Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 20 April 2021

Case Number: T 2167/17 - 3.3.04

Application Number: 04754321.0

Publication Number: 1631313

IPC: A61K39/395

Language of the proceedings: EN

Title of invention:
Combination therapy for B cell disorders

Patent Proprietor:
Genentech, Inc.

Opponent:
GlaxoSmithKline Intellectual Property Management Limited

Headword:
Combination therapy/GENENTECH

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:
Late-filed argument - admitted (no)
Inventive step - (no)

Decisions cited:

Catchword:
-

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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 2167/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 April 2021

Appellant: (Opponent)	GlaxoSmithKline Intellectual Property Management Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Hitchcock, Lucy Rose GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 August 2017 concerning maintenance of the European Patent No. 1631313 in amended form.**

Composition of the Board:

Chair	B. Claes
Members:	B. Rutz
	P. de Heij

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the opposition division's interlocutory decision that European patent No. 1 631 313 (hereinafter "the patent") in the form of auxiliary request 1 complied with the requirements of the EPC. The patent is entitled "*Combination therapy for B cell disorders*".

Claim 11 of auxiliary request 1 reads:

"11. A BLyS antagonist and a CD20 binding antibody in combination for use in a method of depleting B cells from a mixed population of cells, wherein the BLyS antagonist is selected from the group consisting of: an anti-BLyS antibody, wherein the anti-BLyS antibody partially or fully blocks BR3 interaction with a BLyS polypeptide; an anti-BR3 antibody; a BR3 immunoadhesin; or a polypeptide having the sequence of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8 or SEQ ID NO. 9; and wherein the method comprises administering the BLyS antagonist and CD20 binding antibody in combination to a human in need thereof."

II. The patent was opposed on the grounds in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and 100(c) EPC.

III. In the statement of grounds of appeal, the appellant argued, *inter alia*, that the subject-matter of claim 11 of all the auxiliary requests lacked an inventive step. In this context they referred *inter alia* to documents E18 and E2.

IV. With their reply to the appeal, the patent proprietor (respondent) filed sets of claims of a main request (identical to the set of claims of auxiliary request 1 on which the decision under appeal was based; see section I) and auxiliary requests 1 (identical to auxiliary request 4 in the opposition proceedings), 2 to 7 (newly submitted), 8 and 9 (identical to auxiliary requests 2 and 5, respectively, in the opposition proceedings), and 10 to 15 (newly submitted).

Claim 11 of auxiliary request 1 is identical to claim 11 of the main request.

Claim 11 of auxiliary requests 2 and 3 differs from claim 11 of the main request in that the BLyS antagonist is limited to "an anti-BLyS antibody".

Claim 11 of auxiliary requests 4 and 5 differs from claim 11 of the main request in that the expression "and partially or fully blocks, inhibits, or neutralises native sequence BLyS signalling" is added.

Claim 11 of auxiliary requests 6 and 7 differs from claim 11 of the main request in that the BLyS antagonist is limited to "an anti-BLyS antibody" and in that the expression "and partially or fully blocks, inhibits, or neutralises native sequence BLyS signalling" is added.

Claim 11 of auxiliary request 8 reads (differences as compared with claim 11 of the main request highlighted):

"11. A BLyS antagonist and a CD20 binding antibody in combination for use in a method of depleting marginal zone and germinal center B cells in the spleen~~from a~~

~~mixed population of cells~~, wherein the BLyS antagonist is selected from the group consisting of: an anti-BLyS antibody, wherein the anti-BLyS antibody partially or fully blocks BR3 interaction with a BLyS polypeptide; an anti-BR3 antibody; a BR3 immunoadhesin; or a polypeptide having the sequence of SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8 or SEQ ID NO. 9; and wherein the method comprises administering the BLyS antagonist and CD20 binding antibody in combination to a ~~human~~mammal in need thereof."

Claim 11 of auxiliary request 9 differs from claim 11 of auxiliary request 8 in that "and germinal center" is deleted.

Claim 11 of auxiliary request 10 differs from claim 11 of auxiliary request 8 in that the BLyS antagonist is limited to "an anti-BLyS antibody".

Claim 11 of auxiliary request 11 differs from claim 11 of auxiliary request 8 in that "and germinal center" is deleted and the BLyS antagonist is limited to "an anti-BLyS antibody".

Claim 11 of auxiliary requests 12 to 15 differs from claim 11 of auxiliary requests 8 to 11, respectively, in that the expression "and partially or fully blocks, inhibits, or neutralises native sequence BLyS signalling" is added.

V. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

VI. Oral proceedings before the board took place in the form of a videoconference with the parties' consent. At

the end of the oral proceedings, the chair announced the board's decision.

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

E1 WO 03/014294

E8 Edwards J. C. W. et al., "*B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders*", Biochemical Society Transactions 30(4), 2002, 824-828.

E9 Mackay F. et al., "*BAFF and APRIL: A tutorial on B Cell Survival*", Annual Review Immunology 21, 2003, 231-264.

E18 Silverman G. J. and Weisman S., "*Rituximab Therapy and Autoimmune Disorders*", Arthritis & Rheumatism 48(6), 2003, 1484-92.

VIII. The appellant's arguments, as far as relevant to the decision, may be summarised as follows.

Main request

Amendment to the appellant's appeal case (Article 13(2) RPBA)

The reference to document E2 instead of to document E1 in the statement of grounds of appeal in the context of the inventive step of claim 11 in view of the disclosure in document E18, representing the closest

prior art, was an obvious error. This was apparent from the decision under appeal, which, in the same context, only mentioned E1 ("*E18 does not contain a pointer to preferably select such an agent over the other three approaches discussed. Also E1 does not provide an incentive for achieving the aforesaid technical effect*"). Furthermore, document E2 was not part of the state of the art. It was therefore clear that only document E1 could have been meant. The inventive step objection based on the combination of the disclosures in documents E18 and E1 had therefore been raised in the statement of grounds of appeal and was part of the appellant's appeal case.

Inventive step (Article 56 EPC) - claim 11

The disclosure in document E18 represented the closest prior art. It discussed the depletion of B cells and explained that a monotherapy using rituximab (a CD20-binding antibody) for patients with autoimmune diseases was not successful because the cells responsible for producing disease-causing autoantibodies were plasma cells on which CD20 was not present (see page 1489, last paragraph).

Document E18 additionally provided the rationale of how to overcome the deficiencies of targeting CD20 alone, namely also to target cells that did not express CD20 but that were causative of disease (page 1489, last paragraph). Lastly, it proposed using agents in combination with CD20-binding antibodies that blocked BLyS/BAFF/zTNF4, i.e. a BLyS antagonist (see page 1490, second column, middle paragraph).

The difference between the disclosure in document E18 and the claimed subject-matter was the combination of a

CD20-binding antibody with a BLyS antagonist, and the objective technical problem was to provide a method for improving B cell depletion.

The fact that rituximab only depleted CD20-expressing cells had already been recognised in document E18, which suggested a solution of additionally blocking the BLyS system (see page 1490, right-hand column, second paragraph).

As agents that block the BLyS system, anti-BLyS antibodies were an obvious choice since they were known from a number of prior art documents. These included document E1, which also disclosed an example in which the BLyS system was blocked using a BR3-Fc immunoadhesin in a mouse lupus model. Both the reported greater survival rate and the statement that the "*treatment blocked production of auto-antibodies by B cells*" (see document E1, page 131, lines 32 to 34) provided the skilled person with the necessary motivation to combine the rituximab treatment in document E18 with a BLyS antagonist in order to improve B cell depletion as claimed.

The argument that the skilled person would not consult document E1 when starting from the disclosure in document E18, representing the closest prior art, because document E9 taught away from targeting the BAFF/BLyS system, failed because document E9 in fact concluded that the BAFF system was well studied and "*yielded a clear and relatively unambiguous picture*" which was "*unusual in immunology*" (see page 253, last paragraph).

Auxiliary request 8

Amendment to the respondent's appeal case (Article 13(2) RPBA) - claim 11

The effect and problem put forward by the respondent in support of the inventive step of the subject-matter of claim 11 were submitted for the first time during the oral proceedings and thus amounted to an amendment to the respondent's appeal case that should not be allowed at such a late stage. Auxiliary request 8 had been filed to overcome objections for insufficient disclosure.

The response to the statement of grounds of appeal did not contain any arguments in support of an inventive step of the claimed subject-matter.

Inventive step (Article 56 EPC) - claim 11

The arguments made with regard to the main request applied equally to the subject-matter of this claim.

Auxiliary requests 1 to 7 and 9 to 15

Inventive step (Article 56 EPC) - claim 11

The arguments made with regard to the main request applied equally to the subject-matter of these claims.

IX. The respondent's arguments, as far as relevant to the decision, may be summarised as follows.

Main request

Amendment to the appellant's appeal case (Article 13(2) RPBA)

The respondent did not make any arguments on this issue.

Inventive step (Article 56 EPC) - claim 11

Document E8 represented the closest prior art, but the claimed subject-matter involved an inventive step even if the disclosure of document E18 were considered to represent the closest prior art.

Since the patent showed improved depletion of B cells in terms of number and type in a synergistic manner due to the use of the combination compared with the individual compounds (see Figures 29 to 31), the objective technical problem was to provide a method for the improved depletion of all types of B cells.

Document E18 proposed various alternatives to improve the efficacy of rituximab treatments (see page 1490, right-hand column, second paragraph), yet all of these were speculative ("*may be improved*"; "*may be desirable*") and the skilled person had no reason to choose any specific combination.

Furthermore, while document E18 referred to "*agents that block the recently discovered BLyS/BAFF/zTNF4 system*", there was no particular reference to the interaction between BLyS and BR3, although it was known

that BLyS had three different receptors (BR3, TACI and BCMA; see patent, page 2, lines 48 to 55).

Document E18 did not disclose that blocking the BLyS system improved the depletion of B cells; it merely made a vague reference to an improved treatment (see page 1490, right-hand column, second paragraph). Moreover, none of the other cited art (e.g. document E8 or E9) disclosed that a combination treatment could result in the depletion of more types and higher numbers of B cells. On the contrary, document E9, which was a review published shortly before the priority date of the patent, raised serious doubts about targeting the BLyS system (see e.g. page 242, second paragraph and page 244, second paragraph). Document E8, which disclosed treating autoimmune disorders with rituximab, would also have discouraged the skilled person from combining rituximab with agents targeting the BLyS system (see page 828, left-hand column, last paragraph: "*no safe and effective anti-plasma cell agents are available*").

The skilled person was therefore not prompted to consult document E1 and had no reasonable expectation that the combination as claimed would successfully improve B cell depletion. Therefore, the claimed solution was not obvious.

Auxiliary request 8

Amendment to the respondent's appeal case (Article 13(2) RPBA) - claim 11

The respondent had addressed the depletion of different types and numbers of B cells in the context of inventive step from the outset of the opposition

proceedings. As auxiliary request 1 (now the main request) was considered inventive in the decision under appeal, it was not necessary to argue inventive step with regard to the auxiliary requests.

The board should therefore take account of the inventive step arguments set forth during the oral proceedings in the context of the assessment of this request.

Inventive step (Article 56 EPC) - claim 11

The specific depletion of marginal zone and germinal center B cells (MZ-cells and GC-cells, respectively) was not disclosed in any of the cited prior art documents. The claimed subject-matter thus involved an inventive step.

Auxiliary requests 1 to 7 and 9 to 15

Inventive step (Article 56 EPC) - claim 11

No further arguments were provided in response to the appeal or during oral proceedings. Reference was merely made to the submissions during the opposition proceedings.

X. The appellant requested that the decision under appeal be set aside and that the patent be revoked. They also requested that the auxiliary requests that had not been filed in the opposition proceedings not be admitted into the appeal proceedings.

The respondent requested, as far as relevant for the decision, that the appeal be dismissed (main request, i.e. that the patent be maintained on the basis of

auxiliary request 1 – now the main request – which the opposition division considered to comply with the EPC) or, alternatively, that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims of any of auxiliary requests 1 to 15, all filed with the reply to the statement of grounds of appeal. They also requested that auxiliary requests 4 to 7 and 12 to 15 be admitted into the proceedings.

Reasons for the Decision

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

Main request

Amendment to the appellant's appeal case (Article 13(2) RPBA)

2. The board notes that the statement of grounds of appeal mentioned document E18 in combination with document E2, not with document E1. Therefore, the question is whether the inventive step attack based on documents E18 and E1 represents an amendment to the appellant's appeal case.

3. Document E2 is a document published after the filing date of the patent. Accordingly, any inventive step argument based on the disclosure in this document is unlikely to have been intentionally formulated in the statement of grounds of appeal unless the validity of the priority was simultaneously challenged. The board thus sees merit in the appellant's argument that the reference to document E2 instead of document E1 in the context of inventive step was an obvious error. This

can also be backed up by the detailed discussion of the disclosure of document E1, rather than of document E2, in the appellant's alternative inventive step attack starting from the disclosure in document E8, as the closest prior art, in the statement of grounds of appeal, and taking into account that document E8 discloses similar subject-matter to document E18, i.e. treating autoimmune diseases with rituximab. The board further notes that the respondent was apparently prepared for the discussion of this combination of documents and did not contest that the reference was an obvious error.

4. In view of the above considerations, the board decided that the combination of the disclosures of documents E18 and E1 in the context of the inventive step of claim 11 is not an amendment to the appellant's appeal case. The board has therefore taken the inventive step attack into account.

Inventive step (Article 56 EPC) - claim 11

Closest prior art and objective technical problem

5. What is claimed is a combination of a CD20-binding antibody (such as rituximab) and a BLyS antagonist for use in a method of depleting B cells from a mixed population of cells by administering it to a human in need of this, e.g. systemic lupus erythematosus (SLE) patients (see section I). An anti-BLyS antibody and a BR3 immunoadhesin are explicitly specified as examples of useful BLyS antagonists.

6. Whereas the opposition division considered the disclosure in document E8 to represent the closest prior art, the board agrees with the appellant that the

disclosure in document E18 is an equally suitable starting point for analysing inventive step. This was not disputed by the respondent.

7. In a section entitled "*Rituximab for SLE*", document E18 discloses that administering rituximab reduces the levels of peripheral B cells in SLE patients (see page 1487, second-to-last paragraph: "*rituximab often resulted in significant depletion in the levels of peripheral B cells*"; and page 1488, left-hand column, lines 1 to 3: "*After treatment, the levels of B lymphocytes were depleted in the peripheral blood for at least 3-16 months*"). Moreover, with regard to rheumatoid arthritis patients, document E18 discloses that following rituximab treatment "[a]*ll patients had significant depletion of peripheral B cells*" (see page 1488, right-hand column, second full paragraph).

8. Document E18 accordingly teaches that depletion of B cells is relevant for treating autoimmune diseases such as SLE and rheumatoid arthritis, and that this can be achieved, at least partially, by administering rituximab.

9. The claimed subject-matter differs from the therapy disclosed in document E18 in that the CD20-binding antibody (rituximab) is used in combination with a BLyS antagonist (such as a BR3 immunoadhesin or an anti-BLyS antibody) to deplete B cells from a mixed population of cells in a human in need of this.

10. Both parties agreed that this difference results in improved B cell depletion in treated patients. The respondent further submitted that depletion was improved "*not only in terms of the number of B cells depleted, but also in terms of the types of B cells*

depleted - all populations of B cells were depleted in the spleen".

11. Example 4 of the patent demonstrates improved B cell depletion for the combination referred to in the claim as compared with a CD20-binding antibody (rituximab) or a BLyS antagonist (BR3-Fc) alone. In particular Figures 29 to 31 show the reduction of B220+ splenocytes and of CD21- and CD23-positive subpopulations, representing MZ and T2/FO cells, in response to the combination treatment. During oral proceedings the parties agreed that B220 was a marker for "all B cells". The board thus concludes that B cell depletion is improved at least in the spleen as manifested by the reduced numbers and types of B cells.

12. The objective technical problem can thus be formulated as providing an improved method for depleting B cells in a human in need of this.

Obviousness

13. Document E18 discloses that monotherapy with rituximab is not sufficient for treating autoimmune diseases because it does not eliminate cells producing autoantibodies (see page 1489, right-hand column, last paragraph: "*Available clinical experience also suggests that rituximab as a single agent may not be adequate for the treatment of diseases resulting from the production of pathogenic autoantibodies*"). In the same paragraph the authors caution that "*even after a course of rituximab has depleted susceptible mature B cells, plasma cells may still continue to produce disease-causing autoantibodies*" leading to the proposal that "*optimal treatment of diseases that have autoantibody mediated pathology may require a regimen that also*

affects plasma cells" and that the "*long-term goal of therapy should be to eliminate all components of the disease associated autoimmune process, including the offending autoreactive B cells, plasma cells, and memory cells*" (see page 1490, left-hand column, first paragraph). Document E18 thus teaches that treating autoimmune diseases should also eliminate cells that produce autoantibodies and which rituximab alone failed to deplete.

14. Document E18 offers a potential solution to this problem by suggesting that "*the efficacy of rituximab treatments for patients with autoimmune diseases may be improved by the addition of second agents*" (see page 1490, right-hand column, second paragraph) and that "*it may be desirable to utilize agents that block the recently discovered BLyS/BAFF/zTNF4 system (for review, see ref. 47), to interfere with these potent survival signals directed toward membrane-associated receptors on peripheral B cells*" (page 1490, right-hand column, second paragraph). It was commonly known that BLyS played an important role in the survival of B cells (see background section of the patent, page 2, paragraph [0005]: "*BLyS (also known as BAFF, TALL-1, THANK, TNFSF13B, or zTNF4) is a member of the TNF1 ligand superfamily that is essential for B cell survival and maturation*" and "*signaling through BR3 mediates the B cell survival functions of BLyS*"). Document E18 accordingly further teaches that a solution to the ineffective treatment of autoimmune diseases with rituximab might be to combine it with a BLyS-blocking agent to interfere with the survival signals on peripheral B cells.

15. Document E1 discloses specific solutions for blocking the BLyS system by stating, for example, that "*BR3*

receptor immunoadhesins ... preferably block or reduce the respective receptor binding or activation by TALL-1 [BLyS] *ligand*" and that "*anti-TALL-1* [BLyS] *antibodies ... are capable of blocking or reducing binding of the respective ligands to the ... BR3 receptors*" (page 10, line 39 to page 11, line 8). The document also discloses the specificity of BR3 for BLyS and its relevance to the treatment with BR3-Fc ("*Since BR3 is specific for TALL-1* [BLyS]*, it is believed that administration of BR3-Fc (such as administration of the immunoadhesin to mice) should block TALL-1* [BLyS] *but not APRIL induced activation of TACI and BCMA*"; page 121, lines 32 to 34) and highlights the relevance of the BLyS/BR3 pathway for B cell proliferation and homeostasis ("*It is presently believed that the signaling pathway engaged by BR3 may be responsible for the B cell proliferative effects of TALL-1* [BLyS] *and that in the absence of BR3, B cell homeostasis may be compromised*"; page 122, lines 16 to 19). On page 112, lines 7 to 8, document E1 specifically suggests also administering "*antibodies against other antigens, such as antibodies which bind to CD20*".

16. Accordingly, and in summary, document E1 teaches that BLyS antagonists, such as BR3 receptor immunoadhesins (e.g. BR3-Fc) or BLyS antibodies, can be used to block the binding or activation of BLyS to its receptor BR3 and could be combined with CD20-binding antibodies.

17. In Example 7 of document E1 ("*Effects of BR3-Fc Polypeptides in* in vivo *lupus model*") the following conclusions are drawn (page 131, lines 23 to 34): "*BR3-Fc is capable of blocking proteinurea during the course of lupus and protects against kidney damage ... BR3-Fc treated animals also exhibited enhanced survival ... Levels of anti-dsDNA antibodies were also significantly*

lower in the BR3-Fc treated animals ... BR3-Fc treatment blocked production of auto-antibodies by B cells in the lupus mice and enhanced survival by blocking TALL-1 [BLyS] *function in vivo*".

18. The board is satisfied that, in the light of the teaching in document E1 about the signaling pathway engaged by BR3 (see point 15. above), the skilled person would thus conclude from the disclosure of that document that the blocked production of autoantibodies by B cells was due to the interference with the B cell proliferative effects of BLyS, i.e. that B cells producing autoantibodies were effectively depleted.

19. The skilled person thus derived from the disclosure in document E1 that it was possible to block B cell proliferation and homeostasis with soluble BR3 immunoadhesin (BR3-Fc) in a lupus context, which is in fact consistent with the proposal in document E18 to block the BLyS system in order to interfere with peripheral B cell survival signals (see point 14.).

20. The respondent argued that the skilled person seeking a solution to the objective technical problem would in fact dismiss the disclosure in document E1 in view of the teaching in documents E8 and E9, which taught away from the solution proposed in document E18. Document E8 raised questions as to the relevance of anti-DNA antibodies (see page 827, left-hand column, second-to-last paragraph: "*In SLE, anti-DNA antibodies are not related closely to clinical improvement, but the pathogenicity of these antibodies is uncertain.*") and plasma cells (see page 827, right-hand column, second paragraph: "*our understanding of human B-lymphocyte and plasma cell kinetics is rudimentary*"). Document E9 disclosed that the "*role of BAFF* [BLyS] *in the*

generation and survival of memory cells is also currently unexplored", that "*BAFF* [BLyS] *dependence* [of plasma cells] *needs to be established*" (page 242, second paragraph) and that "several observations *call into question the involvement of BAFF [BLyS] in the GC reaction*" (page 244, second paragraph).

21. The board does not agree. Document E8 also states that "*longer-term remission in autoimmune disease may only be achievable if B-lymphocyte depletion is combined, with some form of plasma cell depletion strategy*". It then concludes that "[a]*t present, no safe and effective anti-plasma cell agents are available, but increased understanding of the survival signals required by plasma cells may lead to new therapeutic avenues*" (page 828, left-hand column, last paragraph). The skilled person thus learned from document E8 that targeting the survival signals required by plasma cells as proposed in document E18 and exemplified in document E1 was an avenue worth pursuing.

22. Document E9 is a scientific review article which identifies certain knowledge gaps about BLyS (BAFF). The board notes, however, that document E9 concludes on a rather confident note by stating that "[t]*he biochemical and genetic dissection of the BAFF* [BLyS] *system has yielded a clear and relatively unambiguous picture of an obligate survival signal for both maturing and fully differentiated B cells*" (page 253, last paragraph). The board is hence satisfied that document E9 teaches that BLyS is required for B cells to survive, which is in line with the teaching of documents E18 and E1.

23. The board further notes that document E1 was published after documents E8 and E9, meaning that the skilled

person would consider document E1 to independently disclose information of which the authors of documents E8 and E9 might not have been aware when drafting the review article. The board therefore sees no merit in the argument that the skilled person would dismiss combining the disclosure of document E18 with the teaching in document E1.

24. The respondent further argued that the suggested interference "*with these potent survival signals directed toward membrane-associated receptors on peripheral B cells*" (in this case by using agents which block the BLyS/BAFF/zTNF4 system) in document E18 (page 1490, right-hand column, second paragraph; see also point 14 above) was only one alternative available to the skilled person for improving the efficacy of rituximab treatment, and that choosing this particular alternative was not obvious to the skilled person.

25. The board does not agree because all the listed alternatives are disclosed as being equally valid (see document E18, page 1490, right-hand column, second paragraph: "... *addition of second agents, such as conventional chemotherapeutic drugs. Alternatively, it is likely that future studies will also evaluate co-treatments with specific biologic agents to interfere with T cell helper signals, such as ... As an alternative approach it may be desirable to utilize agents that block the recently discovered BLyS/BAFF/ zTNF4 system*") and there was no reason for the skilled person to reject any of them. Selecting one of the suggested alternatives for improving the efficacy of rituximab, and thus one of several obvious courses of action, cannot involve an inventive step.

26. The question remains whether the skilled person, having regard to the combined teachings of documents E18 and E1, would have reasonably expected improved depletion of B cells by combining rituximab with a BLyS antagonist (e.g. BR3-Fc) and not just the same level of depletion as with rituximab alone.

27. In Figure 2, document E18 discloses that plasma cells do not express CD20 ("CD20-neg"; see figure legend: "*CD20 is expressed only at intermediate stages and not on plasma cells*"). On page 1489, right-hand column, last paragraph, the authors find it "*likely that the dominant cellular source of disease-associated autoantibodies, especially IgG antibodies, are plasma cells that do not bear CD20 (Figure 2)*" and that "*plasma cells may still continue to produce disease-causing autoantibodies*". Since document E18 goes on to state that "*optimal treatment of diseases that have autoantibody-mediated pathology may require a regimen that also affects plasma cells*", the board concludes that the suggestion in document E18 to use an "*agent that blocks BLyS/BAFF/zTNF4*" (page 1490, right-hand column, second paragraph) in combination with the CD20-binding antibody rituximab was aimed at addressing non-CD20 cells, e.g. plasma cells, "*the major source of antibodies in the body*" (see sentence bridging pages 1485 and 1486). Furthermore, Example 7 of document E1 demonstrates that anti-DNA autoantibodies and proteinurea - a hallmark of SLE - are reduced after BR3-Fc administration, thus confirming that "*BR3-Fc treatment blocked production of auto-antibodies by B cells in the lupus mice and enhanced survival by blocking TALL-1 function in vivo*" (see last sentence on page 131).

28. In view of the above-mentioned disclosures, the board concludes that the skilled person was aware that targeting BLyS with a soluble BR3-Fc immunoadhesin or an anti-BLyS antibody could result in the depletion of autoantibody-producing cells lacking CD20, including plasma cells (see also points 15. to 17. above).

29. The skilled person therefore had a reasonable expectation that the combined use of a CD20-binding antibody and a BLyS antagonist (such as a BR3-Fc immunoadhesin) resulted in the depletion of additional (non-CD20) B cell types, such as plasma cells. It was therefore obvious to the skilled person to combine rituximab with a BLyS antagonist for depleting B cells in a human in need of this.

30. In view of the above considerations, the claimed subject-matter does not involve an inventive step.

Auxiliary request 8

Amendment to the respondent's appeal case (Article 13(2) RPBA)

31. In their reply to the statement of grounds of appeal, the respondent argued that auxiliary request 8 addressed the appellant's assertion that neither the data in the patent nor post-published data supported a therapeutic effect. It was not until the oral proceedings before the board that the respondent argued - for the first time - that the subject-matter of claim 11 of auxiliary request 8 involved an inventive step because the amendment compared with the same claim of the main request, i.e. the specific depletion of marginal zone and germinal center B cells (MZ-cells and GC-cells, respectively), resulted in an additional

effect. These new arguments represent an amendment to the respondent's case.

32. An amendment to a party's appeal case at this stage of the proceedings is governed by Article 13(2) RPBA, under which any such amendment to the appeal case "*shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned*".

33. The respondent justified the late submission of arguments in favour of inventive step by asserting that, because the opposition division had found that the subject-matter of the main request (in the form of former auxiliary request 1; see section I) involved an inventive step, the respondent had not needed to argue for an additional effect related to specific cell types in their reply to the statement of grounds of appeal. Moreover, the purpose of depleting different types of B cells had featured in the respondent's arguments from the outset of the opposition proceedings.

34. However, the board considers that when the respondent submitted the auxiliary requests, including the one now under consideration, in their reply to the statement of grounds of appeal, they should have anticipated the possibility – which was by no means unlikely – that the board would deem the subject-matter claimed in the main request not to involve an inventive step. The respondent, however, chose to refer only to sufficiency of disclosure as a reason for introducing this request.

35. The board has thus not been presented with any exceptional circumstances which could justify taking the new arguments into account.

Inventive step (Article 56 EPC) - claim 11

36. In view of the considerations in points 31. to 35. above, the board has not seen any arguments, beyond those submitted for the subject-matter of claim 11 of the main request, to the effect that the claimed subject-matter involves an inventive step.

37. Therefore, the board holds that the claimed subject-matter lacks an inventive step for the same reasons as those regarding claim 11 of the main request.

Auxiliary requests 1 to 7 and 9 to 15

Inventive step (Article 56 EPC) - claim 11

38. The respondent has not submitted any arguments to the effect that the subject-matter of claim 11 of these auxiliary requests involves an inventive step beyond those submitted for the subject-matter of claim 11 of the main request.

39. For want of any further arguments, the board holds that the claimed subject-matter of auxiliary requests 1, 4, 5, 9, 12 and 13, which all encompass a BLyS antagonist that is a BR3 immunoadhesin, lacks an inventive step for the same reasons as those regarding claim 11 of the main request.

40. The subject-matter of claim 11 of auxiliary requests 2, 3, 6, 7, 10, 11, 14 and 15 differs from that of claim 11 of the main request in that, *inter alia*, it is specified that "the BLyS antagonist is an anti-BLyS antibody". The respondent has not argued that this feature alters the technical effect resulting from the

difference between the claimed subject-matter and the rituximab therapy disclosed in document E18. The objective technical problem is therefore no different from that outlined above for the main request.

41. The question to be answered is thus whether the skilled person, starting from the rituximab therapy disclosed in document E18 as the closest prior art and further consulting document E1, would have used an anti-BLyS antibody to block the BLyS system. Document E1 discloses that "*TALL-1* [BLyS] *antagonists and APRIL antagonists contemplated for use further include anti-TALL-1* [BLyS] *antibodies ... capable of blocking or reducing binding of the respective ligand to the TACIs or BR3 receptors*" (see page 11, lines 5 to 8). In the board's opinion, the skilled person would have therefore considered an anti-BLyS antibody to be an obvious alternative to the BR3-Fc immunoadhesin tested in Example 7 of document E1. In view of the teaching in document E1, it would also have been evident to the skilled person that the interaction between BLyS and BR3 could be blocked in both directions, i.e. by "a*nti-TALL-1* [BLyS] *antibodies ... capable of blocking or reducing binding of the respective ligand* [BLyS]" or by "*an antagonist (such as a BR3 immunoadhesin) which blocks or neutralizes activity of TALL-1* [BLyS]" (see page 11, lines 7 to 8 and lines 19 to 20).

42. The skilled person would therefore have considered combining a CD20-binding antibody with an anti-BLyS antibody "*capable of blocking or reducing binding of the respective ligand to the TACIs or BR3 receptors*" to provide an improved method for depleting B cells in a human in need of this as one of several available obvious solutions to improve on the known method.

43. The subject-matter of claim 11 of auxiliary requests 2, 3, 6, 7, 10, 11, 14 and 15 thus lacks an inventive step.

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:

I. Aperribay B. Claes

Decision electronically authenticated