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Datasheet for the decision of 26 October 2023

Case Number: T 0294/20 - 3.3.04

Application Number: 11162681.8

Publication Number: 2397156

IPC: A61K31/713, A61K38/17, A61K39/00, C07K16/28, G01N33/50, G01N33/574

Language of the proceedings: EN

Title of invention:

Methods and compositions for the treatment of persistent infections and cancer by inhibiting the programmed cell death 1 (PD-1) pathway

Patent Proprietors:

Dana-Farber Cancer Institute, Inc.
The Brigham and Women's Hospital, Inc.
Emory University
The President and Fellows of Harvard College

Opponents:

Ares Trading S.A.
Pfizer Inc.
Regeneron Pharmaceuticals, Inc.
Janssen Biotech, Inc.
Sanofi

Headword:
NLPHL/DANA-FARBER

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0001/03, G 0002/21, T 0609/02, T 1329/04, T 0895/13, T 0950/13

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Beschwerdekammern

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Case Number: T 0294/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 26 October 2023

Appellants: (Patent Proprietors)	Dana-Farber Cancer Institute, Inc. 450 Brookline Avenue Boston, MA 02215 (US) The Brigham and Women's Hospital, Inc. 75 Francis Street Boston, MA 02115 (US) Emory University 1599 Clifton Road NE 4th Floor Atlanta, GA 30322 (US) The President and Fellows of Harvard College 17 Quincy Street Cambridge, MA 02138 (US)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 30 October 2019 revoking European patent No. 2397156 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Chakravarty
Members: D. Luis Alves
L. Bühler

Summary of Facts and Submissions

I. European patent EP 2 397 156, entitled "*Methods and compositions for the treatment of persistent infections and cancer by inhibiting the programmed cell death 1 (PD-1) pathway*", was granted on European patent application No. 11 162 681.8, a divisional application of European patent application No. 06 784 684.0, filed as an international application and published as WO 2006/133396.

II. Five parties filed oppositions, 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.

III. The opposition division decided to revoke the patent. The decision under appeal deals with a main request (the patent as granted) and five auxiliary claim requests. The opposition division held *inter alia* that none of the claim requests complied with the requirements of Article 83 EPC.

IV. The patent proprietors (appellants) filed an appeal against that decision.

V. With the statement setting out the grounds of appeal, the appellants refiled sets of claims of auxiliary requests 1 to 5, all identical to those pending before the opposition division.

VI. Opponents 1 to 5 (respondents I to V) replied to the statement setting out the grounds of appeal. Respondent V filed document D63.

VII. With letters dated 26 September 2023 and 19 October 2023, the appellants filed further arguments and document D64.

VIII. Oral proceedings were held by video conference in attendance of the appellants and respondent III. Respondents I, II, IV and V had previously withdrawn their requests that oral proceedings be held and informed the board that they would not be attending the oral proceedings. At the end of the oral proceedings, the Chair announced the board's decision.

IX. Claim 1 of the patent as granted (**main request**) reads:

"1. A compound that reduces the activity or expression of a Programmed Cell Death-1 (PD-1) polypeptide for use in a method of alleviating or preventing a symptom of cancer in a subject, wherein said compound is an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-1 RNAi, an anti-PD-L1 RNAi, an anti-PD-1 antisense RNA, or an anti-PD-L1 antisense RNA; wherein the cancer is nodular lymphocyte predominant Hodgkin lymphoma."

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

In claim 1 of **auxiliary requests 3 to 5**, the following compounds have been deleted: an anti-PD-L1 antibody, an anti-PD-L1 RNAi and an anti-PD-L1 antisense RNA.

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

D4: Blank *et al.*, Cancer Immunol Immunother 54(4), 2005, pages 307-314

D9: Dorfman *et al.*, Am J Surg Pathol 30(7), 2006, pages 802-810

D10: Blank *et al.*, Int J Cancer 119(2), 2006, pages 317-327

D27: Dong and Chen, J Mol Med 81, 2003, pages 281-287

D28: Carter and Carreno, Immunol Res 28, 2003, pages 49-59

D29: Khoury and Sayegh, Immunity 20, 2004, pages 529-538

D38: Poppema, Am J Pathol 135(2), 1989, pages 351-357

D39: Boudová *et al.*, Blood 102(10), 2003, pages 3753-3758

D42: Iwai *et al.*, Immunol Lett 83(3), 2002, pages 215-220

D55: Declaration of Dr. Rafi Ahmed dated 13 March 2018

D56: Chen *et al.*, Clin Cancer Res 19(13), 2013, pages 3462-3473

D57: Janeway *et al.*, Immunobiology, 6th edition, Garland Science Publishing, published June 2004, pages 353 and 379

D58: Shurin *et al.*, Springer Semin Immunopathol, 21(3), 1999, pages 339-359

D59: Nam-Cha *et al.*, Am J Surg Pathol 32(8), 2008, pages 1252-1257

D60: EMA Publication "EMA restricts use of Keytruda and Tecentriq in bladder cancer", dated 1 June 2018

D61: Agilent Dako Publication "PD-L1 IHC 22C3 pharmDx for Autostainer Link 48"

D62: Patent proprietor's reply in opposition against EP 2 397 155, dated 7 February 2019

D63: Patent proprietor's response to opposition against EP 2 397 156

D64: Gunawardana *et al.*, Blood 138, 2021, pages 3513-3515

XI. The appellants' arguments, as far as relevant to this decision, may be summarised as follows:

Disclosure of the invention (Articles 100(b) and 83 EPC)

Case law of the boards of appeal

A successful objection of insufficiency of disclosure presupposed serious doubts, substantiated by verifiable facts. In *inter partes* proceedings, the burden of proof initially was on the opponent. Moreover, in case of contradictory unsubstantiated assertions by the parties, the benefit of the doubt was given to the patent proprietor (see Case law of the Boards of Appeal of the European Patent Office, 10th edition ("Case Law Book") II.C.9 and decisions T 19/90, T 72/04, T 1437/07).

In the present case, no evidence had been filed by the opponents to the effect that the invention was not reproducible, i.e. that the claimed compounds did not treat nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).

The requirement developed in the case law applying specifically to claims directed to medical uses, in particular in decision T 609/02, was that the suitability of the compound to the claimed therapeutic effect required that the patent showed a metabolic mechanism specifically involved in the disease (see Case Law Book II.C.7.2.1 and 7.2.2). This could be demonstrated by a plausible technical concept (see in particular T 578/06 and T 950/13). A concept was plausible if it was not implausible.

Moreover, it was not required that the patent contained evidence showing a direct effect of the compound on the specific disease, only that it had a direct effect on the immune system. In the present case, an increase in T cell activity, by reactivation of the exhausted T cells, increased the immune response.

Decision G 2/21 did not change the established case law concerning the level of evidence required for a sufficient disclosure in the context of a claim relating to a therapeutic effect.

The common general knowledge

It was part of the common general knowledge at the relevant date that lymphoma was a specific type of cancer and that NLPHL differed greatly from other lymphomas (see document D55).

It was also part of the common general knowledge that the PD-1 pathway had been implicated in other types of cancer (see document D4).

Information in the patent

The patent described that, by contacting T cells with a compound reducing the expression or activity of PD-1, T cell cytotoxicity was increased and the immune response specific to an infectious agent was enhanced (see paragraphs [0007], [0026], [0052] and [0053]). Example 1 showed that chronic viral infections were concomitant with PD-1 expression, that exhausted T cells were concomitant with PD-1 expression, and that inhibition of PD-1 restored T cell activity. Example 9 showed PD-1 expression in T cells in the tumour microenvironment in all 14 cases of NLPHL tested. These results made it at least plausible that T cell exhaustion was present in NLPHL. Thus, the patent disclosed a link between NLPHL and restoring T cell activity by PD-1 blockade.

Exhausted T cells in NLPHL

T cell exhaustion was characteristic of cancer, as stated in document D55.

Moreover, the conclusions from the chronic infection model in example 1 could be extrapolated to cancer (see document D55) because the lymphocytic choriomeningitis virus (LCMV) infection model in Example 1 was "*a model for investigating immune responses in an environment of exhausted T cells, which is common to both persistent infection and cancers*".

PD-1/PD-L1 signalling pathway in NLPHL

In Example 9 expression of PD-1 was detected in T cells in the tumour microenvironment in all 14 cases of NLPHL tested. As stated in declaration D55, the uniformity of these results showed that the PD-1 pathway was active and the absence of data on PD-L1 expression was not relevant (see point 4 of declaration D55).

Post-published document D9

Document D9 did not constitute evidence of serious doubts that the invention could be carried out by the skilled person. On the contrary, it disclosed expression of PD-L1 in NLPHL (see page 806, right-hand column, top of the page and page 808, last full sentence).

Evidence filed to substantiate serious doubts

Document D56 was not relevant for assessing sufficiency of disclosure of the patent. Moreover, the criterium it used for classifying a tumour as PD-L1-positive, which was expression in at least 5% of the tumour cells, was called into question in the same document (see page 3463, right-hand column, paragraph 3 and page 3469, right-hand column, paragraph 2).

Documents used to substantiate serious doubts should represent common general knowledge. This included textbooks but did not include scientific publications. It should be noted that the documents cited in this regard by the respondents included scientific articles which were not reviews.

The respondents' argument that PD-1 expression by T cells in the tumour microenvironment in NLPHL did not demonstrate the presence of exhausted T cells was speculative. No evidence was submitted in support of this argument. An argument that there might be other explanations for T cell PD-1 expression did not amount to serious doubts. Also $CD4^+$ T cells could be exhausted (see document D38). The PD-1 pathway was known for CD4+ as well as for $CD8^+$ T cells (see documents D10 and D38).

XII. The respondent's arguments, as far as relevant to this decision, may be summarised as follows:

Case law of the boards of appeal and the information in the patent

It was contested that the burden of proof was on the opponents to show that the invention was not reproducible. Rather, according to the case law, the application had to disclose the suitability of the claimed compounds for the treatment of NLPHL. A mere verbal statement to this effect was not sufficient. Decision T 950/13 did not contradict this.

The patent relied on an indirect effect of the claimed compounds, which was that they enhanced T cell function. However, a mechanistic link between enhancement of T cell function and treatment of NLPHL was not shown in the patent. Example 9 did not relate to testing of T cells in NLPHL or testing for PD-L1 in NLPHL. The expression of PD-1 alone did not make a therapeutic effect on NLPHL plausible.

The common general knowledge

It was common general knowledge that antibody blockade for inhibiting growth in certain tumours relied on inhibition of engagement of PD-1 with its ligand (documents D4 and D27 to D29).

Exhausted T cells in NLPHL

The expression of PD-1 alone did not necessarily correlate with T cell exhaustion, since PD-1 was also expressed by activated T cells (see document D4, paragraphs 308 to 309) and germinal centre-associated cells (see documents D38, D38 and D42 and paragraph [0061] of the patent). Also example 9 of the patent referred to the similarity of PD-1 staining between NLPHL cells and $CD57^+$ cells, CD57 being a marker of germinal centre-associated T cells.

It was not correct that in a tumour environment the T cells were necessarily exhausted. The PD-1 pathway was not involved in every cancer type and its involvement could not be extrapolated from one cancer type to another (see declaration D55, paragraphs 10 and 11).

Whereas example 1 of the patent showed PD-1 and PD-L1 expression in exhausted lymphocytes in the context of the LCMV infection model, no such data was present in example 9. This example did not demonstrate that the relevant T cells were exhausted and it also did not prove that the PD-1-expressing T cells were $CD8^+$ T cells. The presence of PD-1 expression may also be explained by the germinal centre-origin of T cells surrounding the neoplastic cells in NLPHL. However it was known that germinal centre-associated T cells were

$CD4^+$ T cells (see documents D39 and D41). There was no teaching in the patent that PD-1 blockade would have any effect on $CD4^+$ T cells.

Post-published document D9

Document D9, which was post-published, could not be taken into account in the context of sufficiency of disclosure because the patent did not show a mechanistic link underlying the claimed therapeutic effect. This view was supported in decision G 2/21.

Notwithstanding this, document D9 confirmed a germinal centre origin of the PD-1 T cells (see title).

Documents filed to substantiate serious doubts

Document D56 disclosed lack of PD-L1 expression in NLPHL tumour cells. While it indicated the usefulness of PD-1 blockade for treatment of a number of lymphoproliferative disorders it did not draw such conclusions for treatment of NLPHL.

XIII. The requests of the parties were as follows:

The appellants requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or, alternatively, that the patent be maintained in amended form on the basis of the sets of claims of any of auxiliary requests 1 to 5, all filed with the statement of grounds of appeal. The appellants further requested that the board remit the case to the opposition division for further prosecution, to deal with the issues of novelty and inventive step, or, alternatively, that the appellants be given the opportunity to file submissions on this issue. They

also requested that document D64 be admitted into the appeal proceedings and that documents D56 to D61 not be admitted.

Respondent I requested in writing that the appeal be dismissed. They further requested that auxiliary requests 2 to 5 not be admitted into the appeal proceedings and that, should the board find that one of the requests complies with the requirements of sufficiency of disclosure, the board decide on inventive step.

Respondent II requested in writing that the appeal be dismissed.

Respondent III requested that the appeal be dismissed and that the case not be remitted to the opposition division for further prosecution. They also requested that the opposition division's decision to admit documents D56 to D61 be upheld, and that document D64 not be admitted into the appeal proceedings.

Respondent IV requested in writing that the appeal be dismissed. They further requested that auxiliary requests 1 to 5 not be admitted into the appeal proceedings, that the opposition division's decision to admit documents D56 to D61 be upheld, and that document D62 be admitted into the appeal proceedings.

Respondent V requested in writing that the appeal be dismissed. They further requested that documents D62 and D63 be admitted into the appeal proceedings and that the case not be remitted to the opposition division for further prosecution.

Reasons for the Decision

Admittance of documents D56 to D61

1. The appellants requested that documents D56 to D61 not be admitted into the appeal proceedings. Since the documents are not used by the board in reaching a decision and the appellants are not adversely affected by this decision, there is no need for the board to decide on this issue.

Document D64

2. The appellants filed this document in appeal proceedings in the context of sufficiency of disclosure, the issue decided on in this appeal. Moreover, admittance of this document into the appeal proceedings was disputed.

3. However at the oral proceedings before the board, the appellants stated that they no longer wished to rely on it. Therefore, the contents of this document and arguments relying on it have not been considered in this decision and there was no need for the board to decide on its admittance.

Main request - claim 1

Sufficiency of disclosure - Articles 100(b) and 83 EPC

4. Claim 1 is drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, and is directed to a compound that reduces the activity or expression of a Programmed Cell Death-1 (PD-1) polypeptide (in the following "PD-1 inhibitor") for use

in the treatment of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) (see point IX.).

5. According to decision G 2/21 (OJ EPO 2023, A85, point 77 of the Reasons), "*[i]n order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence.*" This intermediate conclusion of the Enlarged Board of Appeal can be understood as confirming the established case law that post-published evidence cannot be used to remedy a lack of sufficient disclosure in respect of a medical use (cf. T 609/02, headnote). By this statement, the Enlarged Board of Appeal can also be seen to have endorsed the jurisprudence of the boards of appeal that attaining a claimed therapeutic effect is a limiting functional technical feature of a claim directed to the use of a substance or composition in a method of treatment (see also G 2/21, point 74 of the Reasons). The above statement by the Enlarged Board of Appeal might also be understood to suggest a high standard of proof (i.e. "beyond reasonable doubt" rather than on "the balance of probabilities") which would require that the claimed therapeutic effect must, as a rule, be demonstrated in the application as filed by direct experimental evidence. However, in decision G 2/21 the Enlarged Board of Appeal focussed on the issue of whether or not post-published evidence can be used by an applicant or patent proprietor in the assessment of Articles 83 and 56 EPC, but did not

address the question of the level of proof in an application as filed required to substantiate a therapeutic effect as a prerequisite for using post-published evidence for assessing the requirements of Article 83 EPC.

The above question has nevertheless been part of considerations on "plausibility" in the assessment of sufficiency of disclosure of claims directed to the use of a substance or composition in a method of treatment in the case law cited by the Enlarged Board in G 2/21 (see point 74 to 76 of the Reasons) (see, e.g., T 609/02, point 9 of the Reasons: "*The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such*.").

6. The board therefore does not understand G 2/21 to have quashed the principles established by leading decision T 609/02 despite having qualified the term "plausibility" merely as a generic catchword. Indeed, as decision T 609/02 clearly sets out, a balance should be struck between enabling early patent protection for therapeutic uses and avoiding that the claimed invention is only completed at a later point in time. As a consequence, in order to fulfil the requirements of Article 83 EPC, the suitability of the product for the claimed therapeutic application must be derivable from the application, unless this is already known to the skilled person at the priority date (see T 609/02, point 9 of the Reasons and T 895/13, points 3 to 5 of the Reasons).

7. On how the suitability may be derived from the patent or application, the board in decision T 609/02 held:

"*It is required ... the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease ...*" (point 9 of the Reasons, emphasis added by the board).

8. Thus, in the case at hand it must be assessed whether the patent contains information on a direct effect of PD-1 inhibitors on a mechanism specifically involved in NLPHL.

9. It is undisputed that the patent does not report any testing of the suitability of a PD-1 inhibitor in an animal model of cancer or in cancer cells *in vitro*.

10. A central issue in this appeal concerns the information that the patent must contain about a direct effect of PD-1 inhibition on a mechanism specifically involved in NLPHL.

11. The appellants relied on decision T 950/13 to argue that such information may be in the form of a "plausible technical concept". However, the board considers that a "plausible technical concept" may not be stretched to include a mere hypothesis which has not to be supported by any evidence. Instead, the board confirms the principles developed in decision T 609/02, quoted above, that, "*it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement* [...] *is enough to ensure sufficiency of disclosure* [...]. *It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the*

prior art or demonstrated in the patent per se." (point 9 of the Reasons).

12. The board cannot accept the appellants' line of argument, that "plausible" in this context means that the "technical concept" and hence the suitability of the claimed compounds for the claimed therapeutic application is "plausible" as long as it is not shown to be "implausible". That would be in direct contradiction with the principles set out in decision T 609/12. The burden to show the suitability is on the applicant (see G 1/03, OJ EPO 2004, 413, point 2.5.3 of the Reasons: "*When an application for a patent is filed, the process of making the invention has to be completed. The requirement of sufficiency of disclosure ensures that a patent is only granted if there is a corresponding contribution to the state of the art. Such a contribution is not present as long as the person skilled in the art is not able to carry out the invention. Therefore, the decisive date for fulfilling the requirement has to be the date of filing or priority, as the case may be. Deficiencies in this respect cannot be remedied during the proceedings before the EPO.*"). This burden cannot be discharged or shifted to the EPO or the public by merely alleging that a claimed therapeutic effect has to be regarded as having been demonstrated as long as it has not been disproven.

13. The board therefore assesses below what can be inferred from the information provided in the patent as to a direct effect of a PD-1 inhibitor on a metabolic mechanism specifically involved in NLPHL.

14. The patent proposes that $CD8^+$ T cells expressing PD-1 no longer have the ability to proliferate and express

cytokines (they are "exhausted T cells"). Because PD-1 expressing T cells were detected in the tumour microenvironment in NLPHL, these had to be exhausted $CD8^+$ T cells. This exhausted state can be reversed by blockade of PD-1. It follows that reversing T cell exhaustion can be used to treat this cancer.

15. Example 9 is the only example that relates to proliferative disorders or mentions NLPHL. It shows the expression of PD-1 in samples of a number of B cell and T cell lymphoproliferative disorders. In NLPHL samples, there was no expression of PD-1 in the neoplastic cells, however, there was PD-1 expression in the T cells surrounding them ("rosettes" of T cells surrounding the neoplastic cells is a characteristic pattern in NLPHL). There is no report on expression of ligand PD-L1.

16. The appellants argued that the skilled person reading example 1 would learn that inhibition of PD-L1 has a direct effect on exhausted T cells and that, in a chronic infection environment, this effect leads to reversal of virus-specific T cell exhaustion and increased viral clearance. According to one line of argument, this reversal of T cell exhaustion by PD-1 inhibitor was suitable to treat NLPHL because the expression of PD-1 by T cells in this tumour microenvironment indicated T cell exhaustion.

17. The board notes however that example 1 does not concern cancer and the question of whether the reversal of T cell exhaustion is relevant for NLPHL is not investigated in the patent and is not derivable from the prior art either. Indeed, out of the examples in the patent, only example 9 refers to NLPHL, however it neither shows that cancer-specific $CD8^+$ T cells were

present in NLPHL nor that reversal of T cell exhaustion contributed to treatment of the NLPHL. Instead, as summarised above, Example 9 merely shows PD-1 expression in T cells surrounding the neoplastic cells.

18. Consequently, the skilled person reading the information contained in the patent at the relevant date, would not have concluded that an effect of PD-1 inhibitors on exhausted T cells was relevant to treatment of NLPHL. The board is therefore not persuaded by the appellants' argument that the patent shows that a compound as defined in the claim is suitable for alleviating or preventing a symptom of NLPHL. Indeed, the appellants on the one hand argued that tumours are characterised by T cell exhaustion and on the other hand that PD-1 expression is concomitant with T cell exhaustion. This explanation would lead to the conclusion that all cancers may be treated by PD-1 blockade, which manifestly is not the case. This is acknowledged in the declaration D55 submitted by the appellants:

"*All cancers are distinct and it is not possible to predict that a specific pathway, such as the PD-1 pathway, is present in any given type of cancer*" (see point 10), and

"*Lymphomas are a specific class of cancer, and NLPHL is a distinct type of lymphomas. NLPHL differs greatly from other lymphomas, such as classic Hodgkin's lymphoma and non-Hodgkin's lymphoma. Each type of lymphoma has its own unique tumour microenvironment, and you cannot predict which pathways will be present.*" (see point 11)

This passage, also illustrates why it is justified to require that the patent contains a mechanistic explanation specific to the claimed therapeutic use, in the case at hand treatment of NLPHL.

This point is further illustrated in document D4, which provides an overview of the knowledge on the blockade of PD-1/PD-L1 interaction for cancer therapy in 2005, and shows that a potential therapy relied on the presence of tumour-specific CD8+ T cells and on the expression of ligand PD-L1 by the tumour cells: "*Clinical responses have been found to correlate with $CD8^+$ lymphocyte infiltration of the carcinomas and with $CD8^+$ T cells producing IFN-γ [28, 30]. Interestingly, in vitro studies have revealed increased IFN-γ production by $CD8^+$ T cells upon stimulation with tumor cells when PD-L1 was blocked [7, 33]. Thus, the blockade of negative regulation via PD-L1/PD-1 might improve the induction of type I immune responses.*

Despite the presence of tumor-specific T cells within the tumors [42], tumor cell lysis is often prevented, and the clinical outcome of adoptive T-cell therapies is often disappointing [13, 20]. It is thought that the tumor microenvironment can restrict the effectiveness of activated antitumor lymphocytes [26, 65]. The blockade of PD-L1 on the tumor cells might improve stimulation of T cells after infiltration and thus allow for improved lysis of target cells in vivo [7, 68]." (see "Implications of PD-L1 for immunotherapy", on page 312).

19. A further line of argument was that the suitability of PD-1 inhibitors for treatment of NLPHL could be extrapolated from Example 1. In the appellants' view, this was the case because an environment of exhausted

T cells is common to both chronic infections (addressed in example 1) and cancer.

20. In the board's view, this line of argument must fail for the reasons set out above (see point 17.) which already considered and dismissed the argument that a direct effect on the immune system, in the case in hand on exhausted T cells, demonstrated the suitability of the claimed compound for the therapy of NLPHL.

21. In a still further line of argument, the appellants asserted that T cell expression of PD-1, as shown in Example 9 of the patent, was in itself evidence of an active PD-1/PD-L1 pathway, so that the absence of data concerning PD-L1 expression by the tumour cells in NLPHL did not affect the completeness of the disclosure.

However, as set out in point 15. above, the patent does not demonstrate that this is the case and it was not derivable from the art at the relevant date.

22. In a final line of argument the appellants put forward that post-published document D9 confirmed the expression of PD-L1 by the tumour cells in NLPHL.

23. However, in line with the established case law (see decision T 609/02, point 13 of the Reasons and T 1329/04, point 12 of the Reasons), in a case where the patent provides only a vague indication of the suitability of the claimed compound for the therapeutic effect, post-published evidence may not be taken into account to remedy the insufficiency of disclosure. In the present case, for the reasons set out above in point 15., document D9 would be the first disclosure of an interaction between PD-1 and its ligand PD-L1 in

NLPHL, and therefore would be the first disclosure of a possible mechanism underlying the claimed therapeutic effect. This line of argument must fail.

Auxiliary requests 1 to 5 - claim 1

Sufficiency of disclosure - Article 83 EPC

24. Claim 1 of auxiliary requests 1 and 2 is identical to claim 1 of the main request. Accordingly, the conclusions above apply equally to auxiliary requests 1 and 2.

25. In comparison with claim 1 of the main request, in claim 1 of auxiliary requests 3 to 5 the compound is limited to an anti-PD-1 antibody, an anti-PD-1 RNAi or an anti-PD-1 antisense RNA. Since the reasoning above in the context of the main request relates to inhibitors targeting PD-1, it applies equally to claim 1 of auxiliary requests 3 to 5.

Conclusion

26. None of the claim requests is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Chavinier-Tomsic A. Chakravarty

Decision electronically authenticated