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Datasheet for the decision of 17 March 2016

Case Number: T 0402/12 - 3.3.04

Application Number: 00928916.6

Publication Number: 1187632

IPC: A61K39/395, A61P35/00

Language of the proceedings: EN

Title of invention:
Treatment with anti-ErbB2 antibodies

Patent Proprietor:
Genentech, Inc.

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Neoadjuvant therapy/GENENTECH

Relevant legal provisions:
EPC Art. 56, 115

Keyword:
Inventive step - main request (no) - auxiliary request (no)
Observations by third parties - relevant (no)

Decisions cited:
T 1756/11

Catchword:

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Case Number: T 0402/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 17 March 2016

Appellant: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Cripps, Joanna Elizabeth Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Respondent: (Opponent)	Teva Pharmaceutical Industries Ltd. 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 15 December 2011 revoking European patent No. 1187632 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietor (hereinafter "the appellant") against the decision of the opposition division to revoke European patent No. 1 187 632. The title of the patent is "*Treatment with anti-ErbB2 antibodies*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty and inventive step and under Article 100(b) EPC.

III. The impugned decision dealt with a main request and an auxiliary request both submitted during the oral proceedings. The opposition division held that the subject-matter of claim 1 of both requests lacked an inventive step.

IV. With its statement of grounds of appeal the appellant submitted a main and an auxiliary request which were both identical to the claim requests underlying the impugned decision. The appellant further submitted arguments why the opposition division had erred in its decision that the main and auxiliary requests did not involve an inventive step.

Claim 1 of the main request reads:

"1. Use of an anti-ErbB2 antibody for the manufacture of a medicament for treating a human patient diagnosed with a tumour in which ErbB2 protein is expressed, wherein the medicament is for treating the patient prior to steps of surgical removal of the tumour and treatment of the patient after the surgical removal of the tumour with anti-ErbB2 antibody and/or a chemotherapeutic agent."

Claim 1 of the auxiliary request reads:

"1. Use of an anti-ErbB2 antibody for the manufacture of a medicament for treating a human patient diagnosed with a tumour in which ErbB2 protein is expressed, wherein the medicament is for treating the patient prior to steps of surgical removal of the tumour and treatment of the patient after the surgical removal of the tumour with anti-ErbB2 antibody and/or a chemotherapeutic agent, wherein the patient is further treated with one or more chemotherapeutic agents prior to the surgical removal of the tumour."

V. In reply to the statement of grounds of appeal, the opponent (hereinafter "the respondent") submitted arguments why the subject-matter of claims 1 of both requests lacked an inventive step.

VI. Third party observations were filed pursuant to Article 115 EPC. The appellant replied to the board's invitation to comment on the observations by submitting *inter alia* that they were "*without substance*".

VII. Oral proceedings before the board were held on 17 March 2016. At the end of the oral proceedings the chairwoman announced the board's decision.

VIII. The following documents are cited in this decision:

D3: Valero V., Seminars in Oncology 1998, 25(2), 36-41

D4: Perez E.A., The Oncologist, 1998, 3, 373-389

D5: McNeil C., J. Natl. Cancer Inst. 1998, 90(12), 882-883

IX. The appellant's arguments may be summarised as follows:

Main request

Inventive step (Article 56 EPC)

Document D3 represented the closest prior art. It disclosed a treatment regimen of administering chemotherapeutic agents prior to and after the surgical removal of breast cancer. The subject-matter of claim 1 comprised several embodiments. One of them differed from the regimen disclosed in document D3 in that a combination of anti-ErbB2 antibodies and chemotherapeutic agents was administered prior to the surgical removal of tumours expressing the ErbB2 protein instead of administering the chemotherapeutic agents alone. The technical effect associated with this difference was an extended survival time of the patients treated. The objective technical problem was thus the provision of means for an improved neoadjuvant therapy for human ErbB2-expressing tumours.

Document D3 also reported that an anti-ErbB2 antibody was administered either alone in a therapy of stage IV breast cancer or together with chemotherapeutic agents in a first-line therapy for metastatic disease (page 39, column 2, third paragraph, to page 40, column 1, first paragraph). However, since both of these disorders indicated to the skilled person a late-stage of breast cancer where surgery was not a therapeutic option, the application of antibodies and chemotherapeutic agents before surgery was not suggested by this disclosure.

Document D3 further proposed that the role of anti-ErbB2 antibody-based therapies "*in conjunction with primary chemotherapy should be assessed in patients with early breast cancer*" (page 40, column 1, first paragraph). However, since chemotherapy differed fundamentally from an antibody-based therapy, the skilled person would not have understood the term "*primary chemotherapy*" in this context to refer to an anti-ErbB2 antibody-based therapy. Hence, the skilled person would have inferred from this statement that document D3 proposed to assess treatment regimens based on chemotherapy before surgery, followed by post-surgical administration of a combination of anti-ErbB2 antibodies and chemotherapeutic agents to prevent metastases. The opposition division in its decision had come to a different interpretation of this statement in document D3 on the basis of hindsight, *i.e.* it had read this statement in the light of the invention. Document D3 therefore disclosed no pointers for the skilled person to administer a combination of chemotherapeutic agents and anti-ErbB2 antibodies instead of chemotherapeutic agents alone, prior to the surgical removal of the tumour.

The teaching of the other cited prior art documents likewise did not motivate the skilled person to use anti-ErbB2 antibodies in a pre-surgical treatment regimen in patients with breast cancer. Document D5, for example, disclosed a clinical study which showed that the administration of an anti-ErbB2 antibody (Herceptin™) extended the remission time in metastatic, *i.e.* stage IV, breast cancer patients and suggested in view of this result that "*The most logical place to use this drug will likely be earlier and up front*". However, the only ongoing trial mentioned in document D5 for testing the prediction that Herceptin™ in

combination with chemotherapeutic agents was effective in the therapy of earlier stages of the disease related to patients with a stage III breast cancer which would have indicated to the skilled person - like the stage IV disclosed in document D3 - an advanced tumour stage with unclear surgical treatment options. Hence, the skilled person would not have inferred from this statement in document D5 that anti-ErbB2 antibodies should be applied in a pre-surgical treatment regimen.

Thus, the subject-matter of claim 1 met the requirements of Article 56 EPC.

X. The respondent's arguments may be summarised as follows:

Main request

Inventive step (Article 56 EPC)

Document D3 represented the closest prior art. The document reported on present and future strategies for the improvement of neoadjuvant therapies in the management of breast cancer. Although the disclosed standard agents for neoadjuvant therapy in locally advanced breast cancer (LABC) patients were chemotherapeutics, the document also reported that anti-ErbB2 antibodies either alone or in combination with a chemotherapeutic agent could be promising anti-breast cancer therapeutic agents. In this context the document proposed that the role of antibody-based therapies "*in conjunction with primary chemotherapy should be assessed in patients with early breast cancer*". *"Primary chemotherapy"* was a synonym for pre-surgical or neoadjuvant chemotherapy. Although an antibody-based therapy would not necessarily be

considered as a chemotherapy, the skilled person would nevertheless have inferred from the teaching of document D3 as a whole - dealing exclusively with the improvement of pre-surgical therapies in breast cancer - that the proposal in fact meant *inter alia* assessing the role of a combination of anti-ErbB2 antibodies and chemotherapeutic agents in pre-surgical treatment regimens.

Document D5 disclosed that the administration of a combination of anti-ErbB2 antibodies and chemotherapeutic agents had a synergistic anti-cancer activity compared to the administration of chemotherapeutic agents alone, thereby improving the therapy of metastatic, *i.e.* late-stage, breast cancer. Document D5 suggested, in view of this effect, an "*earlier and up front*" administration of both of these agents in the therapy of breast cancer. A pre-surgical treatment regimen in LABC patients was an earlier and up-front therapy, and accordingly the teaching of document D5 motivated the skilled person to administer anti-ErbB2 antibodies in addition to chemotherapeutic agents - instead of chemotherapeutic agents alone, as disclosed in document D3 - to improve pre-surgical breast cancer treatment regimens.

Thus, the subject-matter of claim 1 was obvious in the light of the teaching of document D3 either alone or when combined with that of document D5 and therefore did not meet the requirements of Article 56 EPC.

XI. The appellant requested that the decision under appeal be set aside and that a patent be maintained on the basis of the main request or the auxiliary request, both filed with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Main request

Introduction to the invention

1. The therapeutic application underlying the invention relates to ErbB2-expressing tumours in human patients. The ErbB2 protein is a cell surface-exposed growth-factor receptor which is over-expressed in about 25% to 30% of human breast cancer patients. It is also referred to in the art as HER2/neu and $p185^{HER2}$ (see e.g. patent in suit, paragraph [0002], and document D5, page 1, third paragraph).

2. Furthermore, the pre-surgical or pre-operative administration of therapeutic agents in tumour therapy is commonly also referred to as neoadjuvant or primary therapy (see e.g. document D3, page 36, column 1, first paragraph), while their post-surgical or post-operative administration is also referred to as adjuvant therapy (see e.g. document D3, page 37, column 1, second paragraph).

Claim construction

3. The subject-matter of claim 1 concerns the use of anti-ErbB2 antibodies for the manufacture of a medicament in

the therapy of human patients positively diagnosed for ErbB2-expressing tumours by administering the medicament "prior to steps of surgical removal of the tumour and treatment of the patient after the surgical removal of the tumour with anti-ErbB2 antibody and/or a chemotherapeutic agent". It was common ground between the parties that the invention as defined in claim 1 comprised several alternative treatment regimens. The administration of a combination of anti-ErbB2 antibodies and chemotherapeutic agents prior to the surgical removal of the tumour, followed by post-surgical administration of solely chemotherapeutic agents, is one of them and will be considered in the following.

Inventive step (Article 56 EPC)

Closest prior art

4. The parties considered that document D3 represented the closest prior art and the board has no reason to differ.

5. Document D3 is a review article dealing with current and future directions of neoadjuvant, *i.e.* pre-surgical (see point 2 above), therapy in human breast cancer. It discloses that this therapy was initially introduced in patients with locally advanced breast cancer (LABC) with the main purpose of eliminating distant micrometastatic tumours and that it now forms an integral part in the management of the disease (see title, page 36, column 1, first paragraph, and column 2, second paragraph). As an example of a treatment regimen in LABC patients the document discloses that

patients receive a first chemotherapy, prior to the surgical removal of the tumour, followed by a second post-surgical chemotherapy (see page 39, column 1, first paragraph).

Document D3 also reports on "*New biologic-genetic therapies*" in breast cancer patients consisting *inter alia* of the administration of a combination of anti-HER2/neu, *i.e.* anti-ErbB2, antibodies and chemotherapeutic agents (see point 1 above and page 39, column 2, third paragraph, to page 40, column 1, first paragraph, of document D3). It is not disclosed, however, that the therapy involves the surgical removal of the tumour.

6. Thus, the board considers that the regimen disclosed in document D3 of administering chemotherapeutic agents prior to and after the surgical removal of a tumour in patients with a diagnosed breast cancer represents the closest prior art for the embodiment of claim 1 under consideration (see point 3 above).

Technical problem and solution

7. This embodiment differs from that of the closest prior art by the pre-surgical administration of both anti-ErbB2 antibodies and chemotherapeutic agents instead of the pre-surgical administration of chemotherapeutic agents alone. The technical effect associated with this difference is a further extension of patient survival time.

8. Thus, the objective technical problem to be solved is formulated as the provision of an improved pre-surgical treatment regimen in the therapy of human ErbB2-expressing cancer.

9. The board is satisfied that the embodiment of claim 1 under consideration is a solution to this problem.

Obviousness

10. It remains to be assessed whether the skilled person starting from the treatment regimen of document D3 and faced with the technical problem defined in point 8 above would modify the teaching of document D3 in view of this document either alone or in combination with a teaching in another prior art document so as to arrive at the claimed embodiment under consideration in an obvious manner.

11. Document D3, after summarising the achievements of the current compared to the historic therapy of LABC, discloses that "*Although the natural history of LABC was changed by the introduction of systemic therapies, more than 60% of these patients still died of metastatic breast cancer* [...], *suggesting that there is room for considerable improvement. New research directions in primary chemotherapy* [*i.e.* pre-surgical chemotherapy (see point 2 above); note added by the board] *to improve the outcome of patients with breast cancer are priorities in basic and clinical research*" (see page 37, column 1, third paragraph).

12. Document D3 then presents several current research directions for improving primary chemotherapy, including "*New biologic-genetic therapies*" (see page 37, column 1, fourth paragraph and page 39, column 2, third paragraph). It reports in this context on two clinical studies in which the administration of anti-ErbB2 antibodies either alone or in combination with

chemotherapeutic agents attained a beneficial therapeutic effect in pre-treated patients with a stage IV breast cancer or in a first-line therapy of patients with metastatic diseases, respectively (see page 39, column 2, third paragraph, to page 40, column 1, first paragraph). "First-line therapy" means that the patients have not received any kind of prior anti-cancer therapy (see e.g. document D4, page 373, column 2, second line). Moreover, it was uncontested that the patients enrolled in both of these studies had a late-stage cancer disease.

In view of the results of the two studies document D3 suggests that "*The role* of *these novel strategies* [*i.e.* therapies based on anti-ErbB2 antibodies either alone or together with chemotherapeutic agents; note added by the board] *in conjunction with primary chemotherapy should be assessed in patients with early breast cancer.*" (see page 39, column 2, third paragraph, to page 40, column 1, first paragraph).

13. In the board's opinion, document D3 thus teaches the skilled person that, because of the high mortality rate of patients with LABC, there is a need for improving the existing pre-surgical treatment regimens based on chemotherapeutic agents. Moreover, since its teaching as a whole focuses exclusively on means for improving pre-surgical treatment regimens (see point 5 above), the skilled person would have inferred from the suggestion in document D3 to assess the role of anti-ErbB2 antibodies either alone or in combination with chemotherapeutic agents "*in conjunction with primary chemotherapy*" that this means the use of anti-ErbB2 antibodies combined with chemotherapeutic agents in a pre-surgical treatment of patients with early breast cancer.

14. In contrast, the appellant submitted that the passage in document D3 disclosing that "*The role of these novel strategies in conjunction with primary chemotherapy should be assessed in patients with early breast cancer*" would have been construed by the skilled person as suggesting an improved treatment for LABC patients a regimen consisting of pre-surgical chemotherapy followed by post-surgical therapy based on *inter alia* the combination of anti-ErbB2 antibodies and chemotherapeutic agents. This was so since the term "*chemotherapy*" would have been understood by the skilled person not to refer to antibody-based therapies.

Thus, in the appellant's view, the skilled person would have inferred from document D3 that the standard LABC treatment regimen consisting of the administration of chemotherapeutic agents prior to and after the surgical removal of a tumour (see point 6 above) could be improved by leaving the pre-surgical therapy unaltered while altering the post-surgical therapy to include antibodies in addition to the chemotherapeutic agent.

15. In the board's view, if this interpretation of document D3 were adopted, the improvement of the cancer therapy would lie in the post-surgical treatment, because the pre-surgical one is not changed. This would be at odds, however, with the overall teaching of document D3 which, as noted in points 5 and 13 above, is exclusively concerned with new strategies for improving pre-surgical treatment regimens in patients with breast cancer.

16. The appellant argued that a further reason why the passage on pages 39 and 40 of document D3 would not have suggested to the skilled person to administer anti-ErbB2 antibodies together with chemotherapeutic agents in a pre-surgical treatment regimen was that the breast cancer stages of the patients enrolled in the two studies disclosed were too advanced, such that surgery was excluded as a therapeutic option.

17. The board is not convinced by this argument because document D3 explicitly proposes that "*The role* of *these novel strategies in conjunction with primary chemotherapy should be assessed in patients with early breast cancer*" (see point 13 above; emphasis added), *i.e.* in stages of cancer when surgery is an option.

18. Thus, in summary, the board concludes that document D3 would motivate the skilled person to administer a combination of anti-ErbB2 antibodies and chemotherapeutic agents in a pre-surgical treatment regimen of patients with a diagnosed ErbB2-expressing cancer.

19. The appellant in a further line of argument referred to document D5 and its disclosure on page 3 in the second paragraph and in the first sentence of the third paragraph, which reads: "*Some of the excitement surrounding Herceptin stems from the probability that the drug, now proven in metastatic breast cancer, will have an impact in other settings. Hope focuses particularly on other stages of breast cancer. "The most logical place to use this drug will likely be earlier and up front. [...].*

At least one trial to test the prediction in stage III breast cancer is now being designed [...]."

20. The appellant submitted that the skilled person, in the light of the disclosure in this passage of the "*proven*" effectiveness of the anti-ErbB2 antibody Herceptin™ in "*metastatic breast cancer*" and of an ongoing trial with patients in "*stage III breast cancer*", would have inferred that Herceptin™ could effectively be administered only in late-stages of the disease, *i.e.* stage III or the metastatic stage of the disease (stage IV), where surgery was not an option. In other words, the skilled person would have been taught by document D5 not to administer the antibody at stages contemplated by claim 1, *i.e.* stages where surgery was an option.

21. The board does not agree with this interpretation. The cited passage in document D5 discloses that "*now*" that efficacy was "*proven*" in "*metastatic breast cancer*", "*hope focuses particularly on other stages*", which, logically were stages which were "*earlier*". The board considers that, in this context, the skilled person would have understood that "*earlier*" does not only refer to stage III of the cancer disease, but that it in fact refers to all stages which are earlier than the metastatic stage. Therefore, the sentence following the second paragraph reading "*At least one trial to test the prediction in stage III breast cancer is now being designed*" would not have indicated to the skilled person that necessarily only trials with patients in stage III were ongoing. The statement on page 1, second paragraph of document D5 supports this view. It reads "*Plans to test the drug in earlier stage breast cancer are well under way*".

22. Thus, in the board's view, the disclosure in document D5 referred to by the appellant would not have

discouraged the skilled person from following the suggestion disclosed in document D3 to administer a combination of anti-ErbB2 antibodies and chemotherapeutic agents in a pre-surgical treatment regimen. And all the more so since document D5 discloses that the two agents had a synergistic effect when they were administered in the therapy of metastatic disease (see page 2, second and third paragraphs).

23. Hence, in the light of the observations in points 11 to 22 above, the skilled person would have arrived at the embodiment of claim 1 under consideration (see point 3 above) in an obvious manner in view of the teaching of document D3.

24. Consequently, this embodiment of claim 1 - and hence the main request as a whole - fails to meet the requirements of Article 56 EPC.

Auxiliary request

25. The subject-matter of claim 1 of the auxiliary request differs from that of the main request in that pre-surgical treatment regimens are limited to the administration of a combination of anti-ErbB2 antibodies and chemotherapeutic agents.

26. Accordingly, the invention as defined in claim 1 of the auxiliary request comprises an embodiment which corresponds to the embodiment of claim 1 of the main request considered above (see point 3). However, the board has decided that such an embodiment is obvious in the light of the teaching of document D3 alone (see point 23 above).

27. Consequently, the auxiliary request does not meet the requirements of Article 56 EPC either.

Third party observations (Article 115 EPC)

28. Third party observations were filed during the appeal proceedings.

29. According to established case law, submissions emerging from third party observations filed after expiry of the time limit for filing a notice of opposition are treated by legal fiction as being late (see e.g. decision T 1756/11, point 2.3 of the Reasons). Therefore their admission into the appeal proceedings is at the board's discretion.

30. The appellant submitted that the third party's observations were "*without substance*" (see section VI). The respondent did not rely on them. The board has thus decided to disregard the third party's observations.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated