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumour antigens for use in treating cancer.

8. An antibody which specifically binds to CD223 and blocks it ability to function and an anti-cancer vaccine comprising isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumor antigens for use in treating cancer in a patient with regulatory T cells which suppress an immune response in response to an anti-cancer vaccine.

10. An inhibitory agent of CD223 protein or CD223 mRNA selected from: an antibody which specifically binds to CD223 protein and blocks its ability to function; an antisense oligonucleotide which specifically binds to CD223 mRNA; a ribozyme which specifically binds to CD223 mRNA; a RNA interference molecule which specifically binds to CD223 mRNA; and an antisense construct encoding said antisense oligonucleotide, and an anti-cancer vaccine comprising isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumor antigens, for use in treating cancer in a mammal by increasing the number of T cells in the mammal."

Claim 1 of auxiliary request 1 is identical to claim 7 of the main request.

Claim 1 of auxiliary request 2 is identical to claim 8 of the main request, while dependent claim 2 reads as follows:

"2. The antibody and anti-cancer vaccine for use according to claim 1 wherein the antibody is monoclonal."

XV. The arguments of the appellants submitted in writing and at the oral proceedings relevant for the present decision may be summarised as follows.

Admittance of documents D24 to D29 and D34 to D36 and lines of argument filed by letter of 27 August 2021

The lines of argument submitted with the letter of 27 August 2021 and documents D34 to D36 addressed whether cancer patients with regulatory T cells (Treg cells) which suppress an immune response in response to an anti-cancer vaccine represented a subset of cancer patients. The issue had been raised for the first time in the board's communication. The submission prior to the oral proceedings allowed the board and the respondent to fully consider the appellants' position before the oral proceedings.

Main request

Claim construction

Paragraphs [46] and [56] of the application as filed differentiated between i) isolated antigens, ii) groups of antigens and iii) whole tumour cells. Therefore, the term "isolated" had to be understood as being distinct from and not to comprise "groups of antigens" or "whole

cells".

Novelty (Article 54 EPC) - Claims 1, 4, 7, 8 and 10

The claimed subject-matter was novel over the disclosure in document D3 because document D3 did not disclose an anti-cancer vaccine comprising the claimed "isolated tumor antigens or isolated polypeptides comprising one or more epitopes of tumor antigens".

Auxiliary request 1

Novelty (Article 54 EPC) - Claim 1

The claimed subject-matter was novel for the same reasons as given for the main request.

Auxiliary request 2

Inventive step (Article 56 EPC)

Closest prior art

Document D26 was a better starting point for assessing inventive step than document D6 since it related to *in vivo* data. Even when starting from document D6 as the closest prior art, the claimed invention was not obvious.

Objective technical problem

The claimed subject-matter differed in two aspects from the disclosure in document D6, namely in the use of an anti-cancer vaccine and in the treatment of a subpopulation of patients characterised in that they

have Treg cells which suppress an immune response in response to an anti-cancer vaccine.

The technical effect caused by these differences was the generation of a targeted immune response in patients with Treg cells which suppress an immune response in response to an anti-cancer vaccine.

The technical problem was how to generate a targeted immune response to treat cancer in patients with Treg cells that suppress an immune response to an anti-cancer vaccine.

Obviousness

Without an understanding of the role of LAG-3 in tolerance *via* Treg cells as elucidated in the patent, the skilled person would not and could not have expected that the combination of an anti-LAG-3 antibody and an anti-cancer vaccine would have any utility in treating this group of patients.

The examples of the patent showed that antibodies to LAG-3 inhibited the suppressor activity of Treg cells both *in vitro* and *in vivo*. Furthermore, the examples showed that LAG-3 was both necessary and sufficient for maximal Treg cell function, i.e. the patent identified LAG-3 as a marker of Treg cells that modulated their suppressor activity. It was not until the role of LAG-3 in tolerance via Treg cells was elucidated in the patent that the skilled person would have had any confidence that LAG-3 blockade could be used to break tolerance, leading them to develop an anti-cancer therapy based on this combination. Treg cells could be found to a varying degree in all cancer types, but not

all patients with a particular cancer type had LAG-3+ Treg cells.

Disclosure of the invention (Article 83 EPC)

Patients with Treg cells which suppress an immune response in response to anti-cancer vaccine could be easily identified as these patients would have failed to respond to an anti-cancer vaccine due to peripheral tolerance mediated by their LAG-3+ Treg cells. These cells could be easily identified by staining tumour biopsies and could also be sorted by flow cytometry using specific markers, such as FoxP3, LAG-3 etc., as described in the legend to Figure 6 on page 5, lines 22 to 29 and in paragraph [0063] of the patent.

The data in the patent showed that blocking LAG-3 alone would be necessary and sufficient to overcome Treg cell-mediated tolerance on T cells. Thus, it was plausible that a blocking anti-LAG-3 antibody could provide in combination with an anti-cancer vaccine a therapeutic anti-cancer response *in vivo* in the claimed subgroup of cancer patients.

Given that the murine and the human immune system were very similar, data obtained in mice could be extrapolated to humans as also apparent from document D6.

XVI. The arguments of the respondent, submitted in writing, relevant for the present decision may be summarised as follows.

Admittance of documents D24 to D29 and D34 to D36 and the appellants' letter of 27 August 2021

Documents D24 to D29, filed by the appellants should only be admitted into the proceedings under Article 12(4) RPBA if the entirety of the reply together with documents D30 to D33 were also admitted.

Main request

Amendments (Article 123(2) EPC) - Claim 8

There was no basis in the application as originally filed for combining an anti-cancer vaccine as claimed with inhibitory antibodies, let alone antibodies which bind to CD223/LAG-3 and block its ability to function. In the application as originally filed, the embodiments which combined antibodies with an anti-cancer vaccine did not specify that the antibodies were blocking antibodies. There was also no basis for an antibody which binds to CD223 with the feature "blocks its ability to function", nor for the feature "comprising isolated tumour antigens or isolated polypeptides comprising one or more epitopes of tumour antigens". Finally, there was no basis for a combination of the feature "a patient with regulatory T-cells which suppress an immune response to an anti-cancer vaccine" with the requirements for the vaccine to comprise isolated tumour antigens or polypeptides as claimed, nor for the antibody to block CD223 function. Claim 8 referred to an undisclosed combination of features.

Claim construction

The term "isolated" was not defined in the patent and so could take any reasonable meaning.

Novelty (Article 54 EPC) - Claims 1, 4, 7 and 10

Document D3 disclosed on page 9, lines 22 to 29 the combination of an antibody to LAG-3 and an anti-cancer vaccine for administration to a patient to induce immunity against the cancer. In document D3, the antigens in the tumour tissue were "isolated" from the patient and then reimplanted later. Thus, the claims lacked novelty over document D3.

Auxiliary request 2

Inventive step (Article 56 EPC)

Claim 1 of auxiliary request 2 was limited to the treatment of a subset of patients defined functionally by reference to the patient having a suppressed immune response. No comparative data were provided for this patient subgroup, and no new effect was mentioned by the patentee. The skilled person had known from the prior art that the effect of an anti-cancer vaccine would be augmented by combining the vaccine with an anti-LAG-3 antibody, regardless of the subgroup of patients tested. There was no evidence to suggest that the skilled person's expectation for the subgroup claimed in auxiliary request 2 would have differed.

Disclosure of the invention (Article 83 EPC)

There was no example in the patent testing the claimed combination of an anti-LAG-3 antibody with a cancer

vaccine comprising isolated tumour antigens. The examples of the patent made the same link already made in the prior art, i.e. that LAG-3 is a negative regulator of T cells and that anti-LAG-3 antibodies could be used to enhance T cell proliferation. Any feature that could not have been expected to work from the prior art could also not be plausibly expected to work based on the teaching of the patent. A second medical use claim required attaining successful treatment as a functional feature.

The application as filed had to disclose the suitability of the product to be manufactured for the claimed therapeutic application and clearly and unambiguously reflect the therapeutic effect.

If the skilled person could not arrive at the invention from documents D6 and D13 because some key information was missing, that information was missing from the patent as well.

Thus, there was nothing in the patent to show that an effect on CD8+ cells would occur *in vivo* when the antibody was administered with the broad class of anti-cancer vaccines claimed. Expansion of antigen-specific T cells in an immune tolerant *in vivo* tumour model had not been shown in the patent.

Moreover, the scope of the claims encompassed any blocking anti-LAG-3 antibody in combination with any isolated tumour antigen anti-cancer vaccine. If it was only possible to predict whether an anti-LAG-3 antibody would work with additional information beyond what was in the prior art, such as an understanding of the "intercellular mechanisms" mentioned in the appeal statement, this level of complexity meant that it was

unreasonable to suggest that all LAG-3 antibodies would work with all cancer vaccines as claimed. The only *in vivo* Example 6 was in mice, not humans, and tested just one LAG-3 antibody and no vaccines of any type. There was nothing anywhere in the patent to show how an anti-cancer vaccine would interact with a LAG-3 antibody. There were no disease model data.

Requests of the parties relevant to this decision

XVII. *The appellants (patent proprietors) requested that:*

- the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request, filed with the statement of grounds of appeal;
- alternatively, the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 5, all filed with the statement of grounds of appeal;
- documents D24 to D29 be admitted into the appeal proceedings.

XVIII. *The respondent requested in the written submissions that:*

- the appeal be dismissed;
- the new evidence filed by the appellants only be admitted into the appeal proceedings under Article 12(4) RPBA 2007 if the entirety of the respondent's reply together with the enclosed documents, D30 to D33, also be admitted;
- the board consider both sufficiency and inventive step.

Reasons for the Decision

Admittance of documents D24 to D36 and the appellants' lines of arguments provided in their letter of 27 August 2021

1. Documents D24 to D29 were filed with the appellants' statement of grounds of appeal; documents D30 to D33 were filed with respondent's reply. Their admittance is thus governed by Article 12(4) RPBA 2007. No objections to admittance were raised by the parties, and the board has no reason to hold these documents inadmissible *ex officio*.

2. Since the appellants' lines of argument submitted by letter of 27 August 2021 as well as documents D34 to D36 are considered to be a legitimate reaction to issues newly raised in the board's communication (see section VIII.), the board decided to admit them into the appeal proceedings (Article 13(2) RPBA 2020).

Main request

Amendments – (Article 123(2) and 76(1) EPC)

3. This claim request was auxiliary request 1 underlying the decision under appeal. It was considered to meet the requirements of Article 123(2) EPC by the opposition division. On appeal, the respondent contested that claims 1, 4, 7, 8 and 10 met the requirements of Article 123(2) EPC and 76(1) EPC.

4. The board considers that the decision under appeal was correct on this point. However, in view of the board's conclusion on novelty (see point 20 below), there is no need for the board to give reasons for holding so, except for the subject-matter of claim 8, which is

identical to the subject-matter of claim 1 of auxiliary request 2.

5. Regarding the features of claim 8, the opposition division considered that the feature "isolated polypeptides" found basis in paragraph [56] of the application as filed. The combination of CD223 inhibitory antibodies and an anti-tumour vaccine found basis in paragraphs [45], [46], [48] and [56] of the application as filed. Finally, the feature "in a patient with regulatory T cells which suppress an immune response to an anti-cancer vaccine" found basis in paragraph [17] of the application as filed. The respective passages (same numbering) were also present in the parent application.

6. The respondent argued that claim 8 referred to an undisclosed combination of features.

7. Under the "gold standard" (see G 2/10, OJ 2012, 376), an amendment is allowed under Article 123(2) EPC only if it remains within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed (see G 3/89, OJ 1993, 117; G 11/91, OJ 1993, 125). After the amendment, the skilled person may not be presented with new technical information (see Case Law of the Boards of Appeal, 9th edn., 2019, II.E.1.3.).

8. Paragraph [17] of the application as filed and the parent application discloses that the invention provides a method for overcoming suppression of an immune response to an anti-cancer vaccine by administering an antibody which binds to CD223 to a

cancer patient with Treg cells which suppress an immune response to an anti-cancer vaccine. An anti-cancer vaccine is also administered to the patient. The antibody increases the response of the cancer patient to the anti-cancer vaccine. That such an antibody has to be an inhibitory antibody is directly and unambiguously derivable from paragraph [45] of the application as filed (as well as the parent application).

Similar disclosure to paragraph [17] is provided in paragraph [56] (see also the identical paragraphs in the parent application), which in addition specifies that the anti-cancer vaccines can be isolated tumour antigens or polypeptides comprising one or more epitopes of tumour antigens. Finally, paragraph [46] of the application and the parent application refers to the use of an inhibitory agent that binds to CD223 protein or mRNA and also discloses co-administration of an anti-tumour vaccine.

9. Therefore, the board agrees with the opposition division's finding that the subject-matter of claim 8 does not provide the skilled person with technical information not contained in the original application documents. Consequently, the subject-matter of claim 8 of the main request does not extend beyond the content of the application as filed (Article 123(2) EPC) or the parent application as filed (Article 76(1) EPC).

Claim construction

10. In accordance with established case law, if a term used in a claim has (*per se*) a clear (ordinary) technical meaning, the description cannot be used to interpret such a term differently. In case of a discrepancy

between the claim and the description, the unambiguous claim wording prevails. Hence, it must be interpreted as it would be understood by the person skilled in the art without the help of the description (see Case Law of the Boards of Appeal, 9th edn., 2019, II.A.6.3.1, especially decisions T 2221/10 and T 197/10).
The appellants' argument that the claims had to be read in the context of the description thus fails.

11. The board considers that the expression "anti-cancer vaccine comprising isolated tumour antigen or polypeptides comprising one or more epitopes of tumour antigens" is clear. A person skilled in the art of vaccines would have understood this terminology to include vaccine compositions comprising tumour antigens isolated from their natural environment. This is not limited to a composition comprising only purified proteins, etc. but also includes, for instance, compositions comprising (small amounts of) tumour tissue isolated from a patient's body and comprising the tumour antigen.

Novelty (Article 54 EPC) - claims 1, 4, 7, 8 and 10

12. The opposition division held that the subject-matter of claims 1, 4, 7, 8 and 10 was novel over the disclosure in document D3 and that the subject-matter of claims 1 to 16 was novel over the disclosure in document D7.

13. The respondent contested the opposition division's decision on novelty over document D3. It also maintained that document D7 anticipates the subject-matter of claims 1, 4, 7 and 10.

14. Document D3 discloses the treatment of small amounts of tumour tissue before reimplantation with anti-LAG-3

(CD223) antibodies (Ab) to prevent T cell inhibition induced by LAG-3 and allow induction of cellular and humoral immunity against it (see page 9, lines 19 to 29).

15. The board considers that utilisation of the term "anti-cancer vaccine" in compound claims requires only that the disclosed isolated tumour antigens or polypeptide (fragments) be in a form "suitable" for use as an anti-cancer vaccine (see also Case Law of the Boards of Appeal, 9th edn., 2019, I.C.8.1.5).

16. Accordingly, document D3 anticipates the subject-matter of claims 1, 4, 7 and 10 of the main request.

17. The appellants' counter-argument, which was solely based on claim construction, cannot succeed in view of the claim construction adopted by the board (see points 10 and 11 above).

18. The respondent argued that page 9, lines 22 to 29 of document D3 disclosed the combination of an antibody to LAG-3 and an anti-cancer vaccine comprising isolated tumour antigens for administration to a patient to induce immunity against the cancer.

19. However, document D3 fails to disclose the treatment of the patient subgroup characterised by having Treg cells which suppress an immune response in response to an anti-cancer vaccine (see page 8, line 6; page 9, lines 19 to 29 and page 15, lines 15 to 17), and the respondent's argument does not address this difference. Consequently, the board does not find the respondent's line of argument persuasive.

20. The board concludes from the above that the subject-matter of claims 1, 4, 7 and 10 of the main request lacks novelty in view of the disclosure in document D3, while the subject-matter of claim 8 is novel over the disclosure in document D3.

21. In view of the board's conclusion on lack of novelty of the subject-matter of claims 1, 4, 7 and 10 over the disclosure in document D3 (see above), there is no need to consider the respondent's objection to these claims based on document D7.

Auxiliary request 1

Novelty (Article 54 EPC) - claim 1

22. The appellants did not contest that the subject-matter of the claim is anticipated by the disclosure in document D3 for the same reasons as set out above for claim 7 of the main request (see points 14 to 21 above).

Auxiliary request 2

Amendments (Article 123(2) and 76(1) EPC) - claim 1

23. Claims 1 and 2 of auxiliary request 2 are identical to independent claim 8 and its dependent claim 9 of the main request. The subject-matter of claim 1 does not extend beyond the content of the application as filed for the same reasons as set out above for claim 8 of the main request (see points 5 to 9 above).

Claim construction

24. Claim 1, drafted as a second medical use claim pursuant to Article 54(5) EPC, is directed to the treatment of a purposely selected subgroup of cancer patients characterised by the presence of Treg cells which suppress an immune response in response to an anti-cancer vaccine. The claimed treatment is restricted to patients refractory to anti-cancer vaccines due to Treg cells. The respondent did not contest that the patients represent a subgroup of cancer patients.

As set out by the appellants, the patent discloses how these patients with suppressive or "anergic" Treg cells can be identified, e.g. using the differentially expressed markers FoxP3, LAG3, CD25 and/or IL-10 (see Examples 2, 4 and 5 as well as Figures 2, 3 and 6 of the patent).

Inventive step (Article 56 EPC)

Closest prior art

25. Regardless of which document is ultimately considered to be the closest prior art, pursuant to Article 56 EPC, the claimed invention must not be obvious to the person skilled in the art having regard to any prior art, subject to Article 56, second sentence, EPC.

26. The purpose or objective of a purpose-limited product claim under Article 54(5) EPC is, generally, the therapeutic indication recited in the claim. In the case at hand, this is the treatment of cancer. The board therefore concurs with the opposition division and the respondent that document D6 represents a

suitable springboard for assessing inventive step (see Case Law of the Boards of Appeal, 9th edn., 2019, I.D.3.1).

Indeed, this document discloses the same purpose and has the most relevant technical features in common with the current claim. Document D23, on the other hand, investigates the consequences of the absence of LAG-3 (= CD223) in knock-out mice, describing that these animals exhibit a defect in the natural killer cell, rather than the T cell, compartment (see abstract).

27. Review article D6 summarises the knowledge on LAG-3 (= CD223) as an important negative regulator of T cell homeostasis (see abstract; page 619, left-hand column). Soluble anti-LAG-3 antibodies which block LAG-3–MHC-II interactions are described to upregulate CD4 T cell clone activation. LAG-3 is expressed as a co-receptor on T cells and modulates effector T cell activity as well as Treg cell suppressor activity (see page 619, right-hand column; page 620, left-hand column). Document D6 concludes that "*This suggests that LAG-3 blockade through systemic administration of mAb or sLAG-3 could be used for breaking tolerance to human cancer antigens for cancer immunotherapy, as shown recently for CTLA-4 [25]*" (see page 621, right-hand column, last sentence).

28. This suggestion is based on a successful approach disclosed in document D13 (reference [25] in document D6) which blocks CTLA-4, another T cell inhibitory receptor, with an anti-CTLA-4 antibody (see page 621, left-hand column of document D6).

Difference, its technical effect and problem to be solved

29. The subject-matter of claim 1 differs from the teaching in document D6 in that a subgroup of cancer patients, i.e. patients having Treg cells which suppress an immune response in response to an anti-cancer vaccine, is treated.

30. The technical effect arising from this difference is that Treg cell-mediated tolerance to the anti-cancer vaccine is broken in these anti-cancer vaccine tolerant patients such that an immune response is generated.

31. The board does not concur with the technical problem as formulated by the opposition division and the respondent for the following reasons.

32. "[P]*roviding further means for cancer immunotherapy*" or "*providing an alternative means for cancer immunotherapy*" as defined by the opposition division and the respondent is too generic and fails to take into consideration the difference with the teaching in document D6 and the technical effect provided.

33. The technical problem as defined by the appellants, i.e. generation of a targeted immune response to treat cancer in patients with Treg cells that suppress the immune response to an anti-cancer vaccine, on the other hand, comprises a pointer to the solution. This is contrary to established case law, under which the technical problem addressed by an invention has to be formulated in such a way that does not contain pointers to the solution or partially anticipate the solution (see Case Law of the Boards of Appeal, 9th edn., 2019, I.D.4.3.1.).

34. The board considers that the objective technical problem can be defined as the provision of a further cancer therapy in anti-cancer vaccine tolerant patients.

35. The claimed solution is the use of the combination of an antibody which binds and blocks CD223 and an anti-cancer vaccine comprising an isolated tumour antigen in those anti-cancer vaccine tolerant patients that have Treg cells which suppress an immune response in response to an anti-cancer vaccine.

Obviousness

36. The question to be answered is whether starting from the teaching in document D6 it was obvious to use the combination of an antibody which binds and blocks CD223 and an anti-cancer vaccine comprising an isolated tumour antigen to treat cancer in the subgroup of patients characterised by having Treg cells which suppress an immune response in response to an anti-cancer vaccine and if so, whether the skilled person had a reasonable expectation of success.

37. At the filing date of the application, it was common general knowledge that immune tolerance to cancer may be based on different mechanisms.

38. For instance, document D28 discloses that "*In cancer patients, the absence of efficient tumor-specific immunity can be related to inadequate APC* (antigen presenting cell) *function or to T cell tolerance/ ignorance towards tumor antigens" (see Introduction, second sentence)*.

39. Document D31 reviews a number of successful therapies that combine an immunostimulatory antibody targeting one of the different inhibitory pathways with a cancer vaccine.

40. Finally, document D13 reveals CTLA-4 to be a critical immunoregulator on activate T cells and shows that blocking CTLA-4 with specific antibodies results in autoimmune manifestations and cancer regression (see abstract). Blocking CTLA-4 with antibodies is reported to break tolerance against self antigens and to result in enhanced anti-tumour immunity in response to vaccination with tumour-antigens (see page 8372, paragraph bridging left- and right-hand columns). However, the patients treated in document D13 had never been immunised against the gp100 antigen used for vaccination (see page 8372, right-hand column, last paragraph), nor are they described as having failed to respond to an anti-cancer vaccine before.

41. Considering the skilled person's common general knowledge about the complex mechanisms involved in the induction of immunological tolerance (see e.g. document D31 or D35), and considering that various mechanisms of tolerance are responsible for immunosuppression in cancers (see point 37 above), the respondent's argument that the combination of the anti-cancer vaccine with an anti-LAG-3 antibody would have been expected to augment the immune response regardless of the subgroup of cancer patients is not persuasive for the reasons set out below.

42. The application is the first document to show that LAG-3 is expressed at higher levels on Treg cells and that its expression alone is sufficient to convert cells from activated effector T cells into

immunosuppressive Treg cells (see Examples 2 to 9). The application also shows that LAG-3-deficient mice have increased numbers of CD4+ as well as CD8+ T cells compared to wild-type mice, while the CD4:CD8 T-cell ratio was unchanged. Suppressive Treg cells can be identified by the differential expression of LAG-3, IL-10, CD25 and/or FoxP3 (see Examples 2, 4 and 5 as well as Figures 2, 3 and 6). The suppressive activity of induced Treg cells is shown to be directly proportional to LAG-3 expression (see Example 5), and LAG-3 expression alone is shown to be sufficient to induce the suppressive phenotype of Treg cells (see Example 8).

Finally, inhibitory anti-CD223 antibodies are shown to eliminate the *in vitro* (see example 10) and *in vivo* (see example 12) suppressive activity of the Treg cells, and ectopic LAG-3 expression on auto-antigen-specific T cells is shown to be sufficient to prevent the onset of autoimmune diabetes in a transgenic mouse model *in vivo* (see Examples 10 to 12).

43. Without this knowledge, the skilled person had no reason to use the combination of an antibody which binds and blocks CD223 and an anti-cancer vaccine comprising an isolated tumour antigen in the claimed subgroup of patients, let alone a reasonable expectation of success that treating them with a combination of CD223 blocking antibodies and isolated tumour antigens would overcome immunosuppression.

44. The board therefore considers that the teaching of document D6 alone, or even in combination with the teaching of document D13, would not have led the skilled person to treat a subgroup of cancer patients characterised by the presence of immunosuppressive Treg

cells with a combination of an antibody which binds and blocks CD223 and an anti-cancer vaccine comprising an isolated tumour antigen.

45. Consequently, the subject-matter of claim 1 and, *a fortiori*, dependent claim 2 of auxiliary request 2 involves an inventive step (Article 56 EPC).

Disclosure of the invention (Article 83 EPC)

46. Under established case law (see Case Law of the Boards of Appeal, 9th edn., 2019, II.C.7.2.), the requirement of sufficiency of disclosure is considered fulfilled for a claim to a second medical use if the application discloses the suitability of the compound/composition for the claimed therapeutic application.

47. The disclosure of the application showing that LAG-3 is necessary and sufficient for the suppressive function of Treg cells has been summarised above (see point 42). The application also shows an about 50% increase in the number of dividing cells in CD223-/- mice *in vivo* and an increase in the number of CD4+ and CD8+ cells but also of B cells and macrophages (see Example 1). The person skilled in tumour immunology moreover knew that Treg cells are also located in tumours and that they influence CD8 T cell responses (see e.g. review articles D35 and D36).

48. The application furthermore provides a mechanism on how anti-LAG3 antibodies can break tolerance making it plausible that an antagonistic anti-LAG-3 antibody is able to block Treg cell-mediated tolerance to cancer-antigens *in vivo* and is thus suitable for treating cancer in a patient with Treg cells which suppress an immune response to an anti-cancer vaccine. The board

therefore sees no need for any additional *in vitro* or *in vivo* data, such as an effect of an anti-CD223 antibody on CD8+ cells or the expansion of antigen-specific T cells in an immune tolerant, *in vivo* tumour model.

49. Moreover, as evidenced e.g. by document D6 (see "Abstract" and "Concluding remarks"), the skilled person would have extrapolated LAG-3-related mouse *in vivo* evidence to humans. No evidence to the contrary has been provided by the respondent.

50. The board furthermore considers that based on the evidence on file, the skilled person was in a position to provide appropriate inhibitory anti-CD223 antibodies without undue burden. Again, no evidence to the contrary has been presented by the respondent.

51. Finally, inventive step is acknowledged on the basis of the subgroup of patients claimed and not because some key information on CD8+ cells, antigen-specific T cells or intercellular mechanisms is missing in the prior art (see points 27 to 45 above). The board therefore does not agree with the respondent's argument that such information, if missing from the prior art, is also missing from the application.

52. The board concludes that the requirements of Article 83 EPC are met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of the set of claims of the auxiliary request 2 filed with the statement of grounds and a description as well as drawings possibly to be adapted thereto.

The Registrar: The Chair:

I. Aperribay R. Morawetz

Decision electronically authenticated