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Datasheet for the decision of 10 May 2021

Case Number: T 0795/17 - 3.3.04

Application Number: 08744263.8

Publication Number: 2121008

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Language of the proceedings: EN

Title of invention:
Uses of monoclonal antibody 8H9

Applicant:
Sloan-Kettering Institute for Cancer Research

Headword:
Antibody 8H9 for treatment of brain cancer/SLOAN KETTERING

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - sole request (no)

Decisions cited:

Catchword:

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Case Number: T 0795/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 May 2021

Appellant: (Applicant)	Sloan-Kettering Institute for Cancer Research 1275 York Avenue New York, NY 10021 (US)
Representative:	Lecca, Patricia S. Cabinet Lecca 21, rue de Fécamp 75012 Paris (FR)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 26 October 2016 refusing European patent application No. 08744263.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. The appeal by the applicant (appellant) concerns the decision of the examining division to refuse the European patent application No. 08 744 263.8, entitled "*Uses of monoclonal antibody 8H9*".

II. The decision under appeal dealt with a main request and an auxiliary request. The examining division held that the claims according to the main request were not clear (Article 84 EPC) and that their subject-matter extended beyond the content of the application as filed (Article 123(2) EPC). The subject-matter of the claims according to the auxiliary request did not involve an inventive step (Article 56 EPC).

As regards lack of inventive step, the examining division essentially reasoned in relation to auxiliary request 1 that document WO 03/075846 (document D1) represented the closest prior art to the claimed subject-matter. It disclosed that antibody 8H9 bound specifically to tumour tissues, and, when conjugated to radioactive iodine, it induced tumour suppression in an *in vivo* model of rhabdomyosarcoma. The objective technical problem to be solved by the claimed subject-matter was formulated as "*the adaptation of the medical use disclosed in document D1 to a further alternative type of cancer (primary brain tumor) or to another localisation of peripheral cancers that have metastasized to the CNS*". The application of the radioactive conjugate to the treatment of primary brain tumours or cancers metastatic to the CNS was obvious in view of the disclosure in document D1 of the specificity of the antibody 8H9 for primary brain

tumour tissues. The skilled person had no reason to adopt a skeptical attitude and no such reason was provided by document D1 either.

III. With the statement setting out the grounds of appeal, the appellant filed a set of claims as the sole claim request.

Independent claim 1 read as follows (differences compared with the auxiliary request dealt with in the decision under appeal underlined):

"1. An antibody construct for use as a medicament for improving the prognosis or prolonging the survival of a subject having primary brain tumors or cancers metastatic to the CNS, wherein said antibody construct binds to the CD276 antigen and comprises heavy chain CDRs (Complementary Determining Regions) 1-3 having the sequences of SEQ ID NOs. 1-3 respectively, and light chain CDRs 1-3 having the sequences of SEQ ID NOs. 4-6 respectively, wherein said antibody is directly or indirectly coupled to a radioisotope, and wherein said antibody is administered by intrathecal injection, at a dose of 1 to 100 mCi of 131-iodine, 124-iodine, or biologically equivalent radioactive dosages of beta-emitters, alpha emitters or positron emitters."

IV. The board issued a summons to oral proceedings to be held on 4 December 2019, accompanied by a communication pursuant to Article 15(1) RPBA 2007 in which the board set out its preliminary view on the appeal. The board indicated, *inter alia*, that obviousness of the claimed subject-matter would be discussed at the oral proceedings. In particular, the communication addressed the appellant's argument relating to obstacles that would have deterred the skilled person from using the

antibody as disclosed in document D1 in the treatment of primary brain tumours or cancers metastatic to the CNS. In the board's preliminary view such obstacles were not apparent from this document, in which a radioisotope-antibody conjugate was already used for imaging a CNS cancer and was suggested for therapy of solid cancers. The appellant's argument that other antibodies had been found ineffective for treatment of brain tumours and metastasis in spite of their efficacy for treatment of other tumours was not considered pertinent to the present case.

V. In their reply of 3 November 2019 the appellant informed the board that they did not intend to attend the oral proceedings.

No substantive submissions were made in reply to the board's communication.

VI. The board cancelled the oral proceedings by communication dated 21 November 2019.

VII. The appellant's arguments, submitted in writing and insofar as relevant for the present decision, may be summarised as follows:

Document D1 did not disclose any results concerning the use of the antibody 8H9 for the treatment of primary brain tumours or cancers metastatic to the central nervous system (CNS).

The objective technical problem solved by the claimed subject-matter with respect to the disclosure in that document was the provision of a treatment which could significantly improve the prognosis and/or substantially extend the survival of patients having

primary brain tumours or cancers metastatic to the CNS with minimal toxicity.

This problem was solved by the once-monthly administration of an intrathecal injection of 131-iodine conjugated to antibody 8H9 at a dose in the range of 10 to 40 mCi per injection, as shown by the results in Example 1 of the application.

Whilst it was recognised that document D1 disclosed that anti-CD276 antibody 8H9 bound to a number of cancer tissues including tissues from glioblastoma, astrocytoma and oligodendroglioma, without binding to normal surrounding tissues, it was contested that document D1 disclosed significant *in vivo* antibody-dependent cellular cytotoxicity (ADCC) of tumour cells. In this respect, reference was made to section 2.13 of this document.

The ability of an antibody to be specific for tumour *versus* normal tissue *in vitro* did not render obvious its ability to result *in vivo* in an extension of patient survival. In fact, most commercially available antibodies with such specificity were merely used for diagnostic purposes, without being used for therapy.

It was acknowledged that the results in document D1 showed significant tumour suppression in an *in vivo* model of rhabdomyosarcoma after administration of the 8H9 antibody conjugated to radioactive iodine. The antibody conjugate was also able to localize neuroblastoma tumour in xenografted SCID mice; however, these results in neuroblastoma and rhabdomyosarcoma were not predictive of prolonging survival of patients suffering from primary brain tumours or cancers metastatic to the brain. Both neuroblastoma and

rhabdomyosarcoma were completely different types of cancer to those in the claim in terms of their location in the body and their pathogenesis.

To provide successful therapy, multiple obstacles had to be overcome, related to (i) the blood brain barrier; (ii) the half-life of the monoclonal antibody in the cerebrospinal fluid (CSF); (iii) clearance of cerebrospinal fluid and its irregular distribution; (iv) difficulties in the antibody reaching the tumour tissue; (v) drug resistance; (vi) toxicity of the antibody; (vii) impact of route of administration and dosing in the efficacy and toxicity.

Examples of antibodies which had been investigated without success for the treatment of primary brain tumours or cancers metastatic to the brain included trastuzumab, bevacizumab, fresolimumab, cetuximab and nimotuzumab.

Due to the risks and difficulties associated with the intrathecal delivery route, it was not a matter of routine experimentation to optimise the dose of the conjugate to be delivered.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims in the main request.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Main request

Inventive step - Article 56 EPC
Closest prior art

2. Claim 1 relates to two aspects: the treatment of primary brain tumours and the treatment of cancers metastatic to the central nervous system (CNS). In the following the board is dealing with the second aspect only.

3. The examining division held the disclosure in document D1 to represent the closest prior art with respect to claim 1 of the auxiliary request before it.

4. In comparison to that claim, present claim 1 specifies that the antibody is coupled to a radioisotope and defines a mode of administration and dose (see section III. above).

5. The appellant submitted arguments in support of inventive step of this claimed subject-matter with regard to the disclosure in document D1. The appellant did not submit a different starting point for the assessment of inventive step and the board sees no reason to do so either.

6. Document D1 discloses uses of monoclonal antibody 8H9. This antibody falls within the definition in present claim 1 and is the specific antibody exemplified in the patent application (see claim 1 and Example 1 of the patent application). Document D1 discloses that antibody 8H9 is highly reactive with brain tumour tissue (see page 1, lines 22 to 27 and Table 1, on pages 21 to 22). It binds to the surface protein CD276,

which is expressed on a number of tumour tissues, including various types of brain tumours, and has very restricted expression in normal tissue. Intravenous administration of the antibody conjugated to a radio-iodine, in a dose of 100 µCi, showed that the antibody was able to localise neuroblastoma and rhabdomyosarcoma xenografts in mice (see page 52, second paragraph and page 97, second paragraph). Administration of the conjugate induced greater than 50% reduction in tumour volume in the rhabdomyosarcoma model (see page 145, last paragraph to page 147, first paragraph).

Objective technical problem

7. The subject-matter of claim 1 differs from this disclosure on account of the condition to be treated, namely primary brain tumours or cancers metastatic to the CNS (yet see point 2. above). The claimed subject-matter further differs from the disclosure in document D1 in that a route of administration, intrathecal injection, together with a dose is defined in the claim.

8. Example 1 in the application shows extended survival for CNS metastatic neuroblastoma patients having been administered a dose of 10 to 40 mCi delivered directly to the cerebrospinal fluid (CSF).

Accordingly, the objective technical problem is the provision of a further therapeutic use of the radioisotope-antibody conjugate disclosed in document D1.

9. The application already identifies a similar aim, stating in the background to the invention: "*Monoclonal*

antibody 8H9 can be used for tumor targeting and imaging, and purging of tumor cells. The 8H9 antigen is also a potential target for antibody-based immunotherapy against a broad spectrum of tumor cancers, including neuroblastoma, brain tumors [...] The present disclosure provides further data on using monoclonal antibody 8H9 to improve the prognosis and/or prolong the survival of a subject bearing tumor cells" (see paragraphs [0004] and [0005]).

10. The appellant submitted that the objective technical problem was the provision of a treatment which could significantly improve the prognosis and/or substantially extend the survival of patients having primary brain tumours or cancers metastatic to the CNS but with minimal toxicity. The problem was solved by the intrathecal administration of a single injection, or of a once-monthly injection, of the conjugate ^{131}I-8H9 in a dose of 10 to 40 mCi.

11. The board is not persuaded that the problem should be formulated in the manner proposed by the appellant. This is the case because this problem does not take into account that document D1 already discloses the same conjugate as referred to in the claim and its use for the treatment of a different condition. Therefore, the difference between the claimed subject-matter and the closest prior art is found in the cancer to be treated (see point 7. above), and not in the compound used for the treatment. Consequently, the problem as formulated by the appellant anticipates the solution, which is an inappropriate way of formulating the objective technical problem (see Case Law of the Boards of Appeal, 9th edition, 2019, I.D.4.3.1).

Obviousness

12. In the light of the problem formulated, it remains to be assessed whether the skilled person seeking to provide a further therapeutic application of the radioisotope-antibody conjugate disclosed in document D1 would have provided the conjugate for the treatment of cancers metastatic to the CNS by intrathecal injection and in the dose defined in claim 1.

13. The board holds that the skilled person, starting from the disclosure in document D1 of the specificity of the radioisotope-8H9 conjugate for brain tumour tissue and its efficacy in suppressing a solid tumour in an *in vivo* model, would provide this conjugate for the therapeutic application claimed unless there were reasons not to do so.

14. The appellant argued there were such reasons, and submitted a list of difficulties to be overcome for treatment of brain tumours or metastases, which may be grouped into the following categories: difficulties in the conjugate accessing the tumour tissue and sufficient contact time with it; toxicity and drug resistance.

15. This argument relating generally to difficulties in the treatment of brain tumours and metastases was, however, not supported by any evidence. On the other hand, the teaching in document D1, which discloses administration of a different radioisotope-antibody conjugate to patients suffering from leptomeningeal cancer, a CNS cancer as encompassed by the claim, calls into question the appellant's argument. For the conjugate ^{131}I-3F8,

i.e. a conjugate with an antibody to a different antigen (ganglioside GD2), this document discloses that upon direct administration to CSF of these patients, the conjugate localised to the ventricles, spine and midbrain in agreement with the condition as seen on magnetic resonance imaging (see "Second series of experiments" on pages 35 to 64, in particular page 44). The imaging of solid tumours is regarded in this document as a major indication of the potential of the conjugate for therapy (see page 40, lines 8 to 10). Therefore, instead of reporting any of the difficulties listed by the appellant, this document applies the concept of administering a radio-iodine-antibody conjugate for imaging a CNS cancer and suggests its application in therapy.

In light of this disclosure, the board is not persuaded by the non-specific difficulties argued by the appellant.

16. Further developing this line of argument, the appellant submitted examples of antibodies which they argued were effective in other tumours but proved ineffective for brain tumour and CNS metastasis. The board does not find this argument persuasive as there can be multiple reasons for the lack of efficacy of those antibodies in the therapy of brain tumours, those reasons not necessarily being related to the difficulties listed by the appellant. A possible reason unrelated to such difficulties is, for example, a low antibody discrimination between tumour and healthy tissue. Such a reason is, however, not a limitation applicable to the present antibody; indeed, the discriminatory power of the tumour antigen CD276 and its binding antibody 8H9 is particularly highlighted in document D1 in the context of the therapeutic application of antibodies

(see document D1, "First series of experiments", page 16 and those following, page 1, lines 19 to 27, and page 2, lines 22 to 32).

17. In conclusion, none of the appellant's arguments has succeeded in persuading the board that there were reasons which would have deterred the skilled person from applying the conjugate disclosed in document D1 to the therapy of primary brain tumours and cancers metastatic to the brain.

18. Having come to this conclusion, the question that remains is whether the skilled person would have provided the radioisotope-antibody conjugate by intrathecal injection in the dose claimed.

19. Intrathecal delivery aims to maximise the concentration of the substance to be delivered into the CNS. This is a possibility the skilled person would consider in the context of therapy of brain tumours and metastasis to the CNS. In fact, as summarised in point 15. above, document D1 describes the administration of the radio-iodine-3F8 antibody conjugate by direct delivery to the CSF of patients with leptomeningeal cancer (see page 44).

20. The appellant has not argued to the contrary, i.e. that intrathecal administration was not an option. Instead they submitted that in view of the risks associated with the intrathecal route of administration, it was not a matter of routine experimentation to define the dose.

The board is not convinced that the need to optimise the dose for intrathecal administration would have dissuaded the skilled person from applying the

conjugate in the therapy of brain tumours via the intrathecal route. No evidence in this respect has been submitted to the board. Document D1, on the other hand, discloses that the patients suffering from leptomeningeal cancer received doses of the radio-iodine conjugate in the range 0.7 to 1.9 mCi (page 44, line 11) for imaging and in a phase I toxicity study received an initial dose of 10 mCi. Therefore, in view of this evidence the board comes to the conclusion that the skilled person was aware of suitable doses for therapy by intrathecal administration of a radioisotope-antibody conjugate such that no experimentation, or at least nothing more than routine experimentation, to define a dose was necessary.

21. In conclusion, the subject-matter of claim 1 does not comply with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

A. Chavinier Tomsic G. Alt

Decision electronically authenticated