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Datasheet for the decision of 13 October 2016

Case Number: T 0890/12 - 3.3.04

Application Number: 04789341.7

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IPC: A61K39/385, A61K39/00

Language of the proceedings: EN

Title of invention:
In vivo efficacy of NY-ESO-1 plus adjuvant

Applicants:
Ludwig Institute for Cancer Research
CSL Limited

Headword:
NY-ESO-1 cancer vaccine/LUDWIG INSTITUTE

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request - meets requirements of EPC (yes)

Decisions cited:

Catchword:

-

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European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0890/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 October 2016

Appellant: (Applicants)	Ludwig Institute for Cancer Research 605 Third Avenue New York, NY 10158 (US)
	CSL Limited 45 Poplar Road Parkville, Victoria 3052 (AU)
Representative:	Marshall, Cameron John Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 19 October 2011 refusing European patent application No. 04789341.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application No. 04789341.7. The application was published as WO 2005/032475 with the title *"In vivo efficacy of NY-ESO-1 plus adjuvant"*.

II. The following documents are cited in this decision:

D9 and D10: Cebon *et al.* (2002), Proc. Am. Soc. Clin. Oncol., Vol. 21, Abstract 86.

Note: Whereas documents D9 and D10 have the same title and an almost identical abstract, document D10 includes copies of 16 presentation slides giving additional detail about the phase I clinical trial reported on in the abstract.

D11: Nicholaou *et al.* (manuscript): "Improved survival and persistence of antigen-specific immunity in patients with NY-ESO-1 positive cancers and minimal residual disease."

D12: Marchand *et al.* (2001), *Exp. Opin. Biol. Ther.*, Vol. 1, No. 3, pages 497-510.

D18: Jäger *et al.* (2000), Proc. Nat. Acad. Scien., Vol. 97, No. 22, pages 12198-12203.

III. The examining division held that the subject-matter of claims 1 and 12 of the main request and claim 1 of auxiliary requests 1 and 2 lacked inventive step (Article 56 EPC) in view of the disclosure in document "D9/D10" (the board hereinafter refers to document D9 only since the additional detail contained

in document D10 was not relevant for assessing inventive step).

IV. With the statement of grounds of appeal the applicants (hereinafter "appellant") filed a main and an auxiliary request (identical to the main request and auxiliary request 1 considered in the decision under appeal), arguments in favour of inventive step and three documents. Claim 1 of the auxiliary request read:

"1. An immunogenic composition comprising NY-ESO-1 protein and a saponin based adjuvant, for use in preventing relapse in a patient suffering from a cancer, cells of which express NY-ESO-1."

V. In a communication pursuant to Article 15(1) RPBA, the board expressed its preliminary views regarding claim construction, clarity, sufficiency of disclosure and inventive step. In the context of the latter the board introduced a new document D18 into the proceedings and held that the teaching of this document, rather than the disclosure of document D9, represented the closest prior art for the assessment of inventive step. The board was of the preliminary opinion that the subject-matter of claim 1 of the main request lacked inventive step over a combination of the disclosures in documents D18 and D9.

VI. The appellant submitted, in response to the board's communication, arguments and auxiliary requests 2 to 11 addressing issues of clarity and sufficiency of disclosure.

VII. The appellant was heard by the board during oral proceedings at the end of which the appellant maintained a sole request comprising 13 claims of which claim 1 read:

"1. An immunogenic composition comprising NY-ESO-1 protein having the amino acid sequence SEQ ID NO: 1 and a saponin based adjuvant, for use in preventing relapse in a patient who has previously exhibited a cancer that expressed NY-ESO-1, and who has minimal residual disease."

Claims 2 to 13 of this request depended on claim 1.

Subsequently, the chairwoman announced the decision of the board.

VIII. The appellant's arguments can be summarised as follows:

Article 123(2) EPC

Claim 1 found a basis in claims 1 and 2 of the application as filed combined with the disclosure in examples 1 and 6 and, in particular, the disclosure in paragraphs [0013], [0020], [0022], [0048] and [0049].

Article 56 EPC

The problem to be solved by the subject-matter of claim 1 was the provision of a composition to prevent relapse in patients suffering from a wide range of cancers.

The subject-matter of claim 1 was not obvious to the skilled person when combining the disclosures in documents D18 and D9.

In particular, document D9 reported the results of a phase I medical trial. The skilled person would have understood document D9 as providing information on the

safety of such a composition, and not on its clinical efficacy. Nothing in document D9 or in any of the other cited prior art suggested that the NY-ESO-1 antigen could be targeted for the prevention of relapse or that an immune response to NY-ESO-1 would be effective against residual cancer cells.

On the contrary, in view of the existence of a natural immune response to NY-ESO-1 and the lack of a correlation between immune response and therapeutic benefit in other trials as reported on in document D12, it would not have been obvious to the skilled person that a therapeutic effect against resilient residual cancer cells would be generated.

Document D9 did not suggest to the skilled person to test clinical efficacy of NY-ESO-1 vaccines on patients in danger of relapse, but rather to investigate clinical response in patients with "evaluable cancer" (see document D9, last sentence).

IX. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division with the order to grant a patent with claims 1 to 13 of the main request filed during the oral proceedings and a description to be adapted thereto.

Reasons for the Decision

1. The appeal is admissible.

EPC requirements other than Article 56 EPC

2. In the decision under appeal, the examining division did not question the compliance of the application with the

requirements of Articles 54, 83, 84 and 123(2) EPC. The board does not see any reason to differ and is satisfied that the main request complies with these requirements.

3. The board notes that the subject-matter of claim 1 finds a basis in claims 1 and 2 of the application as filed combined with the disclosure in examples 1 and 6. Reference is made in particular to the disclosure in paragraph [0022] for the patient group now recited in claim 1.

4. Furthermore, although document D9 discloses administration of a composition comprising the full-length NY-ESO-1 protein and a saponin-based adjuvant to patients who have previously exhibited a cancer that expressed NY-ESO-1 and have minimal residual disease, the purpose of the disclosed administration was the evaluation of safety and immunogenicity (see abstract line 5) and not a clinical effect such as the prevention of relapse in such patients (see also point 8 below). Accordingly, the board is satisfied that the requirements of Article 54 EPC are fulfilled.

5. The board considers also that in particular examples 1 and 6 disclose the suitability of the full-length NY-ESO-1 protein and a saponin based adjuvant for use in preventing relapse in the group of patients now defined in claim 1. The results disclosed have been supplemented with further experimental confirmation from document D11. Accordingly, the board is satisfied that the requirements of Article 83 EPC are fulfilled.

Inventive step (Article 56 EPC)

The closest prior art

6. To assess whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention (Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.3.1).

7. Claim 1 is in the "second medical use format" according to Article 54(5) EPC and states explicitly the clinical effect to be achieved and therefore the purpose of the invention, *i.e.* "for use in preventing relapse in a patient who has previously exhibited a cancer that expressed NY-ESO-1, and who has minimal residual disease" (see section VII).

8. Document D9, which the examining division considered to represent the closest prior art for the subject-matter of a similar claim (see section IV), discloses (i) the use of an immunogenic composition which structurally falls under the definition of the immunogenic composition defined in claim 1 and (ii) a patient group as defined in claim 1 (*i.e.* "*46 patients with MRD and NY-ESO-1 positive tumours*", see lines 5 to 6), but the board is not convinced that it relates to the same purpose as the present invention, *i.e.* the effective prevention of relapse in such patients. Indeed, phase I clinical trials, such as those to which document D9 relates, are primarily designed to evaluate safety,

tolerability and pharmacokinetics of a drug, and do not primarily aim at demonstrating an effective clinical effect. This fact is indeed explicitly stated in document D9: "*The objectives of this study were to evaluate the safety and immunogenicity of an NY-ESO-1 ISCOM^{R} vaccine*" (see abstract, lines 4 to 5).

9. In such a situation, where the exact same clinical purpose is not explicitly addressed in the prior art, the board considers that the teaching in the art which represents the closest prior art is a teaching which describes a clinical effect which is similar and related to the claimed one.

10. Document D18, a document cited in in paragraph [0005] of the application as published and introduced into the proceedings by the board (see section V), discloses the results of a clinical trial including 12 patients with NY-ESO-1 expressing metastatic tumours who were administered HLA-A2 restricted NY-ESO-1 peptides either alone or in combination with GM-CSF "*at a distant site to act as a nonspecific immunopotentiator for peptide immunization*" (see page 12202, right-hand column, lines 17 to 20). The results demonstrate not only that the peptide vaccines are safe and generate T-cell responses, but also that several patients showed stabilisation or regression of metastasis (see page 12201, part "*Disease status*" and page 12203, sole full paragraph). The board is therefore satisfied that document D18 discloses a clinical effect on NY-ESO-1-expressing tumours in patients which is similar and related to the claimed technical effect.

11. Consequently, the board is of the view that for the case at hand the teaching in document D18, rather than the

disclosure in document D9, represents the closest prior art for the assessment of inventive step.

The technical problem and its solution

12. Whereas the patient group disclosed in document D18 have NY-ESO-1 expressing tumours including metastatic tumours, claim 1 refers to patients who have minimal residual disease and previously exhibited a NY-ESO-1 expressing cancer.

13. Accordingly, the board considers that the technical problem to be solved by the invention as defined in claim 1 can be formulated as the provision of a composition for use in preventing relapse in a patient who has previously exhibited an NY-ESO-1-expressing cancer, and who has minimal residual disease.

14. The board is satisfied that the application as filed demonstrates that the immunogenic compound defined in claim 1 solves this technical problem (see point 5 above).

Obviousness

15. Document D18 itself does not suggest to the skilled person that vaccines based on full-length NY-ESO-1 protein would have a clinical benefit in the patient group addressed in the document, let alone that they would be effective in preventing relapse in minimal-residual-disease patients.

16. The board considers however that the skilled person, seeking a solution for the technical problem would readily have taken into consideration the disclosure in document D9, which reports on the results of a phase I

clinical trial concerning the administration of a composition comprising full-length NY-ESO-1 protein and a saponin adjuvant (*i.e.* ISCOM^{R}) to patients as defined in claim 1 (*i.e.* "*46 patients with MRD and NY-ESO-1 positive tumours*", see abstract lines 5 to 6, whereby "MRD" stands for minimal residual disease).

17. Document D9 relates to a phase I clinical trial. Such trials are primarily concerned with providing information on the safety of an administered composition and are not intended or designed to provide information about a possible clinical benefit in the patient group treated. The board notes that, although document D9, in addition to the safety aspect, also addresses the immunogenicity of the disclosed composition in terms of antibody titres and T-cell response in the patients, the skilled person was well aware that, particularly in the technical field of cancer immunotherapy, there existed no reliable correlation between the ability of a vaccine to induce an anti-tumour immune response and ability to achieve a beneficial therapeutic effect for the patients (see e.g. document D12, page 502, right-hand column, third paragraph).

18. In view of these considerations the board must conclude that the teaching of the phase I trial disclosed in document D9 cannot be considered to suggest to the skilled person any particular clinical efficacy of the disclosed composition in the patient group in which the trial was conducted, let alone such a clinical efficacy relating to the prevention of relapse in patients who previously exhibited a NY-ESO-1 expressing cancer and having minimal residual disease.

19. The board considers that this conclusion finds also particular corroboration in the disclosure of

document D9 itself. In fact, the final conclusion of the document reads: "*Conclusion: vaccination with NY-ESO-1 ISCOM^R was safe and high titre humoral and cellular immune responses to NY-ESO-1 occurred. Correlation of NY-ESO-1 immunity with clinical response needs to be investigated in patients with evaluable tumours.*" Therefore, the authors of document D9 themselves did not suggest establishing the correlation in the patients in the phase I clinical trial, *i.e.* in patients with minimal residual disease, but in a substantially different patient group, *i.e.* those with evaluable tumours.

20. In view of the above considerations the board concludes that the subject-matter of claim 1 is not obvious to the skilled person in the light of the prior art. Accordingly, the board decides that the subject-matter of claim 1 involves an inventive step (Article 56 EPC). This applies *mutatis mutandis* to the subject-matter of claims 2 to 13 which are dependent on claim 1.

21. The board accordingly concludes that the main request fulfills the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description to be adapted thereto:

   claims 1 to 13 of the main request filed during the oral proceedings and labelled "13th October 2016".

The Registrar: The Chairwoman:

N. Schneider G. Alt

Decision electronically authenticated