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Datasheet for the decision of 19 March 2024

Case Number: T 0203/22 - 3.3.04

Application Number: 13787935.9

Publication Number: 2847223

IPC: C07K16/28, C07K14/725

Language of the proceedings: EN

Title of invention:
Anti-B7-H6 antibody, fusion proteins, and methods of using the same

Patent Proprietor:
Trustees of Dartmouth College

Opponent:
Boehringer Ingelheim RCV GmbH & Co KG /
Boehringer Ingelheim International GmbH

Headword:
Targeting B7-H6/DARTMOUTH COLLEGE

Relevant legal provisions:
EPC Art. 54, 56, 123(2)
RPBA 2020 Art. 12(4), 12(6)

Keyword:

Article 123(2) EPC objections - not admitted
Novelty - yes
Inventive step - yes - improved effect / non-obvious alternative

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Case Number: T 0203/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 March 2024

Appellants: (Opponents)	Boehringer Ingelheim RCV GmbH & Co KG Dr. Boehringer-Gasse 5-11 1121 Wien (AT) and Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Trustees of Dartmouth College Technology Transfer Office 11 Rope Ferry Road Hanover, NH 03755-1404 (US)
Representative:	Goodacre, Jonathan David Keltie LLP No.1 London Bridge London SE1 9BA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 December 2021 concerning maintenance of the European Patent No. 2847223 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	M. Blasi

Summary of Facts and Submissions

I. The joint opponents (appellants) filed an appeal against the interlocutory decision of the opposition division that European patent 2 847 223 as amended in the form of auxiliary request 3, and the invention to which it relates, meets the requirements of the EPC.

II. The patent was granted on European patent application No. 13 787 935.9, which had been filed as an international application under the PCT published as WO 2013/169691 A1 ("application as filed"), claiming priority from US 61/643,456 filed on 7 May 2012 (PRIO1) and US 61/705,227 filed on 25 September 2012 (PRIO2).

III. In its decision, the opposition division held that the main request (patent as granted) extended beyond the content of the application as filed within the meaning of Article 100(c) EPC, that the claims of auxiliary request 1 were not clear within the meaning of Article 84 EPC, and that the subject-matter claimed in auxiliary request 2 was novel within the meaning of Article 54 EPC but lacked an inventive step with in the meaning of Article 56 EPC and clarity within the meaning of Article 84 EPC.

Auxiliary request 3 (with the set of claims filed during oral proceedings entitled "*Replacement Auxiliary Request 3a*") was found to comply with the requirements of the EPC.

The claimed priorities of 7 May 2012 and 25 September 2012 were found not to be valid under

Article 87 EPC for medical use claims 9 to 12 (identical for all the claim requests).

IV. With the statement of grounds of appeal, the appellants raised objections under Articles 54, 56, 83, 87 and 123(2) EPC against the claims of auxiliary request 3. The appellants also filed new document D32.

V. The patent proprietor (respondent) replied to the statement of grounds of appeal, defending auxiliary request 3 as considered allowable by the opposition division (main request).

VI. The appellants reacted filing a further submission.

VII. The board issued a communication pursuant to Article 15(1) RPBA.

VIII. By letter dated 5 March 2024, the appellants submitted documents D25a and D25b.

IX. By letter dated 8 March 2024, the respondent filed the set of claims of auxiliary request 4.

X. Oral proceedings took place as requested by the parties. During the oral proceedings before the board the appellants withdrew

- their objections as to the invalidity of priority under Article 87 EPC;
- their novelty objections under Article 54 based on document D3;
- their inventive step objections starting from document D4 or D13 as closest prior art;
- their objections under Article 83 EPC;
- their request for admittance of document D32.

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

XI. The independent claims of auxiliary request 3 read as follows:

"1. A chimeric antigen receptor comprising:
(a) an antigen binding fragment of an antibody that specifically binds to B7 homolog 6,
(b) a transmembrane region, and
(c) an intracellular T-cell receptor signaling domain."

"4. A recombinant T cell comprising the chimeric antigen receptor of any one of claims 1 to 3.

5. A bi-specific T-cell engager consists of:
(i) an antigen binding fragment of an antibody that specifically binds to B7 homolog 6, and
(ii) an antigen binding domain which binds to a T-cell antigen; and
(iii) a linker
wherein the antigen binding fragment of (i) is a [sic] anti-B7H6 scFv and wherein the antigen binding domain of (ii) is an anti-CD3 scFv, and
wherein the anti-B7H6 scFv and the anti-CD3 scFv are fused together by the linker."

"8. A pharmaceutical composition comprising the chimeric antigen receptor of any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

9. The chimeric antigen receptor of any one of claims 1 to 3 for use as a medicament.

10. A pharmaceutical composition comprising an effective amount of the chimeric antigen receptor of

any one of claims 1 to 3 for use in killing or inhibiting the growth of cells expressing B7 homolog 6 in a subject.

11. A pharmaceutical composition comprising an effective amount of the chimeric antigen receptor of any one of claims 1 to 3 for use in treating a disease or condition associated with elevated expression of B7 homolog 6."

XII. Reference is made to the following documents:

D3: Zhang T. et al., J. Immunol. (2012), 189(5), 2290-9

D4: WO 2012/162067 A2

D5: Baeuerle P. A. et al., Drugs of the Future (2008), vol. 33(2), 137-47

D6: Cartellieri M. et al., J. Biomed. Biotechnol. (2010), vol. 2010, Article ID 956304, 13 pages

D7: WO 2011/070443 Al

D11: Brandt C. S. et al., J. Exp. Med. (2009), vol. 206(7), 1495-503

D12: Wu M.-R. et al., J. Immunol. (2012), 188 (1 Supplement) 53.11, 1 page

D13: Baeuerle P. A. et al., Chapter 15 in Bispecific Antibodies, Edt. Kontermann R. E. (2011), 273-87

D20: Wolf E. et al., Drug Discovery Today (2005), vol. 10(18), 1237-44

D25: Vivier E. et al., Nat. Rev. Immunol. (2012), 12(4), 239-52

D26: Graeves P. and Gribben J., Blood (2013), 121(5), 734-44

XIII. The appellants' arguments relevant to the decision can be summarised as follows.

(a) Amendments - Article 123(2) EPC - admittance of objections

Objections of added subject-matter under Article 100(c) EPC against claims 5, 8 and 10 as granted had already been raised in the notice of opposition and had never been abandoned.

Claims 8 and 10 as granted, except for the deletion of their dependence from claims 5 to 7, were identical to claims 8 and 10 of the present auxiliary request 3, which was considered allowable by the opposition division. As stated in paragraph 17 of the decision under appeal, no further objections under Article 123(2) EPC were raised in respect of auxiliary request 2. However, this clearly did not mean that the objections previously raised against the granted patent and other claim requests, which also applied to the patent as amended, had been abandoned. There was no need to repeat objections against claims of an auxiliary request that were identical to claims of the main request, against which objections had already been raised.

The objections to claims 8 and 10 raised in the statement of grounds of appeal were based on the facts and arguments presented in opposition, on which the

decision was based, in accordance with Article 12(2) RPBA. It was evident that the same objections still applied and there was no need to explicitly repeat all the objections already raised for the main request (claims as granted) during the oral proceedings before the opposition division for the newly-filed auxiliary requests.

Claim 5, on the other hand, had been substantially amended at a very late stage of the oral proceedings. There had been insufficient time for an in-depth analysis. The objection under Article 123(2) EPC had been filed at the earliest opportunity, i.e. with the statement of grounds of appeal.

(b) Novelty - Article 54 EPC - claim 5

The subject-matter of claim 5 was anticipated by document D4, which had an effective date of the first claimed priority of 21 May 2011 and therefore constituted prior art under Article 54(3) EPC, irrespective of whether the claimed priority of the patent was valid or not.

Contrary to the opposition division's decision, no multiple selections were necessary to arrive at the subject-matter of claim 5.

Document D4 described, e.g. in paragraphs [0027], [0048], [0050] and [00138], bispecific molecules, such as a "Dual Affinity ReTargeting reagent" (DART) or a "bispecific T-cell engager" (BiTE), which is singled out in paragraph [0048], which bind to CD3 on T cells and a tumour antigen such as B7-H6 on tumour cells, thereby redirecting the CD3+ T cell to the tumour cells. B7-H6 was disclosed in a single list of

tumour antigens in paragraph [00138]. Selection of B7-H6 from this single list of equivalent alternative tumour antigens was allowable and did not confer novelty. The skilled person would immediately have inferred that B7-H6 was a preferred tumour antigen since it was commonly known as a tumour-specific surface antigen that is not expressed on normal cells, and to be a target for tumour therapy (review articles D25, page 2, paragraph 2; D26, Table 2).

(c) Inventive step - Article 56 EPC

Anti-B7-H6 CAR-related claims 1 to 4 and 8 to 12

Closest prior art, difference, its technical effect, and objective technical problem

Document D12 represented the closest prior art as it related to the same purpose and already disclosed growth inhibition of a B7-H6-expressing murine lymphoma by a chimeric NKp30 receptor containing a CD28 signalling domain, as well as long-term *in vivo* efficacy.

The subject-matter of claim 1 differed from the NKp30 CAR T cell disclosed in document D12 only in that the NKp30 receptor extracellular domain of the CAR construct has been replaced by an antigen binding fragment specifically binding to B7-H6.

The only technical effect derivable from this difference vis-à-vis the disclosure of document D12 was the lack of reactivity of the claimed CARs against dendritic cells (DC). No other technical effect was derivable for an anti-B7-H6 CAR instead of an NKp30 CAR.

The objective technical problem was to provide a CAR that binds to B7-H6 and has no reactivity against normal cells or DC.

Obviousness

Faced with the problem of avoiding reactivity against DCs, it would have been obvious to a skilled person to generate CAR T cells using an antigen binding fragment targeting B7-H6, rather than employing the extracellular domain of NKp30 for targeting.

It was known in the art that B7-H6 is a human tumour cell-specific marker, and that NKp30 binds not only to B7-H6 but also to other non-tumour-specific ligands, such as HLA-B-associated transcript 3 (BAT3) and the pp65 proteins (document D11: page 1496, left-hand column, third sentence).

Document D11 already provided a B7-H6-specific antibody suitable for that purpose. As evidenced by review article D6, the structure of CAR T cells was common general knowledge.

The skilled person therefore had an incentive to provide a CAR comprising an scFv from an anti-B7-H6 antibody and had a reasonable expectation that such CARs would have no reactivity against normal cells, such as DCs.

Anti-B7-H6 / anti-CD3 BiTEs-related claims 5 to 7

Closest prior art, difference, its technical effect, and objective technical problem

Document D7 could be taken to represent the closest prior-art document for assessing inventive step of the subject-matter of claims 5 to 7. Document D7 discloses anti-B7-H6 monoclonal antibodies (paragraph [0032]), their fragments, including scFvs (paragraph [0033]), and the use of these B7-H6 binding agents to target cytotoxic agents at B7-H6-expressing cells in the form of an antibody-drug conjugate(paragraph [0034]), for example in cancer treatment (Examples 8 and 9).

The subject-matter of claim 5 differed from the teaching of document D7 in that a BiTE, targeting B7-H6 and CD3, was used.

The technical effect was to recruit CD3+ T cells to B7-H6+ tumour cells. The patent did not provide any *in vivo* data with regard to BiTEs and there was no unexpected technical effect that could be derived vis-à-vis the anti-B7-H6 monoclonal antibody of document D7.

The objective technical problem was to provide an alternative B7-H6 antibody capable of inducing immune response against B7-H6+ tumour cells by recruiting CD3-expressing T cells.

Obviousness

It was common general knowledge that combining the binding specificity for a tumour-associated surface antigen with that for a T-cell receptor (TCR) component in one antibody molecule holds the promise of not only temporarily connecting a cytotoxic T cell with a tumour cell but of activating the killing potential inherent to most T cells. Different approaches were known, and there was a clear pointer towards using the BiTE format

as being highly active and superior to monoclonal antibodies, since BiTEs activated T cells and led to long-lasting responses through serial killing (document D13: chapter 15.1 "*Introduction*"; Figures 15.1 and 15.2; page 278, paragraph 1; Chapter 15.5 "*Clinical Experience with BiTE Antibodies*"; document D20: page 1239, chapter "*BiTE: a bispecific format with exceptional properties*"; page 1240, right-hand column, last paragraph; document D5: page 139, paragraph spanning left-hand and right-hand columns).

The choice of the BiTE format was not just a choice from among many equivalent solutions but the choice of the most preferred format at the time to overcome the limitations of monoclonal and bispecific antibodies. Thus, starting from the disclosure of document D7 and the common general knowledge represented e.g. by documents D13 or D20, it had been obvious for the skilled person to use the BiTE format.

It was also common general knowledge that a monoclonal antibody and a BiTE acted via different modes of action. While monoclonal antibodies led to the activation of natural killer (NK) cells, BiTEs led to the activation of T cells (document D5, Figure 2 and page 139 "*Unique mode of action*").

The skilled person also knew that B7-H6 was selectively expressed on tumour cells, making it an ideal therapeutic target (document D11, page 1496, left-hand column, penultimate sentence of first paragraph).

The skilled person did not need a reason to apply their knowledge. Moreover, for a solution chosen from various possibilities, it was sufficient that the one chosen be

obvious, and it was not necessarily relevant that there were several other possible solutions.

Thus, starting from the disclosure of document D7 and faced with the problem of providing an alternative agent, the skilled person would have arrived at the claimed subject-matter.

XIV. The respondent's arguments relevant to the decision can be summarised as follows.

(a) Amendments – Article 123(2) EPC – admittance of objections

According to paragraphs 13 and 25 of the minutes of the oral proceedings before the opposition division, the appellants had no objections under Article 123(2) EPC and Rule 80 EPC with respect to auxiliary request 3. The only objection mentioned was the one against claim 7, under Article 56 EPC. Nevertheless, the appellants raised added-subject-matter objections against claims 5, 8 and 10 in the statement of grounds of appeal. However, each of these claims was present in substantially the same form in auxiliary request 3 (claims 8 and 10) and even auxiliary request 2 (claim 5).

The appellants had failed to provide convincing reasons why the objections presented on appeal had not, or could not have, been raised during the opposition proceedings, despite some of these arguments being included in the appellants' written submissions as filed during the opposition procedure.

The appellants' argument that the objections had never been abandoned should not be followed. The objections

could have been raised during the oral proceedings before the opposition division. It was not in accordance with Article 12(4) RPBA to withhold objections during the oral proceedings in opposition and subsequently to resubmit them on appeal, as this necessitated their re-examination during the appeal proceedings.

(b) Novelty - Article 54 EPC - claim 5 - document D4

The subject-matter of claim 5 was novel over the disclosure of document D4, which related very generally to CD3-binding molecules capable of binding to human and non-human CD3 (title). All the actual examples in document D4, and all the claims, related to DARTs. The use of the BiTE format was no more than a speculative alternative for other possible CD3-binding molecules that were neither exemplified nor individualised in document D4.

A selection from two different lists provided in document D4 was necessary, i.e. the list of "a bispecific (or trispecific or multispecific) molecule" and a further list in paragraph [0050] or [0138] including B7-H6 as the tumour antigen.

Moreover, the two-fold selection would still not provide each and every feature of claim 5. For example, there was no definition in this combination that would, explicitly or otherwise, define the BiTE as consisting of an anti-B7-H6 scFv fused to an anti-CD3 scFv via a linker.

Antigen binding fragments that bind B7-H6 were to be considered a genus that includes both specific and non-specific B7-H6 antigen binding fragments. Antigen

binding fragments that specifically bind B7-H6, as claimed in claim 5, had to be considered a species within this genus. For example, NKp30 binds B7-H6 non-specifically, which had been acknowledged by the appellants on a number of occasions.

(c) Inventive step - Article 56 EPC

Anti-B7-H6 CAR-related claims 1 to 4 and 8 to 12

Closest prior art, difference, its technical effect, and objective technical problem

Document D12 represented the closest prior art.

The subject-matter of claim 1 differed from the disclosure of document D12 in that the NKp30 receptor extracellular domain had been replaced by an antigen binding fragment of an antibody specifically binding to B7-H6.

As shown in Figure 2A of the application as filed, treatment with an anti-B7-H6 CAR T cell led to higher IFNγ production compared with treatment with an NKp30 CAR T cell. IFNγ was known to be a T-cell activation marker, thus increased IFNγ levels were an indication that the CAR T cells were activated and going to work.

Document D3 was post-published, so the appellants could not rely on its data.
However, Figure 5B of the patent in suit shows that approximately 90% of mice treated with anti-B7-H6 CAR T cells survived 50 days after tumour challenge, compared with about 25% of those treated with NKp30 CAR T cells, as shown in document D3, Figure 8A.

The objective technical problem was to provide an improved CAR showing improved survival rates.

Obviousness

None of the prior art documents taught the use of anti-B7-H6 CAR T cells.

Anti-B7-H6 / anti-CD3 BiTEs-related claims 5 to 7

Closest prior art, difference, its technical effect, and objective technical problem

The subject-matter of claim 5 differed from the disclosure of the closest prior-art document D7 by the use of the BiTE format comprising an antigen binding domain which binds to a T-cell antigen which is an anti-CD3 scFv, wherein the anti-B7-H6 scFv and the anti-CD3 scFv are fused together by a linker.

The technical effect was to be the first to provide a BiTE specifically binding B7-H6 which was demonstrated to recruit T cells and to kill B7-H6+ tumour cells (paragraphs [0013] and [0052] and Figures 6B, 8A and 8B of the patent in suit).

The objective technical problem was to provide an alternative agent capable of inducing an immune response against B7-H6+ tumour cells.

Obviousness

From the disclosure of document D7, there was no motivation for the skilled person to combine anti-CD3 and anti-B7-H6 specificity using the BiTE format. Document D7 contained no suggestion in that direction.

Many different antibody-based binding formats were described in document D7, and there was no pointer to use BiTEs. A large number of possible antibody variants existed in the art, as exemplified in document D13 (Figures 15.1 and 15.2). Equally large numbers of documents on any of these alternative formats could be found.

Moreover, a full-length antibody and an scFv activated different cell types, as shown in Figure 2 of document D5. Thus there was no expectation that an scFv-based BiTE would act the same as a full-length antibody.

The reference to CD3 in Table 6 of document D7 (page 48) was a spelling error since the antibody ecromeximab was known to be an anti-ganglioside GD3 antibody.

In the absence of any pointer, the skilled person would have arrived at a bi-specific molecule as defined in claim 5 only by hindsight.

XV. The requests of the parties relevant to the decision were as follows:

(a) The appellants requested that
- the decision under appeal be set aside and the patent be revoked;
- the objection under Article 123(2) EPC be admitted.

(b) The respondent requested that
- the appeal be dismissed, i.e. that the patent be maintained as amended in the form of auxiliary request 3;
- the appellants' objections relating to added subject-matter under Article 123(2) EPC not be admitted.

The respondent also requested that the following not be admitted for lack of substantiation: the appellants' submissions concerning novelty over document D4 in relation to claim 5, inventive step starting from document D7 in relation to claim 5 and inventive step in relation to claims 9 to 12 when dependent on claim 1.

Reasons for the Decision

Amendments - Article 123(2) EPC - admittance of objections

1. Objections under Article 123(2) EPC were raised in the statement of grounds of appeal against the subject-matter of independent claims 5, 8 and 10 and of dependent claims 6 and 7 due to their dependence from claim 5 of auxiliary request 3.

2. The opposition division stated on page 5, paragraph 1 of its decision that auxiliary request 1 had resolved the issues regarding Article 123(2) EPC for the reasons set out in the context of the main request, and that no issues regarding Article 123(3) EPC had been identified for auxiliary request 1.
Page 6, point 17 of the decision under appeal states that no further objections under Article 123(2) EPC were raised against auxiliary request 2.
The decision under appeal does not contain any consideration of added subject-matter under Article 123(2) EPC in its reasoning on auxiliary request 3.

According to the minutes of the oral proceedings held before the opposition division, the appellants had no objections under Article 123(2) EPC against auxiliary request 1 (see point 4), new auxiliary request 1 (see point 10) or new auxiliary request 2 (see point 13), and had no "*formal*" objection against new auxiliary request 3, which was considered to meet the requirements of the EPC (see point 25). Point 29 of the minutes also indicates that the parties acknowledged that there had been no outstanding requests.

The appellants did not complain that the contested decision was deficient for lack of reasoning (Rule 111(2) and Article 113(1) EPC). Nor did they request correction of the minutes of the oral proceedings before the opposition division.
It can therefore be taken that the minutes correctly reflect the course of the oral proceedings.

Based on the decision under appeal and the minutes of the oral proceedings in opposition, it cannot be established that any objection under Article 123(2) EPC was raised or maintained against auxiliary request 3.

3. Claims 8 and 10 as granted are identical to claims 8 and 10 of auxiliary request 3, except for the deletion of their dependence from claims 5 to 7.

Amended claim 5 was already submitted during the oral proceedings with "new auxiliary request 2" (see point 12 of the minutes) and a first "new auxiliary request 3" (see point 25 of the minutes), which was later replaced by "amended new auxiliary request 3" (see point 28 of the minutes).

4. Raising objections of added subject-matter on appeal therefore represented an amendment of the appellants' case, and admittance of these objections was therefore at the board's discretion, in accordance with Article 12(4) RPBA.

5. The board considers that objections regarding added subject-matter under Article 123(2) EPC against the claims of auxiliary request 3 could and should have been raised during the oral proceedings in opposition (see Article 12(6), second sentence, RPBA). The appellants neither requested an adjournment nor asked for the oral proceedings before the opposition division to be interrupted to fully consider the amendments and the corresponding basis in the application as filed. Moreover, nothing could be found in the decision under appeal which could be considered a development justifying admittance of these objections at the appeal stage.

6. Thus the objections under Article 123(2) EPC were not admitted into the proceedings (Article 12(4) and (6) RPBA).

Novelty - Article 54 EPC - claim 5

7. While the respondent had requested that the objection not be admitted for lack of substantiation, the board decided to consider the objection on substance. As the objection is without merit, the board deems it not necessary to provide reasons for the admittance of the objection in the decision.

8. The parties agreed that document D4 represents prior art under Article 54(3) EPC.

9. Document D4 discloses multispecific molecules, such as DARTs or BiTEs, capable of binding to CD3 (interspecies cross-reactive) and a second target, preferably a tumour antigen such as a B7-H family member, including B7-H6, and many others (see paragraphs [0048], [0050] and [0138]). The examples describe DART constructs only. Example 11 (see also Figure 11A) discloses a DART targeting CD3 and B7-H3 and capable of redirecting killing of B7-H3+ tumour cells.

10. Document D13 describes in chapter 15.2 "*Diverse Approaches for T-Cell Engagement*". Figures 15.1 and 15.2 disclose "several other T cell engaging antibodies" under clinical and preclinical development, including BiTEs and DARTs. The text preceding Figure 15.1 also states that "*Apart from "bispecific T cell engager" (BiTE)* [...] *several bispecific trifunctional antibodies etc. are currently in clinical development*". From the subsequent chapter 15.3 "*Bispecific T Cell Engager*", it is also evident that e.g. DARTs are not considered to fall within the meaning of the term "bispecific T cell engager".

11. Multiple selections from lists of alternative bi-, tri-, or multispecific antibody formats (see paragraphs [0048] and [0050]) and tumour antigens (see paragraphs [0050] or [0138]) disclosed in document D4 are required in order to arrive at the bi-specific T-cell engager according to claim 5. There is no indication in document D4 that a BiTE targeting CD3 and B7-H6 would be a preferred embodiment over the other possible combinations.

12. Therefore the subject-matter of claim 5 is novel over the disclosure in document D4.

Inventive step - Article 56 EPC

Admittance of objections against claims 9 to 12, when dependent from claim 1

13. Although the respondent requested that the inventive step objection against claims 9 to 12, when dependent from claim 1, not be admitted for lack of substantiation, the board decided to consider the objection on substance. Since the objection is without merit (see below), the board finds it unnecessary to provide reasons regarding the admittance of the objection in the decision.

Anti-B7-H6 CAR-related claims 1 to 4 and 8 to 12

Closest prior art - document D12

14. The parties agreed that document D12 represents the closest prior art.

15. Document D12 discloses that NKp30 is a natural cytotoxicity receptor expressed on natural killer cells and recognises the cell surface protein B7-H6, which is expressed on several tumour types but only on a few normal cells. To target effector T cells against B7-H6+ tumours, NKp30-based chimeric antigen receptors (CARs) have been developed that contain the CD28, Dap10, CD27 and/or CD3ζ signalling domains with the transmembrane domains of CD3ζ, CD28 or CD8α. The NKp30 CAR-expressing T cells produced IFNγ and killed B7-H6+ tumour cells. Inclusion of other signalling domains enhanced the chimeric NKp30 CAR-mediated activity compared with CD3ζ alone. Adoptive transfer of T cells expressing a chimeric NKp30 receptor containing a CD28 signalling domain inhibited the growth of a B7-H6+ murine lymphoma

(RMA-B7-H6) *in vivo* – no information on the survival rates of treated animals is given. In addition, mice that remained tumour-free were resistant to a subsequent challenge with the wild-type RMA tumour cells, suggesting the generation of immunity against other tumour antigens (see abstract).

Difference, its technical effect, and objective technical problem

16. The subject-matter of claim 1 differs from the teaching of document D12 in that it relates to a CAR comprising an antibody fragment that specifically binds to B7-H6.

17. The patent in suit describes in paragraph [0012] and depicts in Figure 2A that T cells expressing the claimed anti-B7-H6 CAR produced higher levels of IFNγ compared to NKp30 CAR in response to stimulation by B7-H6+ cells, such as K562 and RMA-B7-H6 cells. Although the difference in IFNγ production was less pronounced for RMA-B7-H6, in neither case do the error bars for the values measured for the NKp30 CAR and anti-B7-H6 CAR groups overlap, indicating statistical significance. Additionally, Figure 2B highlights that, unlike NKp30-based CAR T cells, the anti-B7-H6 CAR T cells do not react against autologous dendritic cells (DC), resulting in significantly reduced IFNγ production in response to peripheral blood mononuclear cells PBMCs and immature DC (iDC).

18. Based on the commonly-known correlation between T-cell activation and IFNγ production, as shown e.g. in Fig. 2 of document D6, the skilled person would have interpreted the specific induction of IFNγ production in Figure 2A of the patent in suit as a marker for B7-H6 antigen-specific T-cell activation, which was

expected to result in functional T cells with killing activity against their target.

19. Figure 5B of the patent in suit shows that a very high number - said to be about 90% by the respondent - of B6 mice inoculated with RMA-B7-H6 cells (10^5 cells, i.v., day 0) and treated with anti-B7-H6 CAR T cells ($5x10^6$ cells, i.v., days 5, 7 and 9) survived until day 50. In contrast, all mock-treated animals had died by day 30. Additionally, Figure 5C shows that the surviving mice after CAR therapy were resistant to the same tumour. This suggests the induction of an immune response against other tumour antigens, as RMA cells do not express B7-H6.

20. The appellants have not presented any evidence demonstrating that the reported effects could only be observed for the specific combination of scFv, hinge domain and intracellular signalling domain(s) tested in the patent in suit. The data in the patent in suit are considered proof of concept that the exclusive targeting of B7-H6 results in better activation of T cells and an improved anti-tumour response than the more unspecific targeting by NKp30-based CAR.

21. Based on the technical effects discussed in paragraph [0012] of the patent in suit, the objective technical problem can be defined as being to provide an improved B7-H6 targeting CAR.

The claimed solution is a CAR comprising an antibody fragment that specifically binds to B7-H6.

Obviousness

22. As argued by the appellants, it was known in the art that B7-H6 is expressed on human tumour cells but not on normal cells, such as PBMCs, including DC. It was also known that NKp30 binds to B7-H6 as well as to other ligands, such as BAT3 and the pp65 proteins (document D11: page 1496, left-hand column, third sentence; page 1499, second half of the left-hand column).

It might thus have been expected, that replacement of the NKp30 in document D12 by a more specific ligand would lead to a reduced reactivity.

It is also correct that document D11 already discloses the production of B7-H6-specific antibodies capable of blocking NKp30 CAR-dependent T cell activation (Figure 3 C and the corresponding text on page 1498, right-hand column; page 1499, left-hand column, lines 4 to 5; page 1501, right-hand column, paragraph 2). Such anti-B7-H6 antibodies can be assumed to be suitable for constructing a CAR. Also, the structure of CARs was common general knowledge (review article D6).

23. Nevertheless, the skilled person would not have expected the improved IFNγ production observed with anti-B7-H6 CAR T cells compared with NKp30 CAR T cells in response to B7-H6-expressing cells. This improvement in *in vitro* data is mirrored by *in vivo* data. Animals treated with anti-B7-H6 CAR T cells showed a very high survival rate, said to be about 90% by the respondent.

24. Consequently, the skilled person, starting from the disclosure of document D12, alone or in combination with the disclosure in document D11, and faced with the

objective technical problem would not have arrived at the claimed subject-matter.

25. The subject-matter of claim 1 involves an inventive step within the meaning of Article 56 EPC. The same considerations apply *mutatis mutandis* to the subject-matter of compound claims 2 to 4 and 8 and medical use claims 9 to 12.

Anti-B7-H6 / anti-CD3 BiTEs-related claims 5 to 7

26. While the respondent had requested that the inventive step objection against claim 5 starting from document D7 as closest prior art not be admitted for lack of substantiation, the board decided to consider the objection on substance. As the objection is without merit, the board deems it not necessary to provide reasons on the admittance of the objection in the decision.

Closest prior art - document D7

27. Document D7 discloses anti-B7-H6 antibodies (see Examples 1 and 2) and experimental set-ups for testing their capability for inhibiting the growth of different cancer cells (see Examples 3 to 9). Examples 8 and 9 report anti-cancer protective effects for the anti-B7-H6 antibodies tested. Document D7 discloses scFv fragments (see e.g. paragraphs [0033], [0049] and [0094]) but no bispecific constructs, hence also no BiTEs.
D7 provides anti-human B7-H6 monoclonal antibodies (see paragraph [0032]), antibody fragments thereof, including scFvs (see paragraph [0033]), and the use of these anti-B7-H6 antibodies to target cytotoxic agents

at a B7-H6-expressing cell in the format of an antibody-drug conjugate (see paragraph [0034]).

28. Document D7 does not suggest combining an anti-CD3 antibody with an anti-B7-H6 antibody. The reference to CD3 in Table 6 on page 48 is clearly incorrect, as the antibody ecromeximab targets the ganglioside GD3, not CD3.

Difference, its technical effect, and objective technical problem

29. The claimed subject-matter differs from the teaching of document D7 in that a bispecific binder, especially a BiTE, is used, wherein the second specificity is for CD3.

30. The technical effect of this difference is the recruitment of CD3+ T cells to B7-H6+ tumour cells. The patent shows that the anti-B7-H6/CD3 BiTE induces IFNγ production and B7-H6+ tumour cell lysis *in vitro* (see Figures 6 to 8).

31. The objective technical problem lies in the provision of an alternative agent capable of inducing an immune response against B7-H6+ tumour cells.

The claimed solution is the provision of a BiTE targeting CD3 and B7-H6.

Obviousness

32. Document D7 does not comprise any pointer to combine the anti-B7-H6 antibodies and antigen binding fragments thereof with anti-CD3 antibodies, hence the claimed subject-matter would not have been obvious to the

person skilled in the art when considering the teaching of document D7 alone.

33. In an attempt to search for alternative agents capable of inducing an immune response against B7-H6+ tumour cells, the skilled person would have relied on the modes of action disclosed or suggested in document D7, which are: inhibition of the interaction of B7-H6 with NKp30 (see paragraph [0033]), antibody Fc domain-mediated effects, or cytotoxic effects mediated by antibody-drug conjugates (see paragraph [0034], claim 7).

34. The strength of the BiTE format in attracting T cells to attack the tumour cell might have been known, as evidenced for example by review articles D5, D13 or D20. However, based on the teachings of document D7 and the objective technical problem as defined above, the person skilled in the art would not have considered approaches based on a different mode of action, such as recruitment of T cells, and therefore would not have arrived at the BiTE format.

35. Thus the subject-matter of claim 5 and of its dependent claims 6 and 7 is considered to involve an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Vottner M. Pregetter

Decision electronically authenticated