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Datasheet for the decision of 7 February 2018

Case Number: T 1853/16 - 3.3.04

Application Number: 98963840.8

Publication Number: 1037926

IPC: A61K38/00, C07K16/32, A61K39/395, A61K45/06, A61K31/7068

Language of the proceedings: EN

Title of invention:
Treatment with anti-ErbB2 antibodies

Patent Proprietor:
Genentech, Inc.

Opponents:
Generics [UK] Limited (opposition withdrawn)
Dörries, H. Ulrich
Pohlman Patentanwälte Rechtsanwälte PartG mbB
Pfizer, Inc.
Appelt, Christian W.
Taylor Wessing LLP
König Szynka Tilmann von Renesse

Headword:
Combination therapy of breast cancer/GENENTECH

This datasheet is not part of the Decision.
It can be changed at any time and without notice.

Relevant legal provisions:
EPC Art. 100(a), 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0167/93, T 0274/94, T 1859/08

Catchword:

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1853/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 February 2018

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 II: (Opponent 2)	Dörries, H. Ulrich Fünf Höfe Theatinerstrasse 16 80333 Munich (DE)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 80333 München (DE)
Respondent III: (Opponent 3)	Pfizer, Inc. 235 East 42nd Street New York, N.Y. 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)

Respondent IV: (Opponent 4)
Appelt, Christian W.
Boehmert & Boehmert
Pettenkoferstrasse 20-22
80336 München (DE)

Representative:
Engelhard, Markus
Boehmert & Boehmert
Anwaltspartnerschaft mbB
Pettenkoferstrasse 22
80336 München (DE)

Respondent V: (Opponent 5)
Taylor Wessing LLP
5 New Street Square
London EC4A 3TW (GB)

Representative:
Ma, Saufung
Taylor Wessing LLP
5 New Street Square
London EC4A 3TW (GB)

Respondent VI: (Opponent 6)
König Szynka Tilmann von Renesse
Patentanwälte Partnerschaft mbB
Mönchenwerther Strasse 11
40545 Düsseldorf (DE)

Representative:
Hemsath, Lars
König-Szynka-Tilmann-von Renesse
Patentanwälte Partnerschaft mbB
Mönchenwerther Straße 11
40545 Düsseldorf (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 13 June 2016 revoking European patent No. 1037926 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chair G. Alt
Members: R. Morawetz
M. Blasi

Summary of Facts and Submissions

I. The appeal of the patent proprietor ("appellant") lies from the opposition division's decision revoking European patent No. 1 037 926. The patent is entitled "*Treatment with anti-ErbB2 antibodies*".

Claim 1 as granted reads:

"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 which is a taxoid and not in combination with an anthracycline derivative, 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."

II. Six oppositions had been filed against the patent. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC. The opposition division found in the appellant's favour on all grounds of opposition except for patentability in relation to

inventive step. It decided that the set of claims of the main (sole) request (patent as granted) did not meet the requirements of Article 56 EPC and revoked the patent.

III. The following documents are referred to in this decision:

D1 Baselga J. *et al.*, Oncology (March 1997), vol. 11, No. 3, Supplement No.2, pages 43 to 48

D3 Baselga J. *et al.*, Annals of Oncology (1994), vol. 5, Suppl. 5, Abstract A010

D4 Declaration by S.D. Hellmann (20 December 2004)

D5 Interoffice Memorandum Genentech, undated

D7 Voskoglou-Nomikos, Clinical Cancer Research (2003), vol. 9, 4227-4239

D8 Herceptin, Summary of product characteristics (undated), pages 1 to 31

D9 Herceptin®, Genentech (2003), pages 1 to 29

D13 Baselga J. *et al.*, Journal of Clinical Oncology (1996), vol. 14, pages 737 to 744

D20 Baselga, J. *et al.*, Proceedings of the America Association for Cancer Research (1994), vol. 35, Abstract 2262

D31 Nabholtz J.-M. *et al.*, Journal of Clinical Oncology (1996), vol. 14, pages 1958 to 1867

D35 Baselga J. *et al.*, Proceedings of ASCO (1994), Vol. 13, page 63, abstract 53

D36 Dieras V. *et al.*, Seminars in Oncology (1995), vol. 22, pages 33 to 39

D55 Proceedings of ASCO (1999), vol. 18, page 137a, abstract 523

D67 D.F. Hayes, printout from web page (2007)

D68 D.F. Hayes, printout from web page (2007)

D69 B. Leyland-Jones, The Lancet (2002), vol. 3, pages 137 to 144

D70 Genentech Interoffice memorandum, undated

D74 First Declaration of Prof P. Barrett-Lee (2015)

D78 French Epirubicin Study Group, Journal of Clinical Oncology (1991), vol. 9, pages 305 to 312

D80 I. Kola and J. Landis, Nature Reviews (2004), vol. 3, pages 711 to 715

D82 A.H. Calvert and K.R. Harrap, in "The control of tumour growth and its biological bases", W. Davis, C. Maltoni, S. Tanneberger editors, (1983), pages 359 to 365

D83 Kerbel R.S., Cancer and Metastatic Reviews (1999), vol. 17, pages 301 to 304

D84 T. Gura, Science (November 1997), vol. 278, pages 1041 to 1042

D85 Takimoto C.H., Clinical Cancer Research (2001), vol. 7, pages 229 to 230

D86 Second Declaration of Prof P. Barrett-Lee (2016)

D87 S. Harrison, in Teicher B. A. ed., Tumor Models in Cancer Research (1st edition), Springer 2002, pages 3 to 19

IV. With its statement of grounds of appeal, the appellant maintained the main request underlying the decision under appeal (patent as granted) as its sole request and presented arguments as to why the subject-matter of the claims involved an inventive step.

V. The six opponents are the respondents in these appeal proceedings ("respondent I to VI" or "the respondents"). With their responses to the statement of grounds of appeal, all respondents presented, *inter alia*, arguments as regards lack of inventive step of the subject-matter of the sole claim request.

VI. By letter dated 1 August 2017 respondent I withdrew its opposition.

VII. The board summoned the parties to oral proceedings and sent a communication pursuant to Article 15(1) RPBA.

VIII. At the oral proceedings before the board, respondent VI was not represented, as communicated to the board in advance in writing. At the end of the oral proceedings the chair announced the board's decision.

IX. The arguments of the appellant, submitted in writing and during the oral proceedings, may be summarised as follows:

Sole claim request (claims as granted)

Claim construction - claim 1

The opposition division departed from the proper claim construction adopted by the board in decision T 1859/08, i.e. the decision taken in appeal proceedings against the refusal of the application underlying the present patent.

The clinical efficacy as measured by determining time to disease progression was a technical feature of the claim, manifest as the purpose of the treatment referred to in the claim.

Inventive step - claim 1

Closest prior art

Document D1, which summarised previous preclinical and early clinical work and outlined an ongoing phase III clinical trial in which one arm of patients received anti-ErbB2 antibody plus taxoid, another arm received taxoid and the primary endpoint was time to disease progression (TTP) was the closest prior art, whilst document D13 was more distant.

Technical problem and its solution

A distinguishing feature of the claimed invention was the provision of clinical benefit in human patients with malignant breast cancer as measured by increased

time to disease progression compared with treatment with taxoid without anti-ErbB2 antibody.

Obviousness

The invention was based on the enhancement of clinical benefit of chemotherapy by addition of antibody. The question to be addressed in view of the claimed subject-matter was whether the person skilled in the art would have adopted the combination of an anti-ErbB2 antibody and a taxoid in the expectation of achieving an increased time to disease progression in human patients with malignant breast cancer compared with the treatment with taxoid without anti-ErbB2 antibody.

Document D1

Document D1 provided cellular data, xenomouse data, and data from a phase II clinical trial with antibody alone and with antibody and cisplatin. However, to determine time to disease progression, phase III clinical trial data were needed.

There was nothing in document D1 that provided a technical basis for the person skilled in the art to expect to achieve the increased time to disease progression as defined in claim 1 using an anti-ErbB2 antibody and taxoid.

The prior studies in mouse xenograft models disclosed in documents D3, D20 and D35 were summarised in document D1.

The xenograft experiments were not designed to provide insight into any potential effect on time to disease progression in a human patient. The experiments

described inhibition of growth in relative terms. They said nothing about the absolute rate of growth, an increase in tumour size or the appearance of new tumours. While the disappearance of the xenograft was a tumour response, it did not necessarily lead to an increase in the time to disease progression. The xenograft mouse studies at best provided information relating to different endpoints.

No conclusions regarding synergy could be drawn from the report of the antibody with cisplatin study in document D1 since adequate controls and comparisons were not provided (see document D74, paragraphs 107 to 110).

The performance of a clinical trial by Genentech disclosed in document D1 would not have made the ordinary person skilled in the art expect success, see documents D4, D5 and D70, which explained how the invention came to be made.

No other document, if and when combined with document D1 as closest prior art, could have provided a basis for expecting an increased time to disease progression.

Document D13

All patients in document D13 received the same treatment, rhuMAb HER2 alone, and only a selected sub-population had an unusually long response. The statement in document D13 about median time to disease progression only related to patients with minor response or stable disease. Table 4 reported that at 11 weeks, in 22 of 43 patients the disease had already progressed, which meant that - by definition - the median time to disease progression for the entire

population did not exceed 11 weeks.
In document D13, clinical benefit was measured by considering response, i.e. a reduction in tumour size. Tumour response said nothing about the ability of a therapy to increase time to disease progression, which was a comparative measure.

Document D13 itself noted that the observation of "*stable disease*" was "*not considered a reliable measurement of anticancer activity*".

Predictive value of the mouse xenograft models

Mouse xenograft models had significant shortcomings, see e.g. documents D7, D82, D83, D84 and D85 and were not generally predictive of successful human clinical benefit. Many clinical trials failed after promising results in xenograft experiments.

The unpredictability of the results of xenograft experiments for human treatment was further emphasised by the fact that the xenograft experiment described in documents D3, D20 and D35 did not predict the serious toxicity found in humans treated with the antibody in combination with anthracycline derivative.

Expert declarations by Professor Barret-Lee: documents D74 and D86

Professor Barret-Lee provided technical evidence in document D74, paragraphs 66 to 69, and in document D86, paragraphs 18 to 22, explaining that the effect of a drug on tumour response was different from an effect on time to disease progression and that a drug that

elicited a response (shrinks a tumour) did not necessarily increase the time to disease progression, as evidenced by document D78.

Documents D74 and D86 also commented on actual expectations in the field at the time and addressed the limitations of the xenograft experiments disclosed in the respective documents.

Decision T 1859/08

The board previously recognised that the xenograft experiment did not provide a biological effect translating into an increased time to disease progression.

Further evidence

The opposition division had ignored further evidence provided by the appellant.

Declaration D4 and the two scientific publications it cited (documents D5 and D70 in these appeal proceedings) provided contemporaneous evidence of actual expectations in the field at the time. The declaration provided comments on the lack of predictability of results in the phase III clinical trial from the preclinical work. Document D5 was a contemporaneous document illustrating the controversy around the phase III clinical trial.

Document D7 described a retrospective analysis of preclinical work relating to thirty-one cytotoxic cancer drugs.

Document D55 provided results from a phase II clinical trial with women with metastatic breast cancer treated with an anti-ErB2 antibody and the taxoid docetaxel.

Document D67 summarised the clinical significance of a variety of different potential therapeutic outcomes for breast cancer patients. This showed that an increase to time of disease progression was not implicit in any cancer treatment.

Document D68 noted that metastatic breast cancer was not usually curable, but treatment may provide a different outcome, including prolongation of life, delay of progression of cancer, relief of cancer-related symptoms and improvement of quality of life. Document D68 discussed treatment of metastatic breast cancer and disclosed several treatment options, among them the use of the Herceptin antibody.

Document D69 provided information on the therapy of the invention.

Document D80 described a retrospective analysis of clinical trials. Only five percent of oncology drugs were successful and 50% of phase III trials failed.

Document D82 acknowledged that a serious shortcoming of mouse xenograft models was that they may predict activity in drugs which were inactive clinically or vice versa.

Document D83 stated that one of the biggest obstacles faced by investigators involved in the development and assessment of new anti-cancer drugs, was the failure of

preclinical rodent tumour models to reliably predict whether a given drug would have anti-tumour activity and acceptable toxicity in humans.

Document D84 discussed limitations of cellular and animal models in general and xenograft models in particular.

Document D85 confirmed the ongoing recognition of shortcomings of the use of human xenograft models.

Document D87 emphasised that if xenograft models were to be useful in predicting clinical utility, the models must be designed to measure outcomes that corresponded to outcomes sought in the clinic.

X. The arguments of the respondents, submitted in writing and during the oral proceedings, may be summarised as follows:

Sole claim request (claims as granted)

Claim construction - claim 1

In view of the wording of the claim, the use of the antibody with an anthracycline derivative was not part of the claimed combination therapy. The term "increased" in the expression "increased time to disease progression" extended to any increase, no matter how small. The claim covered a treatment achieving stable disease for a longer period.

Inventive step - claim 1

Closest prior art

Document D1 qualified as closest prior art.

Technical problem and its solution

The appellant had not used a structured problem-solution approach. The problem as formulated by the board was accepted.

Obviousness

Document D1

Document D1 disclosed that the taxoid paclitaxel and the antibody rhuMAb HER2 were clinically effective as monotherapies in the treatment of metastatic breast cancer and that, furthermore these agents had been shown to have a synergistic effect in animal models. The xenograft experiments taught that the combination therapy provided an increased response in HER2-positive tumours compared to taxanes.

Thus, document D1 disclosed that anti-HER2 (anti-ErbB2) monoclonal antibodies significantly increased the anti-tumour activity of paclitaxel *in vitro* and *in vivo* (see page 43, middle column, first paragraph).

The impressive 93% tumour growth inhibition of the combination treatment in the xenograft model provided a reasonable expectation for increasing, in human patients, time to disease progression by combining rhuMAb HER2 with paclitaxel. This was so because tumour growth was affected and because of the

"unescapable link" between tumour growth and time to disease progression.

The rate at which tumours grew was one of the factors directly taken into account when determining the time to disease progression. Consequently, this rate also underlay increased time to disease progression. If the tumour was growing slower, the time until its mass was increased by 25% consequently increased. Since the skilled person could expect with high confidence that the combination treatment with the anti-ErbB2 antibody and the taxoid slowed down tumour growth, they could expect a prolongation of the time to disease progression with the same certainty.

If there was no tumour growth, there was a good chance for TTP, in line with document D74, paragraph 67. The odds were good, reasonable at the very least.

Time to disease progression was just an appropriate means of measuring a favourable effect on tumour growth in the context of a human clinical trial. Measuring the median time to disease progression in xenograft models was unnecessary when the clinical benefit in terms of tumour size/growth could be readily observed.

In addition, the skilled person knew that the rhuMAb HER2 antibody (see document D13, abstract and page 741, right hand column, second paragraph) as well as the taxoid paclitaxel (see document D36, abstract) increased the time to disease progression of metastatic breast cancer in monotherapies in human patients.

The combination of two drugs with different mechanisms of action was expected to have some additive effect. Herceptin and paclitaxel both fitted the common

rationale for combination therapy as they were directed at different targets (see document D1, pages 44 and 45). Document D13 showed that the anti-ErbB2 antibody had an effect on tumour growth and explained that it made sense that it had this effect because it was cytostatic. Document D36 showed that paclitaxel alone had an effect on the time to disease progression. Based on how the anti-ErbB2 antibody worked (i.e. cytostatically), the skilled person would expect that the time to disease progression could be improved by adding the anti-ErbB2 antibody to the taxoid. Hence, the skilled person could expect with high certainty that the combination therapy would also have an effect in human breast cancer patients.

Document D1 reflected the view of the skilled person before the priority date (see page 47, left hand column, second paragraph). The results of the preclinical and early clinical work were encouraging and led to the design of clinical studies.

There was a reasonable expectation of providing clinical benefit as measured by an - unspecified - increase in time to disease progression compared to the taxoid alone. While the result of the clinical trial might not have been obvious, "an increase" was obvious.

The skilled person would have had no reason to be sceptical of this. Certainty of success was not required according to the case law, see decisions T 918/01 and T 1577/11.

The skilled person would be comforted by further circumstances, such as the teaching of document D13.

Document D13

Document D13 disclosed the results of a phase II clinical study with the anti-ErbB2 antibody rhuMAb HER2 in the treatment of metastatic breast cancer.

Phase II studies of patients with advanced cancer generally did not include reference patients. Nevertheless, the skilled person would have been able to compare the study results with the expected course of the disease in untreated patients. These patients showed a long time to disease progression which was markedly higher than that of comparable patient groups, for example the patient group treated with mitomycin described in document D36 (see page 38, left hand column, first paragraph). The significant increase in time to disease progression by the antibody treatment was also recognised and emphasised by the authors of document D13 (see page 741, second paragraph).

The skilled person would have expected at least a slight increase in time to disease progression because of the effect of Herceptin alone described in documents D1 and D13. In document D1 the authors classified the stable disease occurring in 14 patients and lasting for a median of 5.1 months as a sign of clinical activity (see page 46, middle column, second and thirds paragraph). Based on the statement in document D13 (page 741, right hand column, central paragraph) the skilled person would conclude that the antibody led to stable disease. Even though this was not based on data compared with a control group, it reflected the clear impression of the authors of document D13 that there was an unusually long duration of stable disease.

Predictive value of mouse xenografts models

The submissions on the unreliability of xenograft experiments as an indicator for human treatment were beside the point. In the present case, there were a lot of data in the prior art on paclitaxel alone in phase II clinical trials; on antibody alone in phase II clinical trials; and on a different combination, antibody and cisplatin, in phase II clinical trials.

The common activity of rhuMAb HER2 in xenograft models and in humans and the common activity of paclitaxel in xenograft models and in humans provided a reasonable expectation of success for the combination therapy in humans, in spite of any potential limitations of the xenograft model. Xenograft experiments were a reliable indicator in the present case.

As regards document D3 and the lack of toxicity which underlines the unreliability of xenograft experiments, it was noted that the skilled person would not have known the data provided by the patent when looking at the xenograft data reviewed in document D1.

The appellant had relied on documents D82 and D84 as showing that xenograft models were not predictive of clinical efficacy in humans. However, in the present case, the skilled person could have ignored these concerns because the clinical trials of the single agents paclitaxel and Herceptin in humans had already shown that the drugs arrived at the tissue of interest and could be used for effective treatment in humans.

Expert declarations by Professor Barret-Lee: documents D74 and D86

Professor Barret-Lee never said that time to disease progression had nothing to do with tumour growth. He said that, if a tumour rapidly regrew, then there was, in effect, no increase in time to disease progression, for which he gave one example reported by document D78 in these proceedings. However, this was not the rule when drugs were combined, in particular not when one drug arrested growth for a long time (see document D13).

The appellant's argument that an increased time to disease progression would not have been expected from a combination of an anti-ErbB2 antibody and a taxoid was both illogical and largely unexplained. Also, documents D74 and D86 only asserted that an increased time to disease progression would not be expected but did not explain why.

Decision T 1859/08

In this decision, the board assessed novelty and held that it was not directly and unambiguously derivable from the disclosure of the ongoing phase III clinical trial that a therapeutic effect was obtained, let alone one translating into increased time to disease progression.

Further evidence relied on by the appellant

Documents D4, D5, D7 to D9, D55, D67 to D70, D74 and D83 were post-published and hence irrelevant for assessing the skilled person's understanding and knowledge at the priority date.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted.

Respondents II, III, IV, V and VI requested that the appeal be dismissed.

Reasons for the Decision

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

2. Respondent VI did not attend the oral proceedings, although it was duly summoned. The board considered it expedient to conduct the scheduled oral proceedings in respondent VI's absence in order to reach a final decision on this appeal, treating respondent VI as relying on its written case (Rule 115(2) EPC and Article 15(3) RPBA).

Respondent I had withdrawn its opposition and issues other than the examination of the patent and the invention to which it relates as to compliance with the EPC had neither been raised by nor against respondent I. Hence, respondent I ceased to be a party to the present appeal proceedings.

Introduction and explanation of terms used

3. The claimed invention concerns the treatment of human patients with metastatic (also referred to as malignant) breast cancer characterised by overexpression of ErbB2 (also known as HER2) with a combination of an anti-ErbB2 antibody, e.g. rhuMoAb HER2, also referred to as rhuMAb HER2 (Herceptin®), and a chemotherapeutic agent that is a taxoid, e.g. paclitaxel (Taxol®) or docetaxel. RhuMAb HER2 or Herceptin® is a humanised version of the murine anti-ErB2 antibody 4D5. The epitope 4D5 is the region in the extracellular domain of ErB2 to which the antibody 4D5 binds.

4. "*Time to disease progression*", also termed "*time to tumour progression*", is a time-to-event endpoint that is measured in clinical trials from the beginning of therapy to disease progression. Two parameters are looked at for determining the "*time to disease progression*": (a) the median time that it takes for a patient's tumour to increase in size by 25%; (b) the appearance of any new tumour lesions. Thus, the disease is considered as having progressed if the tumour size is increased by 25% and/or new lesions have appeared. This time-to-event endpoint is used to assess a drug's ability to delay tumour growth in human patients (see document D13, page 738, right hand column, last paragraph; patent, paragraphs [0146] and [0147]; document D74, points 52, 62 and 58; and document D86, point 18).

5. Other endpoints used in clinical trials are based, for example, on objective tumour response assessments and are a measure of a drug's ability to affect the growth of observable and measurable tumours. Thus, a

"*complete response*" is defined as the disappearance of all known tumours. A "*partial response*" is defined as a 50% or more decrease in the total tumour size of the lesions that are measured to determine the effect of therapy and the absence of new lesions or progression of any known lesions. "*Progressive disease*" is defined as a 25% or greater increase (relative to the smallest measured size) in the size of any one or more measurable lesions, or the appearance of new lesions. Finally, "*stable disease*" means that neither the criteria for a partial response nor for progressive disease are met (see document D13, page 738, right hand column, last paragraph; document D74, points 55 to 59).

Sole claim request (claims as granted)

6. This decision deals with the issue of whether the claimed subject-matter involves an inventive step, all other issues having been decided in the appellant's favour in the decision under appeal.

Claim construction - claim 1

7. The appellant submitted that in the decision under appeal the opposition division departed from the proper claim construction adopted by the competent board in decision T 1859/08 of 5 June 2012, i.e. the decision taken in the *ex parte* appeal proceedings against the refusal of the application underlying the patent.

8. However, neither the opposition division nor this board is bound by the claim interpretation used in decision T 1859/08, *supra*. This is so because of established case law that a decision of a board of appeal on an appeal against the decision of an examining division has no binding effect in subsequent opposition

proceedings or on an appeal therefrom, having regard to both the EPC and the principle of *res judicata* (see Case Law of the Boards of Appeal, 8th edition 2016, IV.E.7.7.3; in particular decision T 167/93, OJ EPO 1997, 229, Reasons points 2 to 2.10).

9. Nevertheless, for coming to the decision on the present appeal, the board accepts the claim construction advocated by the appellant, i.e. the claim construction adopted in decision T 1859/08, *supra*. In view of the outcome of this appeal, the board sees no necessity to give reasons for not adopting the claim construction advocated by the respondents.

10. Thus, the purpose of the treatment recited in claim 1 "to provide clinical benefit as measured by increased time to disease progression of malignant breast cancer" is a technical feature characterising the claimed use.

Further, in accordance with the aforementioned decision T 1859/08, the feature stating a reduced side effect of the claimed treatment in comparison to the treatment with antibody and anthracycline derivatives, i.e. "reduced myocardial dysfunction", is a feature which does not characterise the claimed use.

11. Finally, the term "increased" in the feature "increased time to disease progression" is not specified in claim 1. Therefore, the board agrees with the respondents that the increase does not need to be synergistic or additive. Even a minor increase is sufficient to fall within the scope of this feature.

Inventive step (Article 56 EPC) - claim 1

Closest prior art

12. In the decision under appeal, it was held that either document D1 or document D13 could be taken to represent the closest prior art, while the appellant maintains that document D1 is the closest prior art.

13. Document D1, a review article, summarises previous preclinical and clinical work with paclitaxel (a taxoid) and an anti-ErbB2 antibody. It discloses that paclitaxel was "*selected for clinical development based on impressive antitumor activity against the implanted B16 melanoma and the human MX-1 mammary tumor xenograft. Since then, paclitaxel has been shown to have a high degree of antitumor activity in women with metastatic breast cancer*" (see page 43, left hand column, first and second paragraph) and is "*widely used in the management of advanced breast cancer* (see page 44, right hand column, second paragraph).

Document D1 also sets out the protocol for a phase III clinical trial in which one arm of patients receives rhuMAb HER2 antibody plus taxoid, another arm receives taxoid, and the primary end-point is time to disease progression.

14. Document D13 discloses the results of a phase II clinical study of the anti-ErbB2 antibody rhuMAb HER2 in the treatment of metastatic breast cancer that overexpress HER2. It reports that extensive preclinical studies had shown that certain anti-ErB2 antibodies can inhibit the growth of HER2-overexpressing tumour cells and that the study provides the first clinical evidence of the antitumour activity of rhuMAb HER2 (see page

741, left hand column, first paragraph). The number of patients assessable for treatment response on evaluation day 77 was 43 (see page 739, right hand column, last paragraph). Tumour responses were seen in 5 patients and included 1 complete remission and 4 partial remissions, while minor responses were seen in 2 patients and 14 patients had stable disease at day 77. The patients with minor response and stable disease entered a maintenance phase of weekly antibody administration until progression of disease. The median time to disease progression in these patients was 5.1 months (see page 740, paragraph bridging columns). Document D13 concludes that "*rhuMoAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancer that had received extensive prior therapy*" (see abstract).

15. Both documents thus relate to the treatment of metastatic breast cancer and therefore to the same purpose as the invention. However, the board agrees with the appellant that document D1 is the more promising springboard for the assessment of inventive step as it discloses the established treatment of ErbB2-overexpressing metastatic breast cancer in humans: taxoid (paclitaxel) chemotherapy which was a standard first-line therapy for metastatic breast cancer before the priority date of the patent (see document D1, page 43, left hand column, first and second paragraph and document D74, point 78).

Technical problem and its solution

16. The difference between the known treatment of ErbB2-overexpressing breast cancer with taxoids and the claimed treatment is the combined use of an anti-ErbB2 antibody and a taxoid.

17. Paragraph [0148] of the patent sets out data demonstrating the clinical benefit of the various treatment regimes, assessed separately by response rate (RR) and time to disease progression (TTP) plus severe adverse effects (AE). Paragraph [0150] summarises the findings. Thus, adding antibody to chemotherapy increases the clinical benefit, as assessed on a population basis by response rates and the evaluation of disease progression. Accordingly, an effect of the combination of anti-ErB2 antibody treatment with taxoid, compared to treatment with taxoid without the antibody, is the increased time to disease progression.

18. Based on this effect, the board holds that starting from the known monotherapy with the taxoid paclitaxel as the closest prior art, the objective technical problem to be solved is the provision of an improved treatment for malignant breast cancer in which the improvement is an increased time to disease progression compared to treatment with taxoid alone.

19. In the oral proceedings, the board pointed out that this formulation of the problem is in accordance with the appellant's written submissions in support of non-obviousness. The appellant not having formulated a technical problem itself did not contest the formulation of the problem.

Obviousness of the solution

20. The question that remains is whether the skilled person, aware of the teaching of document D1 and faced with the technical problem formulated above in point 18, would have modified the teaching of the closest prior art document D1 to arrive at the claimed invention in an obvious manner.

21. Document D1 not only summarises previous preclinical and clinical work with paclitaxel (see point 13, above) but also the preclinical and early clinical results obtained with anti-ErbB2 antibody. It states in this respect that "*available data that will be presented in this review suggest that HER2 overexpression may influence response to paclitaxel in patients with metastatic breast cancer and that anti-HER2 monoclonal antibodies significantly increase the antitumor activity of paclitaxel in vitro and in vivo*" (see page 43, middle column, first paragraph).

It then discloses that "*the murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$ (ECD^{HER2}), is a potent inhibitor of in vitro growth and, in xenograft models, of human breast cancer cells overexpressing HER2*" (see page 44, left hand column, second paragraph) and that inhibition of tumour growth with eradication of well-established tumours has been observed in the nude mouse xenograft models (page 46, left hand column, second paragraph).

Document D1 specifically refers to source [39] (document D13 in these appeal proceedings) and discusses the results of the phase II clinical study with rhuMAb HER2 in patients with metastatic breast carcinomas reported in document D13 (see page 46, left

hand column, third paragraph to middle column, third paragraph). Document D1 concludes that rhuMAb HER2 "*is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy*" (see page 46, middle column, fourth paragraph).

In the following chapters, document D1 discusses pre-clinical and early clinical results obtained with combinations of rhuMAb HER2 and chemotherapeutic agents, including paclitaxel.

Thus, it reports as follows on studies disclosed in reference [37] (document D20 in these appeal proceedings) on the combined therapy of paclitaxel in combination with rhuMAb HER2 that were conducted in nude mice bearing breast cancer human tumour xenografts.

Cells which express high levels of $p185^{HER2}$ were grown subcutaneously to a mean size of 200 mm^3 over 11 days. Animals were then treated with antibody alone, paclitaxel alone or both therapies combined. The results are summarised as follows "*therapy with MoAb 4D5 alone produced a 35% growth inhibition, and paclitaxel alone resulted in 35% growth inhibition when compared with animals treated with control MoAb. The treatment with paclitaxel plus 4D5 result in major antitumor activity, with 93% inhibition of growth. This result was markedly better than an equipotent dose of doxorubicin (10 mg/kg IP) and 4D5 (70% inhibition). In addition, paclitaxel combined with 4D5 resulted in the disappearance of well-established xenografts*" (see page 46, right hand column, second and third paragraph.

Document D1 then reports that in parallel with the phase II clinical trial which used rhuMAb HER2 alone, a phase II study of rhuMAb HER2 in combination with cisplatin (a platinum analogue) had been conducted in patients with breast cancer that overexpress HER2 and a history of proven refractoriness to chemotherapy. The observed response rate was 25% "*suggesting that the synergy observed in the laboratory was reproducible in the clinic*" (page 46, right hand column, last paragraph to page 47, left hand column, first paragraph).

22. In summary, document D1 discloses that both, paclitaxel (a taxoid) and rhuMAb HER2, are individually effective in mouse xenograft models of human breast cancer and that both are therapeutically effective in monotherapy in humans having metastatic breast cancer overexpressing HER2. Moreover, a synergistic effect had been shown in a mouse xenograft model for the combination of an anti-ErbB2 antibody and the taxoid paclitaxel. Furthermore, the results in a phase II study of ErbB2 antibody in combination with the platinum analogue cisplatin suggested that the synergy observed in the laboratory was reproducible in the clinic. Finally, document D1 reveals that based on the positive results in preclinical and early clinical studies, a multinational phase III clinical study was designed in which the effects of chemotherapy (paclitaxel or anthracycline) in combination with humanised anti-HER2 antibody (rhuMAb HER2) in patients with HER2-overexpressing metastatic breast cancer were to be compared with treatment with anti-HER2 antibody alone.

23. In the board's opinion, the teaching of document D1 summarised above and, in particular, the xenograft data it reports in combination with the known clinical

efficacy of rhuMAb HER2 antibody and paclitaxel in monotherapy of metastatic breast cancer, would have motivated the skilled person, faced with the technical problem formulated above, to combine the rhuMAb HER2 antibody with paclitaxel for the treatment of HER2-overexpressing metastatic breast cancer.

24. The next question is whether the skilled person would have reasonably expected this treatment to increase time to disease progression when compared to treatment with paclitaxel without antibody.

25. As set out above, a factor measured when determining the time to disease progression is the rate at which tumours grow, the other factor being the appearance of new tumours (see point 4). Document D1 reveals that in xenograft mouse studies, treatment with the combination of anti-ErbB2 antibody and paclitaxel results in "*93% inhibition of growth*" while treatment with paclitaxel alone resulted in "*35% growth inhibition*" and further that the combination of anti-ErbB2 antibody and paclitaxel results in the "*disappearance of well-established xenografts*", a result not reported for the use of paclitaxel alone (see point 22).

In the board's opinion, the effects observed for the combination of anti-ErbB2 antibody and paclitaxel in the xenograft model would have provided a reasonable expectation that TTP would increase vis-à-vis treatment with taxoid alone as there is an "unescapable link" between tumour growth and TTP (see point 4). If a tumour is growing more slowly, the time until its mass is increased by 25% increases per definition. Therefore, in the board's view, given that the combination treatment led to a reduced tumour growth and even tumour disappearance in mice compared to

treatment with paclitaxel alone, the skilled person would have had reason to expect an increased TTP in humans compared to treatment with paclitaxel alone. This view is supported by document D74, paragraph 67 which states that "*in order to extend TTP/PFS a drug need not shrink tumours at all, provided that the cancer is held in abeyance such that the appearance of progressive disease is delayed*".

26. In the present circumstances, xenograft data are demonstrated to be a reliable indicator for clinical efficacy by the fact that both paclitaxel and rhuMAb HER2 were initially shown to have anti-tumour activity in xenograft models and then confirmed to have clinical efficacy in human patients in monotherapy settings (see points 14 and 21 above).

27. Moreover, the skilled person would have known that the rhuMAb HER2 antibody as well as the taxoid are therapeutically effective in monotherapy treatments of metastatic breast cancer overexpressing ErB2 in human patients (see points 15 and 22 above).

Time-to-event analyses for time to disease progression (see point 4 above) in the treatment of metastatic breast carcinoma had been done for these drugs before. Thus, in a phase II randomised study of paclitaxel versus mitomycin in advanced breast cancer, median time to disease progression for paclitaxel was found to be 3.5 months (see document D36, abstract).

Anti-ErbB2 antibody had been shown in document D13 to lead to stable disease (see point 4 above) and this is said to be linked to it being cytostatic, causing growth arrest (see page 741, right hand column, second

paragraph). Median time to disease progression for patients with either minor response or stable disease was 5.1 months (see document D13, page 740, right hand column, first paragraph).

At the cellular level, paclitaxel stabilises microtubules, prevents tubulin depolymerisation and is cytotoxic (see document D1, page 45, left hand column, last paragraph to right hand column, first paragraph). The anti-ErbB2 antibody blocks stimulation of cell proliferation via the human epidermal growth factor and is cytostatic (see document D1, page 44, left hand column, first and second paragraph and document D13, page 741, right hand column, second paragraph). Thus, anti-ErbB2 antibody and paclitaxel fit the common rationale for combination therapy as they are directed at different targets. Based on how the anti-ErbB2 antibody works (cytostatically), the skilled person would have expected that TTP could be improved by adding anti-ErbB2 antibody to the taxoid. Even if no synergy is expected, their combination is expected to have at least some additive effect.

Also for these reasons, the skilled person would have expected that the combination treatment with the anti-ErbB2 antibody and paclitaxel would slow down tumour growth in human patients compared to treatment with paclitaxel without anti-ErbB2 antibody. Accordingly, they could have expected a prolongation of the time to disease progression with the same confidence.

28. The appellant provided three lines of argument as regards the xenograft data described in document D1. Firstly, it submitted that mouse xenograft models had significant shortcomings and were not generally predictive of successful human clinical benefit

(reference was made to documents D7, D82, D83, D84, D85 and D87 and declarations D74 and D86). Secondly, it argued that in the present case, the xenograft mouse experiments were not designed to and did not provide information on time to disease progression in malignant breast cancer (see also paragraphs 24 to 26, 125 of document D74 and paragraphs 9 and 10 of document D86). Thirdly, it submitted that the lack of predictive value of xenograft experiments was further emphasised by the fact that the xenograft experiments described in documents D3, D20 and D35 did not predict the serious toxicity found in humans treated with the antibody in combination with anthracycline derivative.

The board will address these three lines of argument in turn.

28.1 As regards the first line of argument - xenograft models have significant shortcomings and are generally not predictive of successful human clinical benefit - the appellant's technical expert states in document D74 under the heading "Preclinical Studies" that "*the aim of pre-clinical studies is to gather some evidence of activity and toxicity*" (see paragraph 22), that "*in 1997, in vitro studies of a potential new anti-cancer agent would generally have involved cultivating tumour cell lines in tissue culture and observing the effect of the new agent on the proliferation of those cells (...) those [agents] that demonstrated high levels of growth inhibition or cell killing compared to other agents, would be considered for further development, the next stage of which would be animal studies*" (see paragraph 23), further that "*pre-clinical animal studies for potential anti-cancer agents would have consisted primarily of mouse xenograft studies*" (see paragraph 24), that "*xenograft models had a number of*

well-recognised shortcomings (...) as a result it was well known that mouse xenografts were not always reliable predictors of clinical efficacy in humans. Many agents had demonstrated remarkable effects on tumour growth in mouse xenograft models yet subsequently failed to reproduce those effects in humans" (see paragraph 25), that "*evidence of activity in pre-clinical studies provided little assurance that the agent would ultimately demonstrate clinical efficacy in humans*" (see paragraph 26) and finally that "*a potential new agent would also have been subject to toxicity studies in animals*" (see paragraph 27).

28.2 Although everything Professor Barrett-Lee says might be correct, none of it has a bearing on the present case. In the present case, it was already known that rhuMAb HER2 has anti-tumour activity in both xenograft models and in humans. It was also known that paclitaxel has anti-tumour activity in both xenograft models and in humans (see points 21 and 22, above). Thus, the xenograft model was predictive of paclitaxel and rhuMAb HER2 activity in patients. Therefore, the question whether - in general - a xenograft model can reliably predict whether any given drug will have anti-tumour activity in humans does not arise in the present case, and the disclosure of documents D7, D82 to D85 and D87, none of which relates specifically to paclitaxel or rhuMAb HER2, is thus not relevant.

28.3 Moreover, none of the prior art literature on preclinical models cited by the appellant appears to give any reason to doubt that single agents found to be effective in humans and to have synergistic effects in xenograft animal models would also be effective in combination in humans.

28.4 As regards the second line of argument - mouse xenograft experiments were not designed to provide insight into any potential effect on time to progression of disease in a human patient - the appellant submitted (i) that it was not correct that tumour growth inhibition translated directly into an increased TTP, that (ii) tumour response and TTP measure aspects of the disease process that are not necessarily linked, that (iii) a drug which can shrink tumours and thus elicit a tumour response will not also necessarily extend the time to disease progression and that (iv) only relative growth of xenograft tumours treated with various agents was studied which said nothing about the absolute rate of growth and nothing about the absolute increase in tumour size or the appearance of new tumours. Reference was made to declarations D74 and D86. Document D78 was referred to as providing an example of when a combination of two chemotherapeutic agents led to an overall tumour response rate but had no significant effect on time to disease progression.

28.5 While the board does not dispute that tumour growth inhibition does not translate directly into an increased TTP, it is a fact that tumour growth underlies TTP. And while, in the board's opinion, the skilled person would have appreciated that tumour response and time to disease progression are not necessarily linked, they would have likewise appreciated that these endpoints are not unrelated or never linked. After all, as explained above, tumour growth is measured for the determination of TTP and tumour response is a measure of a drug's ability to affect the growth of observable and measurable tumours (see points 4 and 5). Thus, measurement of the endpoint "response rate" in the xenograft studies does not

disqualify this endpoint as an indicator for the increased TTP in humans.

28.6 Of course, when a tumour responds to therapy but then regrows rapidly, no increase in TTP might be seen. However, there is no reason to assume that what has been seen in the specific case of the addition of 5-fluorouracil and cyclophosphamide, two chemotherapeutic drugs, to epirubicin (see document D78) - and this is the only example of such a situation - will also be seen for the combination of anti-ErbB2 antibody and paclitaxel.

28.7 To the contrary, in the present case, there is evidence from preclinical studies, both *in vitro* and in xenografts, *"that anti-HER2 monoclonal antibodies significantly increase the antitumor activity of paclitaxel in vitro and in vivo"* (see points 21 and 22). There is moreover no indication that either rhuMAb HER2 or paclitaxel negatively impacts any other factor having an influence on time to disease progression. The skilled person would thus have had no reason to assume that treatment with the combination of rhuMAb HER2 and paclitaxel would result in more rapid progression to disease in humans compared to treatment with paclitaxel alone. Also, document D74 does not state that a drug which inhibits tumour growth will never prolong TTP, only that it is not always the case (see point 67).

28.8 As explained above (see points 4 and 5), tumour growth, which is the effect assessed in the xenograft model, underlies both TTP and tumour response. It is irrelevant whether absolute or relative growth are measured since the key finding in the xenograft

experiments is that the combination with the antibody inhibits tumour growth more effectively than treatment with paclitaxel alone.

28.9 Therefore, although phase III clinical trials are needed to determine an increased TTP, this does not mean that the skilled person would not have reasonably expected an increased TTP based on the preclinical and clinical data available all showing tumour growth inhibition.

28.10 As regards the third line of argument - xenograft experiments did not predict toxicity of anthracycline in humans - at the priority date, the skilled person would not have been aware of the toxicity observed in the studies reported in the patent. Accordingly, these data could not have influenced the skilled person's reasonable expectation of success based on the prior art xenograft experiments.

29. The appellant also disputed that document D13 showed clinical efficacy of the anti-ErbB2 antibody in the treatment of HER2-overexpressing metastatic breast cancer since no controls were included in the study and because document D13 itself noted that the observation of stable disease was not considered a reliable measure of anti-cancer activity.

29.1 The disclosure of document D13 has been summarised above (see point 14). It is true that the clinical study did not include untreated reference patients. However, this generally is the case in phase II studies of patients with advanced cancer, as can be seen from document D36. This document reports a phase II study in

which patients with metastatic breast cancer were randomised to receive either paclitaxel or mitomycin but no patients were left untreated.

Nevertheless, the skilled person would be able to compare the study results of document D13 with the expected course of the disease in similar patient groups. Without treatment, patients with metastatic breast cancer are generally expected to show tumour progression, with the exception of the rare cases of spontaneous stabilisation of the disease. The significant increase in time to disease progression by the antibody treatment is also recognised and emphasised by the authors of document D13 as follows "*the unusually long duration of minimal responses and stable disease seen in our trial*" (see page 741, right hand column, second paragraph). Hence, even without a direct comparison within the disclosed phase II study, the skilled person could take from document D13 that treatment with the anti-ErB2 antibody significantly increased time to disease progression of metastatic breast cancer in human patients simply by comparison with their experience with similar, differently treated patient groups. Indeed, time to disease progression is markedly higher than that of comparable patient groups, for example, the patient group treated with mitomycin described in document D36 with 1.6 month median time to disease progression (see page 38, left hand column, first paragraph).

29.2 The appellant submitted that document D13 itself stated that stable disease was not considered a reliable measure of anti-cancer activity. However, the appellant has taken this statement out of context. The relevant paragraph, when read in its entirety, actually states the opposite. The authors of document D13 note that in

the laboratory, rhuMAb HER2 is cytostatic, which causes growth arrest, rather than cytocidal, which causes cell death and further that "*in clinical trials of many anticancer drugs, particularly chemotherapy, the achievement of stable disease is not considered a reliable measure of anticancer activity. However, with rhuMAb HER2, stable disease may be an authentic reflection of the biologic action of the drug, which differs markedly from conventional anticancer agents. The unusually long duration of minimal responses and stable disease seen in our trial may relate to this distinction*" (emphasis added, see page 741, right hand column, second paragraph).

30. The board is not persuaded by any of the appellant's other lines of argument, based on documents D4, D5 and D70 and further evidence to the effect that, on the priority date, the skilled person would have had no reasonable expectation of success, as is explained below.

30.1 The appellant submitted that the skilled person would not have derived any expectations of success from the mere disclosure of the performance of the clinical trial by Genentech and that Genentech actually took a leap of faith in running the phase III trial. Document D4 and citations in it (documents D5 and D70 in these proceedings) were relied on to provide contemporaneous evidence of actual expectations in the field at the time.

30.2 The board finds that document D4, authored by the inventor, and dated some seven years after the priority date, and documents D5 and D70, both undated and post-filed, cannot qualify as contemporaneous evidence. Rather document D1, a review article, published shortly

before the priority date, can be taken as contemporaneous evidence reflecting the view of the skilled person before the priority date.

30.3 Document D1 states that "*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*" and "*the main goal of this study is to determine whether the addition of this anti-HER2 antibody increases the time to disease progression*" (see page 47, left hand column, second and fourth paragraph). In the board's opinion, the reasons cited in document D1 for doing the clinical phase III trial and the clinical endpoint chosen reflect the skilled person's expectations before the priority date.

In this context, for reasons similar to those in point 29.1, the board does not find the appellant's criticism of the antibody-with-cisplatin phase II study reported in document D1 persuasive and considers that the skilled person would have had no reason to doubt the statement made in document D1 in this regard.

30.4 The board notes that - with the exception of documents D82 and D84 - the further evidence relied on by the appellant, documents D8, D9, D55, D67 to D70, D74 and D83, was not available to the skilled person at the priority date of the patent as it is post-published. Accordingly, this evidence could not have influenced the skilled person's expectation of success. As to documents D82 and D84, which were relied on by the

appellant as further evidence that the predictive accuracy of mouse xenograft experiments was known to be poor, see points 28.1 and 28.2 above.

31. The appellant's reliance on decision T 1859/08 is not found persuasive either. This decision dealt with the novelty of the claimed subject-matter and in this context found that the xenograft studies reported in document D1 were not novelty-destroying because they "*did not involve humans*" (see Reasons, points 10 and 11).

The consideration which led the board to the conclusion that the subject-matter of claim 1 was not anticipated by the planned or ongoing phase III clinical trial disclosed in document D1 was that "*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*" (emphasis added, see Reasons, point 21). Thus, the board considered that an effect was not disclosed; not that it was not or could not be obtained.

Finally, as regards the xenograft experiments of document D3, the board held that there was no description of the treatment of a human patient, "*nor any disclosure of a biological effect translating into an increased time to disease progression*" (see Reasons, point 23).

32. In the present case, the issue to be decided is not whether the clinical benefit as measured by increased TTP compared with the treatment with taxoid without anti-ErbB2 antibody can be directly and unambiguously derived from the disclosure of document D1 but whether

the teaching of document D1 as a whole - possibly in combination with other prior art teachings - renders the claimed subject-matter obvious. The board concludes that, irrespective of the consideration that the decision T 1859/08 has no binding effect on the present board (see point 8 above), there is no contradiction with the board's findings in decision T 1859/08.

33. Finally, with regard to the circumstances under which subject-matter is considered obvious, in accordance with the case law of the Boards of Appeal, a course of action can be considered obvious within the meaning of Article 56 EPC if the skilled person would have carried it out in expectation of some improvement or advantage. Thus, obviousness is not only present when results are clearly predictable but also when there is a reasonable expectation of success. The amount of information and its quality needed for a skilled person to have a reasonable expectation of success depends on the specific circumstances of each case (see also Case Law of the Boards of Appeal, 8th edition 2016, I.D.7.1).

34. Considering that in the present case, what is to be achieved according to the claimed subject-matter is not curing metastatic breast cancer (which would be an unlikely outcome) but merely a - however minimal - increase in the time it takes for the malignant breast cancer to progress compared to treatment with taxoid alone, the prior art provides the skilled person with the information necessary for reasonably expecting to achieve this goal by adding the anti-ErbB2 antibody to paclitaxel.

35. Thus, based on a scientific evaluation of the facts available (see decision T 207/94, OJ EPO 1999, 273, Reasons, point 31), the person skilled in the art would

have adopted the combination of the antibody and taxoid with a reasonable expectation of achieving, on a population basis, for patients with malignant breast cancer an increased time to disease progression compared with the treatment with taxoid without the antibody. Therefore, the subject-matter of claim 1 is obvious and thus fails to meet the requirements of Article 56 EPC.

36. In view of the above considerations, the board concludes that the ground for opposition under Article 100(a) and Article 56 EPC prejudices the maintenance of the patent as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

B. Atienza Vivancos G. Alt

Decision electronically authenticated