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D E C I S I O N
of 14 July 2005

Case Number: T 0542/03 - 3.3.4

Application Number: 93250090.3

Publication Number: 0616812

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Combination with anti-hormonal compounds and binding molecules for the treatment of cancer

Patentee:
Berlex Biosciences

Opponent:
Hoffmann-La Roche & Co. AG

Headword:
Combination/BERLEX

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request, first and second auxiliary request - inventive step (no)"

Decisions cited:
T 0377/95, T 0333/97, T 1045/98

Catchword:
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Case Number: T 0542/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 14 July 2005

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 13 February 2003 revoking European patent No. 0616812 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the Opposition Division, whereby the European Patent No. 0 616 812 was revoked according to Article 102(1) EPC.

II. The patent has been granted with claims 1 to 14. Claim 1 thereof read as follows:

"A combination comprising

a) at least one anti-hormonal compound taken from the groups comprising anti-oestrogen, anti-progesterone and anti-androgen compounds and

b) a binding molecule or binding molecules specifically binding the protein encoded by the c-erb B-2 oncogene, wherein the binding molecule or molecules induce inhibition of tumour cell proliferation."

III. The patent had been opposed by the Opponents (Respondents) under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC).

The Opposition Division decided that the only request of the Patent Proprietors before them, maintenance of the patent as granted, did not meet the requirements of the EPC, as claim 1 did not involve an inventive step

(Article 56 EPC) in the light of the disclosure in the following documents:

(4) Cancer Research, vol. 51, 1991, pages 4575 to 4580

(12) Breast Cancer Research and Treatment, vol. 24, 1992, pages 85 to 95

IV. The Board expressed their preliminary opinion in a communication dated 20 January 2005.

With letter of 13 May 2005 the Appellants filed two auxiliary requests, each consisting of claims 1 to 6. Claim 1 thereof read:

Auxiliary request I

"Products containing

a) at least one anti-hormonal compound taken from the groups comprising anti-oestrogen, anti-progesterone and anti-androgen compounds and

b) a binding molecule or binding molecules specifically binding the protein encoded by the c-erb B-2 oncogene, wherein the binding molecule or binding molecules induce inhibition of tumour cell proliferation,

as a combined preparation for simultaneous, separate or sequential use in human tumour therapy."

Auxiliary request II

"Products containing

a) at least one anti-hormonal compound taken from the groups comprising anti-oestrogen, anti-progesterone and anti-androgen compounds and

b) a binding molecule or binding molecules specifically binding the protein encoded by the c-erb B-2 oncogene, wherein the binding molecule or binding molecules induce inhibition of tumour cell proliferation,

as a combined synergistic preparation for simultaneous, separate or sequential use in human tumour therapy."

Oral proceedings were held on 14 July 2005.

V. The Appellants requested that the decision under appeal be set aside and that the patent be maintained as granted or, in the alternative, in amended form on the basis of the first or second auxiliary request, both filed by letter of 13 May 2005.

The Respondents requested that the appeal be dismissed.

VI. The submissions made by the Appellants as far as they are relevant for the present decision may be summarized as follows:

Main Request

The patent in suit was concerned with the provision of a pharmaceutical product for use in human tumour therapy. According to established case law of the Boards of Appeal, the closest prior art document should refer to subject-matter conceived for the same purpose as the claimed invention. Document (4) disclosed a combined synergistic preparation comprising a monoclonal antibody against the c-erb B-2 antigen and cisplatin, a cytotoxic chemotherapeutic agent. In the light of the disclosure in this prior art document the problem to be solved by the underlying patent was seen in the provision of an alternative composition for use in human tumour therapy.

The skilled person trying to solve this problem would not have turned to document (12), a scientific study investigating mechanisms in tumour cells by using an artificial model cell line over-expressing the c-erb B-2 antigen (designated $p185^{HER2}$), which cell line did not appear in human tumour tissue. The use of such model cell line did not allow drawing any conclusion with regard to human tumour therapy.

The only message obtainable from document (12), right column, last sentence of first paragraph on page 94, was to further investigate the artificial model disclosed, using a genetically manipulated non-naturally occurring cell line. The skilled reader having seen fundamental flaws and omissions in the experimental design of document (12) would have had severe doubts to follow any suggestion expressed in the final statement of this document.

Accordingly, the disclosure in document (4) or document (12), either if taken alone or in combination, did not enable a skilled person to arrive in an obvious way at the technical contribution made by the patent in suit, namely the provision of medicaments overcoming the resistance of human tumours to cytostatic therapy with anti-hormonal compounds.

Second auxiliary request

Document (4) showed a synergistic effect for a combination of anti-c-erb B-2 antibody and cisplatin only. Document (12) raises the question of possibly existing synergistically enhanced anti-tumour effects of such antibody and tamoxifen in an artificial model cell line. None of these documents allowed a skilled person to draw any conclusion with regard to the provision of a synergistically effective product according to claim 1 of the second auxiliary request.

VII. The submissions made by the Respondents as far as they are relevant for the present decision may be summarized as follows:

Main request

Document (12) and the patent in suit had the same objective, namely the treatment of cancer, in particular of cancer cells which were hormone-dependent and which became resistant to anti-hormonal therapy. Document (4), also referring to the treatment of cancer did not underline the effects of anti-hormonal therapy. As document (12) had thus more relevant technical

features in common with the invention, it represented the closest state of the art. The technical problem underlying document (12) and the patent in suit was identical, namely the provision of a pharmaceutical composition overcoming chemo-endocrine resistance in the treatment of tumours, in particular resistance to the anti-estrogen tamoxifen (TAM). Document (12), in a mouse model, showed a link between c-erb B-2 over-expression and TAM resistance in a genetically modified cell line. The document suggested in its final sentence that anti-c-erb B-2 antibodies should be tested for synergistic effects with TAM by experiments as carried out in document (4) (cited as reference (26) in document (12)). These were exactly the experiments as carried out in the patent in suit. The skilled reader following the suggestion expressed at the end of document (12), directly and without being confronted with unforeseeable difficulties or pitfalls, arrived at the claimed subject-matter.

Second auxiliary request

The appearance of a synergistic effect was an automatic non-avoidable effect of the obvious combination of an anti-c-erb B-2 antibody and TAM. Document (12) explicitly envisaged this effect.

Reasons for the Decision

Novelty - Article 54 EPC

1. The Respondents objected to the novelty of the claimed subject-matter on the basis of the disclosure in

document (12). While the Board during oral proceedings concluded that no case for lack of novelty had been made out, in view of the findings on Article 56 EPC (see points (2) to (21) below) it is not deemed to be necessary to give detailed reasons with regard to Article 54 EPC.

Inventive step - Article 56 EPC

Main Request

2. The patent in suit is concerned with a composition for the treatment of cancer, in more detail for the treatment of tumours which have been characterised as being responsive to anti-hormonal therapies (page 2, lines 1 to 10 of the application as originally filed).

As pointed out on page 2, lines 43 to 44 of the application as filed, in clinical practice, many of these tumours become resistant to the growth suppressing actions of anti-hormonal compounds. According to lines 53 to 54 on the same page, it was the object of the invention underlying the patent to offer a combination of anti-hormonal compounds and of further compounds in order to increase the efficiency of the treatment with the anti-hormonal compounds.

3. Document (4) is a study concerned with treatment of human breast- and ovarian-tumour cell lines with a combination containing TAb 250, a monoclonal antibody against c-erb B-2 (gp 185) antigen, and cis-diamminedichloroplatinum (CDDP). The combined treatment is said to result in a significantly enhanced,

synergistic cytotoxic effect both *in vitro* and *in vivo* (abstract and page 4578, left column, lines 14 to 17).

SKBR-3 cells, an endogenously c-erb B-2 over-expressing human breast cancer cell line (page 4576, right column, lines 12 to 14) *in vitro* exposed to TAb 250 and CDDP were dramatically growth inhibited compared to cells exposed to either TAb250 or CDDP alone (page 4577, left column, lines 2 to 8; figure 3A). No such effect is shown in figure 3B for MDA-MB-468 cells, which is not surprising as this breast cancer cell line is c-erb B2-negative (page 4577, left column, first full paragraph).

The *in vivo* results disclosed in document (4) are obtained by use of a human tumour xenograft model in Balb/c nude mice implanted with SKOV-3 or MDA-MB-468 cells (page 4576, left column, last full paragraph). Figure 5A shows that TAb250 markedly enhanced the inhibitory effect of CDDP *in vivo* using the xenograft model with SKOV-3, a human ovarian tumour cell line. No such effect is shown in figure 5B for MDA-MB-468 cells, for the same reason as explained in the paragraph above with regard to figure 3B.

Document (4) is not concerned with anti-hormonal therapy or with means and methods to overcome resistance to it.

4. Document (12), a report titled *"Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu"*, is concerned with the problem of treating cancer, in particular breast cancer. The first sentence in the summary on page 85 reads:

"Since the poor prognosis associated with HER2 amplified breast cancers might be explained by a mechanistic association between $p185^{HER2}$ overexpression and therapeutic resistance, we assessed the chemo-endocrine sensitivity of estrogen receptor (ER) containing MCF-7 breast cancer cells transfected with full-length HER2 cDNA."

The document discloses the generation of the HER2 (c-erb B-2) overexpressing cell MCF/HER2-18 by transfecting the c-erb B-2-positive and ER-positive human breast adenocarcinoma cell line MCF-7 with a plasmid containing full-length HER2 cDNA coding region.

In vitro growth inhibitory effects of either 4D5, a murine monoclonal antibody specific for c-erb B-2, or TAM on the parental MCF-7 cell line and the transfected subclones were measured and compared with three endogenously c-erb B-2 overexpressing human breast cancer cell lines (page 90 right paragraph and table 2). Of these three control cell lines, MDA-453, SK-Br-3 and BT-474, only BT-474 is ER-positive. It is found that none of the overexpressing subclones was growth inhibited by 4D5 in a statistically significant dimension. While the parental cell, MCF-7 is TAM sensitive, the MCF/HER2 subclone with the highest expression of c-erb B-2 (MCF/HER2-18; 45-fold) demonstrated significantly less *in vitro* sensitivity to 1µM TAM. BT-474 cells were found to be as resistant to TAM *in vitro* as MCF/HER2-18 cells (page 94, left column, lines 5 to 9).

The apparent loss of TAM sensitivity in the c-erb B-2 overexpressing subclones was further investigated by implanting parental MCF-7 cells and transfected subclones into athymic nude mice and to analyse estrogen-dependent, TAM-sensitive/resistant tumourigenic growth (page 91 to 92; figure 3). It was shown that growth arrest of TAM treated MCF-7 and MCF/neo-3 (control) tumours was immediate and sustained. For the MCF/HER2-18 tumours, however, TAM treatment produced a brief growth delay followed by a resumption of its accelerated growth rate that persisted for over a month.

The authors of document (12) drew the following conclusions from this experimental data:

"This pattern of hormone-dependent, TAM-resistant growth exhibited by the MCF/HER2-18 tumours in nude mice supports the possibility that p185^{HER2} overexpression in human breast cancers may be linked to therapeutic resistance" (page 86, first sentence),

and

"It will be important to study the endocrine dependency of serially transplanted MCF/HER2-18 tumors, and to determine if in vivo therapy with muMAb4D5 can reverse the tamoxifen resistance of MCF/HER2-18 tumors or synergistically enhance the antitumor effects of either tamoxifen or cisplatin [26]" (page 94, right column, lines 5 to 11; reference [26] is document (4) in the present proceedings).

5. In accordance with the problem and solution approach, the Boards of Appeal in their case law have developed certain criteria for identifying the closest prior art providing the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3.1).

6. In the present case, documents (4) and (12) both disclose subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention, namely the treatment of cancer. However, as mentioned in point (4) above, contrary to document (12), document (4) is not concerned with anti-hormonal therapy or with means and methods to overcome resistance to it.

Thus, document (12) has the most relevant technical features in common with the claimed invention, and is therefore the most promising springboard towards the invention which was available to the skilled person.

7. In the light of the disclosure in the closest prior art document, the Board finds that the problem underlying the patent in suit is correctly defined on page 2, lines 50 to 51 of the description, namely *"...to offer a combination of anti-hormonal compounds and of further compounds in order to increase the efficiency of the treatment with anti-hormonal compounds."*

8. Document (12), although not explicitly disclosing the combination or product claimed, contains in its last sentence on page 94 a suggestion to the skilled person to combine an anti-c-erb B-2 antibody and TAM and to test this combination for synergistic antitumour effects in the mouse model disclosed in document (4) using a transgenic c-erb B2 overexpressing cell line, which was generated by the authors of document (12) to show a link between c-erb B2 overexpression and TAM resistance.

9. The Appellants emphasised that a skilled person reading document (12) would not consider the conclusion drawn therein and would not therefore follow its suggestion. They stated that the used cell line, MCF/HER2-18 was an artificial construct not existing in human tumours, which, moreover, was not growth inhibited by anti-c-erb B-2 antibodies. At best the last sentence of document (12) was an invitation to do a further experiment in a mouse model using this artificial cell line. The results of such experiment could not be extrapolated to the field of human tumour therapy. Moreover the Appellants stated that the experimental design of document (12) was flawed. No, or inadequate, controls were used in the *in vivo* experiments, so that a skilled reader would have disregarded any conclusive finding expressed at the end of this report.

10. Pre-clinical studies are routinely carried out in the here relevant technical field. They are an irreplaceable tool for the expert wishing to develop new, therapeutically active preparations for use in human medicine.

In vitro tests wherein cells or cell lines are cultured in specific media, and *in vivo* animal models are, to the knowledge of the Board, the most customary embodiments of pre-clinical tests.

Test carried out in an *in vivo* animal model are not carried out for their own sake, that means not to cure a disease in the model animal, but to reflect the situation in human beings. Their aim is to allow the skilled person to draw conclusions and to arrive at a degree of knowledge of the metabolic mechanisms involved in a clinical picture that allows him/her to start clinical trials with human patients.

11. Therefore, a skilled reader confronted with concluding remarks of a report disclosing the results of *in vitro* tests and *in vivo* experiments carried out on an animal model, would not reduce the suggestion in the final sentence of document (12) to an invitation to carry out a further test with the transfected MCF/HER2 subclones, especially generated for the purpose to verify the existence of a link between c-erb B-2 overexpression and TAM resistance. On the contrary, not losing sight of the true purpose underlying the pre-clinical studies disclosed in document (12), namely the provision of a medicament useful in human tumour therapy (see point (10) above), the skilled reader, being referred by reference to the human tumour xenograft model in Balb/c nude mice of document (4), would have considered to use this model to carry out tests to study the endocrine dependency of naturally occurring human breast cancer cell lines.

12. It has to be asked whether the skilled person would have envisaged any obstacles, difficulties or pitfalls which would have made these tests either impossible to carry out or so uncertain in their outcome that any expectation of success would be abandoned.

In fact, exactly these tests have been carried out in the exemplary part of the patent in suit, where two deposited, c-erb B2-positive and ER-positive, breast cancer cell lines, namely MDA-MB-361 (ATCC HTB27) and ZR-75-1 (ATCC CRL 1500) are implanted into Balb/c nude mice (examples 4 and 5). The patent does not mention any obstacles, difficulties or pitfalls, but describes that these examples clearly and unambiguously showed the synergistic effect as suggested and envisaged in document (12), (see figures 1 and 2 of the patent in suit).

13. As a factor which would have deterred the skilled person from making the *in vivo* test in mice, the Appellants referred to the fact that the results of the *in vivo* experiments of document (12) were unreliable because of missing or inadequate control groups.

14. In the Board's judgement, far from being deterred, the skilled person, reading document (12) and the suggestion expressed in its final sentence, would have considered to carry out tests with human breast cancer cell lines using the animal model disclosed in document (4), despite possible shortcomings in the experimental design of document (12). Such tests are the logical next step following from the conclusions drawn in document (12) before clinical testing in patients.

The question is whether these tests would have been approached by the skilled person with scepticism, with a neutral attitude or with some expectation of success.

Although knowing that *in vitro* experiments, or *in vivo* experiments in a specific set up (as described in document (12)), cannot mimic the settings in a different *in vivo* animal model (disclosed in document (4)), and in spite of the inherent uncertainties which always characterise biological experiments, the skilled person had no reasons to adopt a sceptical attitude. He or she would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which - as pointed out e.g. in decisions T 333/97 of 5 October 2000 and T 377/95 of 24 April 2001 - does not equate with an absence of a reasonable expectation of success (cf decision T 1045/98 of 22 October 2001; point (17) of the reasons).

15. Therefore, the Board is convinced that the skilled person would have arrived in an obvious way at the subject-matter of claim 1 in the light of the disclosure in document (12) in combination with document (4), which therefore is found to lack an inventive step.

The main request is not allowable under Article 56 EPC.

First auxiliary request

16. For this request no arguments extending those made in favour of the main request have been submitted by the Appellants.

The findings expressed in points (2) to (15) above which made the Board arrive at the decision that claim 1 of the main request lacks an inventive step, apply in the same way to claim 1 of the first auxiliary request.

Accordingly, also the first auxiliary request does not meet the requirements of Article 56 EPC.

Second auxiliary request

17. Claim 1 refers to a product containing an anti-hormonal compound and a binding molecule, or molecules, specifically binding to c-erb B-2, as a combined **synergistic** combination for use in human tumour therapy.

18. The Appellants argued that the documents representing the relevant state of the art did not allow any conclusion with regard to a synergistic effect caused by the claimed combination. Document (12) did not disclose any pharmaceutical combination for use in human tumour therapy at all. Document (4), disclosing synergistic combinations of an anti-c-erb B-2 antibody and CDDP, disclosed synergy *in vivo* only with regard to the ovarian tumour cell line SKOV-3 in figure 5A only. No *in vivo* synergistic effect was shown in figure 5B for the human breast cancer cell line MDA-MB-468.

19. With regard to Appellants' argument that document (4) does not show any synergy of TAb250 and CDDP *in vivo* when using xenografts containing MDA-MB-468 breast cancer cells, the Board has already pointed out in

point (3) above that this is not surprising as this cell line is c-erb B-2 negative.

20. The Board, having decided in points (2) to (15) above that a claim directed to a combination of an anti-hormonal compound and a binding molecule for c-erb B2 does not involve an inventive step, concedes that, according to the case law of the Boards of Appeal, a surprising effect of such combination, not yet disclosed in the prior art, may result in the acknowledgement of an inventive step.

In the present case, however, the effect in question, namely the synergy of the two components contained in the claimed product when used for growth inhibition of human tumours, is already envisaged on page 94, right column of document (12), (see point (4) above).

21. For this reason it is decided that also claim 1 of the second auxiliary request does not involve an inventive step.

The second auxiliary request is not allowable under Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey