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**Datasheet for the decision
of 5 June 2012**

Case Number: T 1859/08 - 3.3.04

Application Number: 98963840.8

Publication Number: 1037926

IPC: C07K 16/32

Language of the proceedings: EN

Title of invention:

Treatment with anti-ErbB2 antibodies

Applicant:

Genentech, Inc.

Headword:

Anti-ErbB2 antibodies/GENENTECH, INC.

Relevant legal provisions:

EPC Art. 53(c), 54, 54(5), 84

Keyword:

"Main request: Clarity (yes); novelty (yes)"
"Remittal (yes)"

Decisions cited:

G 0002/88, T 0379/94, T 0158/96, T 0715/03

Catchword:

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Case Number: T 1859/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 5 June 2012

Appellant: Genentech, Inc.
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Representative: Cripps, Joanna Elizabeth
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 18 March 2008
refusing European patent application
No. 98963840.8 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Gramaglia
G. Alt

Summary of facts and submissions

- I. The applicant (hereafter "appellant") has appealed against the decision of the examining division refusing European patent application number No. 98963840.8 (published as WO-A-99/31140), having the title "Treatment with anti-ErbB2 antibodies".
- II. The examining division refused the application because it considered that the claims of the main request filed with facsimile on 8 February 2008 did not meet the requirements of Articles 54 and 84 EPC, while those of auxiliary request 1 did not meet the requirements of Articles 123(2) and 84 EPC.
- III. Independent claims 1 and 10 of the main request before the examining division read as follows:
- "1. Use of an anti-ErbB2 antibody in the preparation of a medicament for treatment to provide clinical benefit as measured by increased time to disease progression of malignant breast cancer characterised by overexpression of ErbB2 in a human patient, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence as determined by a cross-blocking assay using said antibody and antibody 4D5 obtainable from deposit ATCC CRL 10463, and wherein the medicament is for combined administration of the antibody with a chemotherapeutic agent other than an anthracycline derivative and not in combination with an anthracycline derivative, wherein said chemotherapeutic agent is a taxoid, wherein the combined administration has clinical efficacy as measured by determining time to disease progression and reduced myocardial dysfunction

compared with combined administration of the antibody and anthracycline derivatives."

"10. An anti-ErbB2 antibody for use in a method of treatment to provide clinical benefit as measured by increased time to disease progression of malignant breast cancer characterised by overexpression of ErbB2 in a human patient, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence as determined by a cross-blocking assay using said antibody and antibody 4D5 obtainable from deposit ATCC CRL 10463, and wherein the method comprises combined administration of the antibody with a chemotherapeutic agent other than an anthracycline derivative and not in combination with an anthracycline derivative, wherein said chemotherapeutic agent is a taxoid, wherein the combined administration has clinical efficacy as measured by determining time to disease progression and reduced myocardial dysfunction compared with combined administration of the antibody and anthracycline derivatives."

Dependents claims 2 to 9 and 11 to 14 were directed to specific embodiments of the use of claim 1 or the antibody of claim 10, respectively.

IV. The following documents are cited in the present decision:

D1 Baselga J. et al., Oncology, Vol. 11, No. 3, Supplement No. 2, pages 43-48 (March 1997);

D2 Mendelsohn J. et al., Annals of Oncology, Vol. 7, Suppl. 1, page 22 (1996);

- D3 Baselga J. et al., *Annals of Oncology*, Vol. 5, Suppl. 5, page A010 (1994);
- J Baselga J. et al., *J. Clin. Oncol.*, Vol. 14, No. 3, pages 737-744 (1996);
- K Pegram M. et al., *Proc. Am. Soc. Clin. Oncol.*, Vol. 14, abstract No. 124 (1995).
- V. The examining division decided that claims 1 and 10 lacked novelty in view of document D1, because this document disclosed the treatment of metastatic breast cancer with a combination of humanised monoclonal antibody 4D5 and the taxoid paclitaxel in a human patient (for more details, see points 9, 14, 16 and 17 of the Reasons of the present decision).
- VI. The appellant requests to set aside the decision under appeal and to grant a patent on the basis of the claims of the main request filed with the letter dated 8 February 2008, which are identical to the claims of the main request refused by the examining division, or on the basis of the claims of one of auxiliary requests I and II filed with its Statement of Grounds of Appeal of 28 July 2008. The appellant also requested oral proceedings if the board was minded to refuse the main request.
- VII. The submissions by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

- For assessment of the novelty of a medical use claim all technical features of the claim had to be taken into account. In the present case the feature "...to provide clinical benefit as measured by increased time to disease progression" in claims 1 and 10 were not disclosed in document D1.
- Document D1 described preclinical studies conducted with an in vitro monolayer cell culture in soft agar as well as with human breast cancer tumour xenografts in nude mice. However, the reported in vivo study did not involve human patients, as required by the claims.
- The phase II trials referred to in document D1 did not involve administration of the anti-Erb2 antibody and a taxoid, but were directed to phase II trials either with the antibody alone or with a combination of the antibody and cisplatin, which is not a taxoid.
- As for the clinical phase III trial referred in document D3, although the theoretical set-up of this clinical trial had been made, the performance of the trial and any result lay in the future. Hence, the rationale of decisions T 158/96 of 28 October 1998 and T 715/03 of 16 January 2006 applied to the present situation, where the claimed therapeutic combination of agents had definitely not been previously employed in any human clinical trials and/or the outcome had not been made available to the public.

VIII. In a communication annexed to a summons to oral proceedings the board informed the appellant of its

provisional view that it did not adhere to the conclusions arrived at by the examining division. The board further indicated that it was minded to remit the case to the department of first instance for the examination of the inventive step of the claims of the main request, since this issue had not been dealt with in the decision under appeal.

- IX. In response to this communication of the board, the appellant expressed its agreement with the proposed remittal and asked that cancellation of the scheduled oral proceedings be confirmed. Subsequently, the board cancelled the oral proceedings.

Reasons for the decision

Main request

1. Having regard to the examining division's decision (see paragraph II supra), the only issues to be dealt with are whether or not the subject-matter of the claims of this request meets the requirements of Article 84 EPC and Article 54 EPC.

Article 84 EPC

2. The examining division maintained in paragraph 1.3 of the decision under appeal that claim 1 did not meet the requirements of Article 84 EPC, having regard to the contradiction between on the one hand, the first part of claim 1, relating to the preparation of a medicament using only an antibody, and on the other hand, the second part of claim 1, relating to a medicament

comprising both an antibody and a taxoid. The examining division held that claim 1 had to be reformulated as "Use of an anti-ErbB2 antibody and a taxoid in the preparation of...".

3. The board first observes that independent claims 1 and 10 are under a medical use format. More precisely, claim 1 is under a so-called classical "Swiss type" form, while claim 10 corresponds to a medical use claim drafted according to Article 54(5) EPC 2000 (as acknowledged by the examining division in paragraph 1.3 of the decision under appeal). Claims having these formats relate to the use of a product for manufacturing a medicament for use in a method according to Article 53(c) EPC.

4. Turning to the present situation, the board notes that the first part of claim 1 indeed specifies that the medical use is for the anti-ErbB2 antibody taken alone, whereas the second part of claim 1 specifies that the medical use involves, inter alia, co-administration of the antibody with a taxoid (see the expression "combined administration" in claim 1). Therefore, the claim satisfies the requirements that it should be directed to the use of a product for manufacturing a medicament for use in a method according to Article 53(c) EPC, where such method may also embrace a combination therapy involving this product and a further active agent (in the present case: a taxoid). In fact, claims drafted in the form "...use of compound A for the preparation of a medicament for the treatment of disease X... involving the use of compound B..." are acceptable medical use claims (see e.g. T 379/94 of 21 May 1996, paragraph III).

5. In view of the foregoing, the board cannot see any contradiction or lack of clarity in claim 1 of the main request. This conclusion also applies, *mutatis mutandis*, to claim 10. Therefore, the claims of the main request satisfy the requirements of Article 84 EPC.

Article 54 EPC

6. As emphasized under point 3 *supra*, independent claims 1 and 10 are in the form of medical use claims ("Swiss type" form or Article 54(5) EPC 2000-type, respectively), where the novelty is derived from the intended medical use (see the "Case Law of the Boards of Appeal", 6th edition 2010, Chapter I.C.5.2.4). As a consequence, all the technical features of the therapeutic indication specified in the claims must be taken into account when considering whether or not the claimed subject-matter is novel.
7. In short, the intended medical use is the provision of a clinical benefit as measured by increased time to disease progression of malignant breast cancer characterised by overexpression of ErbB2 in a human patient, and wherein the method comprises combined administration of an anti-ErbB2 antibody with a taxoid to a human patient.

For the purpose of assessing novelty, it thus has to be examined whether or not the same therapeutic effect is directly and unambiguously derivable from a prior art document, upon using the same combination therapy in a human patient.

8. It should be noted that the language "wherein said chemotherapeutic agent is a taxoid" in independent claims 1 and 10 (see paragraph III supra) requires that the chemotherapeutic agent to be used together with the antibody must be a taxoid. This requirement of necessity excludes the possibility that the chemotherapeutic agent be an anthracycline. By implication, any (deleterious or otherwise) side effect linked to anthracyclines is also excluded by the claim language.

In view of this, the further features in independent claims 1 and 10 represented by the wording "a chemotherapeutic agent other than an anthracycline derivative and not in combination with an anthracycline derivative... wherein the combined administration has clinical efficacy as measured by determining ...reduced myocardial dysfunction compared with combined administration of the antibody and anthracycline derivatives" may be overlooked by the board for the purpose of assessing the novelty. The examining division came to the same conclusion, albeit for other reasons (see paragraph 1.2.b3 of the decision under appeal).

Moreover, anthracyclines have been known to be cardiotoxic since the sixties of the last century. Thus, the feature "...reduced myocardial dysfunction compared with combined administration of the antibody and anthracycline derivatives" is an implicit "non-hidden" feature.

9. The examining division held that the claimed subject-matter lacked novelty over document D1 because this

- document disclosed on page 46, column 3, lines 12-44 the treatment of cancer, particularly metastatic breast cancer, with the recombinant humanised monoclonal antibody (rhuMoAb) Her2 and the taxoid paclitaxel. Monoclonal antibody rhuMoAb Her2 exhibits the same capacity as murine monoclonal antibody 4D5 of targeting epitope 4D5 within the ErbB2 extracellular domain sequence (see page 44 column 1, lines 27-46; see also the Chapter headed "A "Humanized" Antibody" on page 46).
10. Page 46, column 3, lines 14-22 of document D1 describes investigations of the effects of antibody rhuMoAb Her2 combined with chemotherapy with the taxoid paclitaxel or with the anthracycline doxorubicin in monolayer culture soft agar (in vitro) or in xenografts of human breast cancer transplanted into nude mice (in vivo). No results are reported for the in vitro experiment. As regards the in vivo experiment, it is reported on page 46, column 3, lines 36-44 that the antitumor activity was markedly better than an equipotent dose of doxorubicin and antibody 4D5, and that disappearance of well-established xenografts took place.
 11. However, both studies did not involve humans, whereas the claims before the board are directed to the treatment of breast cancer in a human patient. Therefore, this passage of document D1 is not novelty-destroying for the claimed subject-matter.
 12. On page 45, column 3, lines 3-12, of document D1, it is stated that a combination therapy based on an anti-ErbB2 antibody (anti-"p185^{HER2}") and the taxoid paclitaxel is "currently being explored".

13. However, a mere statement that a combination therapy is being explored does not amount to a novelty-destroying disclosure of what is claimed in claim 1, because claim 1 is a medical use claim which includes, as a technical feature of the claim, the achievement of a clinical benefit in breast cancer patients as measured by an increased time to disease progression.

The present "currently being explored" situation, where no clinical benefit is disclosed, falls within the rationale of decisions T 158/96 and T 715/03. According to these decisions, if a prior art document discloses clinical investigations such as phase I, II or III studies (or states that these investigations are ongoing), but the document fails to disclose the final result of these studies, this document is not novelty-destroying.

14. The examining division argued that by applying the combined therapy of document D1, one would inherently come to the claimed effect, which could not render a known therapy novel.

However, decision G 2/88, OJ EPO 1990, 93, see point 10.1) states: "Under Article 54(2) EPC the question to be decided is what has been "made available" to the public: the question is not what may have been "inherent" in what was made available". Therefore, while it may be true that the claimed effect is inherent once applying the claimed therapy, the decisive question to be answered by the board remains whether or not this effect was a "hidden" one or was accessible to the skilled person before the priority date of the patent in suit.

15. A further passage of document D1 relied upon by the examining division for denying novelty can be found on page 47, column 1, under the Chapter headed "Phase III Study of rhuMoAB HER2 combined with Chemo" and Fig. 2, which refers to an earlier phase II clinical trial and describes a planned phase III clinical trial:

"Results from the phase II studies and the activity of rhuMoAb HER2 against xenografts when given in combination with doxorubicin and paclitaxel have been encouraging. These positive results have led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors who have not received prior chemotherapy for metastatic disease (Figure 2)."

16. In paragraph 1.2.b2 of the decision under appeal, the examining division considered that the expression "Results from the phase II studies" (see preceding point) did in fact relate to the claimed combination therapy (rhuMoAB Her2 combined with paclitaxel) administered to human patients. It also argued that the results of this study were encouraging to the extent that they led to the start of a phase III multinational investigation prior to the priority date of the present application.

Therefore, because it was disclosed in document D1 that these phase II studies had a positive outcome, i.e., a pharmacological effect was achieved, the first instance denied that the rationale of decisions T 158/96 and T 715/03 (see point 12 supra) applied to both the

phase II clinical and the planned phase III clinical trial referred to in the passage of document D1 cited in point 15 supra.

17. The assumption by the first instance that the phase II trials had used the claimed combination has been a key factor in its finding of lack of novelty. The board will thus deal with elucidating the nature of these "encouraging" phase II studies referred to in the first sentence of the paragraph highlighted in point 15 supra.
18. Document D1 describes a phase II trial with rhuMoAb HER2 on page 46, in the section headed "A "Humanized" Antibody". This study does not use any combination chemotherapy, as only the antibody is referred to.

A second, different, phase II trial is described in the Chapter headed "Cisplatin/rhuMoAb HER2 Therapy" bridging pages 46-47. This study relates to the anti-ErbB2 antibody taken in combination with cisplatin in human patients. However, cisplatin is not a taxoid.

19. There are two references to the phase II trials cited in document D1, namely reference [39] (document J) on page 46, col. 1, line 9 from the bottom and reference [42] (document K) on page 46, col. 3, line 7 from the bottom. Upon consulting documents J and K, it becomes clear that the former relates to the rhuMoAb HER2 phase II clinical trial where the antibody is used as a single agent, whereas the latter document describes a phase II clinical trial wherein the only agents used were rhuMoAb HER2 and cisplatin (not a taxoid).

20. In view of this, the board must agree with the appellant's view that none of the phase II trial described in document D1 uses an anti-ErbB2 antibody in combination with a taxoid, as required by present claims 1 and 10. Thus, the wording "encouraging" could not relate to this combination. In any case, it cannot be derived from document D1 that the encouraging results translated into a clinical benefit as measured by increased time to disease progression.

21. As for the planned or ongoing phase III clinical trial, it cannot be directly and unambiguously derived from these trials (see Fig. 2 of D1) that a therapeutic effect is obtained, let alone one translating into an increased time to disease progression.

Moreover, since document D1 fails to disclose any encouraging phase II trial using an anti-ErbB2 antibody in combination with a taxoid, the rationale of decisions T 158/96 and T 715/03 (see point 12 supra) applies also to the planned phase III clinical trial referred to in the passage of document D1 cited in point 15 supra, which is not novelty-destroying for claims 1 and 10.

22. In conclusion, document D1 is not novelty-destroying for the subject-matter of claims 1 and 10 and dependent claims 2 to 9 and 11 to 14.

23. Turning to the remaining documents before the board, both documents D2 and D3 deal with a rodent xenograft model wherein the antibody MoAb 4D5 (against the HER2 receptor) is used in combination with paclitaxel or doxorubicin chemotherapy. There is no description in

these documents of the treatment of a human patient, nor any disclosure of a biological effect translating into an increased time to disease progression.

24. Therefore, the claims of the main request satisfy the requirements of Article 54 EPC.

Remittal

25. The examining division merely dealt with the inventive step (Article 56 EPC) of dependent claims 2-4, 12 and 13 filed on 22 May 2006 by stating: "Dependent claims 2-4, 12 and 13 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step (Article 56 EPC). The features are merely several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill." (see paragraph 2.2 of the communication dated 18 October 2007). Hence, the case should be remitted according to Article 111(1) EPC to the examining division for the examination of the inventive step of the claims of the main request presently on file.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first for further prosecution.

The Registrar:

The Chairman:

B. Atienza Vivancos

C. Rennie-Smith