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**Datasheet for the decision
of 23 October 2018**

Case Number: T 0975/14 - 3.3.04

Application Number: 02719260.8

Publication Number: 1383532

IPC: A61K39/00, A61K39/395

Language of the proceedings: EN

Title of invention:
Combination therapy

Patent Proprietor:
Genentech, Inc.

Opponent:
Chapman, Desmond Mark

Headword:
Anti-CD40 and anti-CD20 antibody combination therapy/GENENTECH

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
Inventive step - main request, auxiliary requests 1, 3, 4 (no)
Amendments - auxiliary requests 2, 5, 6 - allowable (no)

Decisions cited:

T 0939/92

Catchword:



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Case Number: T 0975/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 23 October 2018

Appellant:

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Decision under appeal:

**Decision of the Opposition Division of the
European Patent Office posted on 14 February
2014 rejecting the opposition filed against
European patent No. 1383532 pursuant to Article
101(2) EPC.**

Composition of the Board:

Chair

G. Alt

Members:

R. Morawetz

L. Bühler

Summary of Facts and Submissions

- I. The appeal by the opponent ("appellant") lies against the decision of the opposition division rejecting the opposition filed against European patent No. 1 383 532, entitled "*Combination therapy*".
- II. The following documents are referred to in this decision:
- D7 Benoit N.E. and Wade W.F., Immunopharmacology (1996), vol. 35, pages 129 to 139
- D18 Francisco J. A. *et al.*, Cancer Research (2000), vol. 60, pages 3225-3231
- III. The patent had been 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) EPC.
- IV. The opposition division had decided, *inter alia*, that the disclosure in the patent as granted was such that the claimed invention could be carried out by the skilled person and that the subject-matter of the claims as granted was inventive when document D7 was taken as the closest prior art.
- V. With the statement of grounds of appeal, the appellant filed document D18 and based his line of argument regarding lack of inventive step on this document as the closest prior art.
- VI. In reply to the statement of grounds of appeal, the patent proprietor ("respondent") filed a main request, which was the same as the claim request underlying the

decision under appeal (claims as granted), and auxiliary requests 1A to 9.

VII. The board summoned the parties to oral proceedings and sent a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion as regards the issue of sufficiency of disclosure.

VIII. In reply, the respondent filed by letter of 23 August 2018 a new main request and auxiliary requests 1 to 6.

Claim 1 of the new main request reads as follows:

"1. A composition consisting of an antibody directed against CD40, plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers, wherein the antibody arrests the growth of neoplastic cells expressing CD40 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof,

for use in treatment of a neoplastic disease or disorder characterised by neoplastic cells expressing CD40 in a mammal,

wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition consists of an antibody directed against CD20 plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers, and wherein the antibody directed against CD20 arrests the growth of neoplastic cells expressing CD20 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the disease or disorder is defined as "*a B cell malignancy*".

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that the disease or disorder is defined as "*rituximab-resistant lymphoma*".

Claim 1 of auxiliary request 3 reads as follows:

"1. A composition consisting of an antibody directed against CD40, plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers, wherein the antibody arrests the growth of neoplastic cells expressing CD40 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof,

wherein the antibody directed against CD40 is a humanized monoclonal antibody comprising variable heavy chain complementarity determining residues SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, and variable light chain complementarity determining residues SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,

for use in treatment of a neoplastic disease or disorder characterised by neoplastic cells expressing CD40 in a mammal,

wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition consists of an antibody directed against CD20 plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers, and wherein the antibody directed against CD20 arrests the growth of neoplastic

cells expressing CD20 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof.

Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 3 in that the disease or disorder is defined as "*a B cell malignancy*".

Claim 1 of auxiliary request 5 differs from claim 1 of auxiliary request 3 in that the disease or disorder is defined as "*rituximab-resistant lymphoma*".

Claim 1 of auxiliary request 6 reads as follows:

"1. A composition consisting of an antibody directed against CD40, plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers, wherein the antibody arrests the growth of neoplastic cells expressing CD40 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof,

wherein the antibody directed against CD40 is a humanized monoclonal antibody comprising variable heavy chain complementarity determining residues SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, and variable light chain complementarity determining residues SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6,

for use in treatment of a disease or disorder characterised by cells expressing CD40 in a mammal, wherein the disease or disorder is rituximab-resistant lymphoma, wherein the treatment comprises administration of said composition in combination with a second composition, wherein the second composition consists of an antibody

directed against CD20 plus optional pharmaceutically acceptable carriers, pharmaceutical excipients or pharmaceutical stabilisers,

wherein the antibody directed against CD20 is rituximab, and

wherein the antibody directed against CD20 arrests the growth of neoplastic cells expressing CD20 and is optionally conjugated to a radioactive isotope, chemotherapeutic agent, toxin or fragment thereof."

- IX. During the oral proceedings, the respondent withdrew the main request and auxiliary requests 1A to 9 which had been filed in reply to the statement of grounds of appeal. At the end of the oral proceedings, the chair announced the board's decision.
- X. The arguments of the appellant, submitted in writing and during the oral proceedings, may be summarised as follows:

Main request

Admissibility into the appeal proceedings

The respondent had filed this request in reaction to the board's communication but had failed to provide any justification for not filing it earlier, i.e. with its reply to the statement of grounds of appeal. The board's communication did not raise any objections that had not been raised in the statement of grounds of appeal. The request was not clearly allowable and it raised new issues. It should not be admitted into the appeal proceedings.

Inventive step (Article 56 EPC) - claim 1

Closest prior art

Document D18 was the closest prior art. It related to the *in vivo* antitumour activity of the anti-CD40 antibody SGN-14, originally called S2C6, in Ramos Burkitt's lymphoma cells and thus to the use of the same antibody and cell line as used in the examples of the patent. In some of the experiments with xenografted Ramos Burkitt's lymphoma cells, all five of the treated mice were asymptomatic for the entire study period of 120 days (see Figures 4A and 4C). Document D18 described, for the first time, the ability of the anti-CD40 antibody S2C6 to eliminate B-cell disease in animal models (see page 3230, left hand column, third paragraph).

Technical problem and its solution

The difference between the disclosure of document D18 and the subject-matter of claim 1 was that a combination with an anti-CD20 antibody was used.

As regards the effect associated with this difference, there could be no improvement over the treatment of Ramos Burkitt's lymphoma disclosed in document D18, since the treatment with anti-CD40 antibody alone already led to a complete elimination of the tumour in the Ramos Burkitt's lymphoma model. This was confirmed in the patent, which used the same cell line (Ramos Burkitt's lymphoma) and the same antibody (SGN-14), see Figure 2.

It was not correct that a teaching in the prior art, over which no improvement was possible, could not be

the closest prior art - it just meant that the problem to be solved then became the provision of an alternative solution.

It could also not be inferred from Figures 4 and 5 of the patent that the claimed treatment was an improvement over the treatment disclosed in document D18 across the whole scope of claim 1. The data reported in these figures related to the treatment of specific lymphomas known to express both CD40 and CD20 (CD40⁺CD20⁺). The patent provided no data for the treatment of diseases characterised by neoplastic cells expressing CD40 but not CD20 (CD40⁺CD20⁻). Although the patent reported the generation of a rituximab-resistant Ramos lymphoma cell line, it provided no characterisation as regards the expression of CD20 or CD40 on these cells, and therefore the data obtained with this cell line did not reflect an effect seen in CD20-negative cells.

CD40 was significantly more widely expressed than CD20. A number of diseases falling within the definition of neoplastic diseases in claim 1, see also Table 1 of the patent, were not B-cell cancers and were known not to express CD20, e.g. carcinomas. For these diseases, the addition of an anti-CD20 antibody could have no useful technical effect.

The objective technical problem was the provision of an alternative treatment for a disease or disorder characterised by neoplastic cells expressing CD40.

Obviousness

The claimed solution was obvious in the light of the teaching of document D18 alone.

The skilled person would not expect that the addition of an anti-CD20 antibody would add to the successful treatment of Ramos Burkitt's lymphoma known from document D18. Likewise, the addition of an anti-CD20 antibody had no effect in cancers that were not B-cell cancers and did not express CD20. The addition of the anti-CD20 antibody to the treatment known from document D18 was thus arbitrary (for the concept of "arbitrary", see decision T 939/92 and Case Law of the Boards of Appeal of the European Patent Office, I.D.9.18.7).

Auxiliary requests 1, 3 and 4

Inventive step (Article 56 EPC) - claim 1

The same line of argument as provided for the subject-matter of claim 1 of the main request applied.

Auxiliary request 6

Amendments (Article 123(2) EPC) - claim 1

The application as filed disclosed rituximab resistance only in the context of a Ramos Burkitt's lymphoma cell line, see example I, page 42, lines 1 to 4 and Figure 5. The general part of the application as filed did not contain any disclosure as to rituximab-resistant lymphoma. Thus, in claim 1 the disease had been taken out of its context - Ramos Burkitt's lymphoma - and generalised to any rituximab-resistant lymphoma.

The mechanisms underlying the induction of rituximab resistance in the exemplified Ramos Burkitt's lymphoma cell line were not disclosed. Therefore, the skilled person would not extrapolate directly and unambiguously the findings obtained with this cell line to rituximab-resistant lymphoma in general.

Auxiliary requests 2 and 5

Amendments (Article 123(2) EPC) - claim 1

The same line of argument as provided for the subject-matter of claim 1 of auxiliary request 6 applied.

- XI. The arguments of the respondent, submitted in writing and during the oral proceedings, may be summarised as follows:

Main request

Admissibility into the appeal proceedings

The request reacted to concerns raised in the board's communication and should be admitted for reasons of procedural economy because it simplified the discussion and did not raise a fresh case.

Inventive step (Article 56 EPC) - claim 1

Closest prior art

Of the two documents D7 and D18, document D18 was the more appropriate starting point for the assessment of inventive step as it aimed at the same purpose as the invention.

Document D18 disclosed *in vivo* experiments showing that the anti-CD40 antibody SGN-14 (also called "SG2C") had antitumour activity in B-cell lymphoma and multiple myeloma xenografted mice.

Technical problem and its solution

The difference between the subject-matter of claim 1 and the disclosure of document D18 was that the claimed method of treatment also comprised the administration of an anti-CD20 antibody that arrests the growth of neoplastic cells expressing CD20.

The technical effect of this difference was an improved therapeutic outcome as could be inferred from Figures 4 and 5 of the patent.

It was not logical to start from the experiment in Figure 4A of document D18 as the closest prior art because no improvement could possibly be achieved over this experiment.

The treatment of CD20-negative cancers was not specifically claimed. The cells underlying the data shown in Figure 5 were functionally CD20 negative. The appellant had failed to provide data to show that the claimed treatment was not an improvement across the whole scope of the claim.

Starting from document D18, the objective technical problem was to provide an improved therapy for neoplastic diseases or disorders characterised by neoplastic cells expressing CD40.

Obviousness

Even if the problem was formulated as the provision of an alternative therapy, the skilled person would still not have arrived at the subject-matter of claim 1 in an obvious manner because there was nothing in document D18 pointing towards the claimed invention.

Auxiliary requests 1, 3 and 4

Inventive step (Article 56 EPC) - claim 1

The same arguments as submitted in relation to the main request applied.

Auxiliary request 6

Amendments (Article 123(2) EPC) - claim 1

The claim recited that the disease or disorder to be treated was a rituximab-resistant lymphoma. A basis for this amendment was found in the application as filed, in the parts that explicitly referred to lymphoma as a preferred disorder for treatment (e.g. claim 4 as filed), and also in the section describing an experimental mouse model using a rituximab-resistant lymphoma (pages 41 to 43 of the application as filed).

The mechanism underlying the induction of rituximab resistance in the exemplified Ramos Burkitt's lymphoma cell line was not known. The resistance might be due to the down-regulation of CD20 expression. Alternatively, CD20 might still be expressed on the cell surface, but downstream signalling might be impaired.

Auxiliary requests 2 and 5

Amendments (Article 123(2) EPC) - claim 1

The same arguments as submitted in relation to auxiliary request 6 applied.

- XII. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the decision under appeal be set aside and the patent be maintained on the basis of the claims of the main request, or, alternatively, on the basis of the claims of one of auxiliary requests 1 to 6, filed with the letter of 23 August 2018.

Reasons for the Decision

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

Main request

2. Although admittance of this set of claims was contested by the appellant, there is no need to give reasons for the admittance and substantive assessment of the respondent's main request by the board, since, for the reasons given below, this request could not be allowed.

Inventive step (Article 56 EPC) - claim 1

Closest prior art

3. The opposition division held that document D7 was the closest prior art for the subject-matter of the claims as granted (see decision under appeal, Reasons, point 5.3.1)
4. On appeal, both parties agreed that document D18 was the more appropriate starting point for the assessment of inventive step. The board sees no reason to differ.
5. Document D18 relates to the *in vivo* antitumour activity of the monoclonal anti-CD40 antibody SGN-14, originally called S2C6 (see document D18, page 3225, right hand column, third paragraph). This is the same antibody as used in the examples of the patent in suit (see paragraph [0120]).

Document D18 reports that the antitumour activity of mAb SGN-14 was studied in human B-cell lymphoma xenografts in severe combined immunodeficient (SCID) mice. The mice were implanted with 1×10^6 Ramos or HS-Sultan Burkitt's lymphoma cells and groups of mice (five/group) were left untreated, received 1 mg/kg/ injection of a non-binding control mAb starting one day after tumour inoculation, or received 1 mg/kg mAb SGN-14 starting one or five days after tumour inoculation (see Figure 4).

Mice left untreated developed a disseminated disease manifested by hind-limb paralysis and other neurological symptoms and were sacrificed within 42 days of implantation with Ramos cells and within 37 days with HS-Sultan cells.

According to document D18, the anti-CD40 mAb SGN-14 was most effective in the Ramos model, where all five mice implanted with Ramos lymphoma cells and receiving 1 mg/kg SGN-14 starting one day after tumour inoculation were asymptomatic for the entire study period of 120 days (see page 3228, left hand column, second paragraph and Figure 4A).

Document D18 concludes that mAb SGN-14 eliminates B-cell disease in animal models (see page 3230, left hand column, third paragraph).

That Ramos Burkitt's lymphoma cells express CD40 is shown in Figure 1B of document D18.

6. The board concludes from the above that document D18 discloses the successful treatment of a model for Burkitt's lymphoma, a form of non-Hodgkin's lymphoma, *i.e.* a neoplastic disease or disorder characterised by neoplastic cells expressing CD40, with an anti-CD40 antibody.

7. The respondent's argument that it is not appropriate to choose a successful treatment as closest prior art over which no improvement can be shown is not found persuasive because the treatment disclosed in document D18, and as discussed above (see point 6), fulfils the established criteria - same purpose and most relevant technical features in common - for qualifying as the closest prior art (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.3.1).

Technical problem and its solution

8. The subject-matter of claim 1 differs from the disclosure of document D18 in that the anti-CD40 antibody is used in combination with an anti-CD20 antibody that arrests the growth of neoplastic cells expressing CD20 for the treatment of a neoplastic disease or disorder characterised by neoplastic cells expressing CD40.
9. According to the respondent, the technical effect associated with this difference is derivable from Figures 4 and 5 of the patent and results in an improved therapy. Thus, the problem, to which the subject-matter of claim 1 is the solution, would be to provide an improved therapy for neoplastic diseases or disorders characterised by neoplastic cells expressing CD40.
10. According to established jurisprudence of the boards of appeal, the problem and solution approach requires that it be assessed whether the claimed solution solves the technical problem across the whole scope claimed, and that the problem be reformulated if this is found not to be the case (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.9.8.1 and I.D.9.8.3; decision T 939/92, OJ EPO 1996, 309, Reasons, points 2.4 to 2.7).
- 10.1 In the board's opinion, it would be evident to the skilled person from Figure 4A of document D18 that there is no room for improvement over the treatment with anti-CD40 alone in the case of the Ramos Burkitt's lymphoma model, since the treatment with anti-CD40 antibody alone already leads to elimination of the tumour (see point 5 above).

Indeed, the patent also confirms that treatment with anti-CD40 antibody alone results in elimination of the tumours in the Ramos Burkitt's lymphoma model. Moreover, the treatment with a combination of anti-CD40 antibody and anti-CD20 antibody is not disclosed in the patent (see Figure 2).

- 10.2 It is undisputed that the patent demonstrates an improved therapeutic effect of the combination of an anti-CD40 antibody (SGN-14) and an anti-CD20 antibody (Rituxan®) vis-à-vis monotherapy with either antibody in the Sultan (multiple myeloma) xenotransplanted SCID mice (see Figure 4) and in Rituxan®-resistant Ramos Burkitt's lymphoma xenotransplanted SCID mice (see Figure 5). It is also undisputed that the Sultan and Ramos cell lines express both CD20 and CD40, i.e. are CD20⁺CD40⁺.
- 10.3 However, the subject-matter of claim 1 is not limited to the treatment of multiple myeloma or Rituxan®-resistant Burkitt's lymphoma, but relates generally to the "*treatment of a disease or disorder characterised by neoplastic cells expressing CD40 in a mammal*". Moreover, the definition of the disease in claim 1 is not such that it is required that the neoplastic cells expressing CD40 also express CD20.
- 10.4 The skilled person is aware of the fact that the expression patterns of CD40 and CD20 are not identical and that CD40 is significantly more widely expressed than CD20 whose expression is restricted to B cells (see document D18, page 3225, right hand column, first full paragraph and patent in suit, paragraphs [0002] and [0007]). As a consequence of the wider expression of CD40 than CD20, there exist diseases characterised by neoplastic cells which express CD40 but not CD20.

Indeed, Table 1 of the patent lists examples of neoplastic diseases that are characterised by cells expressing CD40 and includes many cancers that are not B-cell cancers and are known not to express CD20, e.g. carcinomas (see also document D18, page 3225, right hand column, lines 11 to 13).

- 10.5 Consequently, claim 1, although not explicitly claiming them, covers the treatment of diseases and disorders in instances where the CD40-expressing neoplastic cells characterising the disease or disorder do not express CD20 as well, e.g. the treatment of CD40⁺CD20⁻ cancers.

In agreement with the appellant's submission, the board fails to see, on the basis of the skilled person's common general knowledge, how in these instances an anti-CD20 antibody could exert any useful effect in the treatment and how the use of a combination of anti-CD40 and anti-CD20 antibodies could provide any improvement vis-à-vis the use of an anti-CD40 antibody alone in these instances.

- 10.6 The respondent's argument that the appellant's argument should fail because it did not provide data to the effect that no improvement could be seen for CD20-negative cancers also does not persuade the board. In circumstances where it is, on the basis of common general knowledge, not credible ("*inherently unlikely*", see decision T 939/92, Reasons, point 2.6.1) that a compound achieves an effect, the burden of proof rests on the party alleging the effect, *i.e.* in this case, the respondent (see e.g. decision T 939/92, *supra*, Reasons, point 2.6.1).

- 10.7 It follows from the above that the subject-matter of claim 1 encompasses as embodiments the treatment of

neoplastic diseases for which the addition of the anti-CD20 antibody will not have any useful effect in addition to the effect achieved by use of the anti-CD40 antibody alone. In the board's judgment, the subject-matter of claim 1 can not thus be considered to provide an improved treatment over the treatment disclosed in document D18 across the scope of the whole claim. Thus, the claimed solution does not solve the technical problem as formulated by the respondent across the whole scope claimed.

11. Therefore, starting from the closest prior art document, document D18, the objective technical problem to be solved is to be formulated as put forward by the appellant and is the provision of an alternative treatment of a neoplastic disease or disorder characterised by neoplastic cells expressing CD40 in a mammal.

Obviousness

12. The question to be assessed is whether or not the skilled person, starting from the treatment disclosed in document D18, would be motivated to use an anti-CD20 antibody in addition to the anti-CD40 antibody.
13. As set out above (see point 10.1), the skilled person would not consider that adding an anti-CD20 antibody would add to the successful treatment of Ramos Burkitt's lymphoma. Hence, there is in fact nothing in document D18 to prompt the skilled person to add an anti-CD20 antibody.
14. However, the skilled person is aware that many compounds could be added to the known successful treatment without any useful technical effect. The

selection of a particular compound - an anti-CD20 antibody - from a host of equally suited compounds, in the absence of a pointer does not involve any inventive step if it is not linked to a technical effect that distinguishes the claimed solution from the other solutions. Such a selection is often qualified as "arbitrary" in the jurisprudence (see also Case Law of the Boards of Appeal of the European Patent Office, I.D.9.18.7).

15. Therefore, the subject-matter of claim 1 does not meet the requirements of Article 56 EPC.

Auxiliary requests 1, 3 and 4

Inventive step (Article 56 EPC) - claim 1

16. The line of argument set out above for the subject-matter of claim 1 of the main request applies *mutatis mutandis* to the subject-matter of claim 1 of each of auxiliary requests 1, 3 and 4. This has not been disputed by the respondent.
17. Therefore, the subject-matter of claim 1 of each of auxiliary requests 1, 3 and 4 is considered to be obvious and thus fails to meet the requirements of Article 56 EPC.

Auxiliary request 6

Amendments (Article 123(2) EPC) - claim 1

18. Claim 1 of auxiliary request 6 further defines the disease or disorder to be treated to be "*rituximab-resistant lymphoma*", see section VIII above for the complete wording of the claim.
19. The respondent indicated claim 4 as filed and pages 41 to 43 of the application as filed as providing a basis for this amendment.
20. The application as filed discloses that Ramos is an Epstein-Barr virus (EBV)-negative Burkitt's lymphoma cell line (see page 41, line 32) which is sensitive to treatment with anti-CD20 antibody (Rituxan®) in a mouse tumour model (see page 42, line 25 to page 43, line 4; Figures 1 and 2). It also discloses that a "*Rituxan resistant Ramos lymphoma cell line was established through exposing the Ramos lymphoma cell line to high doses of Rituxan (500 ug/mouse IP, 3 times/week for 3 weeks) in a subcutaneous xenograft scid mouse*" (see page 42, lines 1 to 4). The antitumour activity of the anti-CD40 antibody S2C6 (SGN-14) and the anti-CD20 antibody Rituxan® product on Rituxan® resistant Ramos lymphoma was then studied in transplanted SCID mice. The results show that the tumour volume in mice receiving a combination of the two antibodies was significantly reduced compared with each of the control animals and animals receiving either antibody alone (see page 43, lines 20 to 27 and Figure 5).

Claim 4 as filed specifies that lymphoma is the malignancy to be treated with the antibody combination.

It was undisputed that the terms "rituximab" and "Rituxan®" denote the same antibody, see page 3, lines 34 to 36 of the application as filed.

It follows from the preceding point that in the application as filed the feature "rituximab-resistant" is disclosed in the context of the treatment of a Ramos Burkitt's lymphoma model, but not in the context of treatment of lymphomas generally.

21. The application is silent as to the mechanism underlying the observed resistance to rituximab in the Ramos Burkitt's lymphoma model.
22. The respondent, when asked at the oral proceedings whether or not rituximab resistance implied necessarily that CD20 was still expressed on the cell surface, replied that the mechanism underlying the development of rituximab resistance in the Ramos Burkitt's lymphoma cell line was unknown and that rituximab resistance could be due to down-regulation of CD20 expression, *i.e.* the absence of CD20, or disruption of cell signalling downstream of CD20 in the presence of CD20.
23. In the board's judgment, the fact that the mechanism underlying the development of rituximab resistance in the model tested in the application is unknown together with the possible involvement of more than one mechanism underlying rituximab resistance - including one where CD20 is no longer expressed on the cell surface - speaks against the skilled person understanding directly and unambiguously that the feature "*rituximab-resistant*" is not inextricably linked with the other features disclosed in combination in the application for that embodiment (see point 20). Accordingly, this feature cannot be extracted from the

context in which it has been disclosed in the application as filed - rituximab resistance of Ramos Burkitt's lymphoma - and applied to the more general context of just any lymphoma.

24. The board concludes from the above that the subject-matter of claim 1 extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary requests 2 and 5

Amendments (Article 123(2) EPC) - claim 1

25. The line of argument set out above for the subject-matter of claim 1 of auxiliary request 6 applies *mutatis mutandis* to the subject-matter of claim 1 of each of auxiliary requests 2 and 5. This has not been disputed by the respondent.
26. Therefore, the subject-matter of claim 1 of each of auxiliary requests 2 and 5 extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Conclusion

27. In the absence of an allowable request, the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chair:



S. Lichtenvort

G. Alt

Decision electronically authenticated