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Datasheet for the decision of 16 June 2015

Case Number: T 0923/10 - 3.3.04

Application Number: 99938326.8

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Title of invention:
Combination of an anti-EP-CAM antibody with a chemotherapeutic agent

Patent Proprietor:
Glaxo Group Limited

Opponent:
Micromet AG

Headword:
Kit-of-parts of an anti-EP-CAM antibody with a chemotherapeutic agent the cell cycle/GLAXO

Relevant legal provisions:
EPC Art. 56, 115
EPC R. 115(2)
RPBA Art. 15(3)

Keyword:
Inventive step - main and auxiliary requests 1 to 6 (no)
Inventive step - auxiliary request 7 (yes)
Observations by third party - relevant (no)

Decisions cited:
T 0009/81, T 1137/98, T 1396/06, T 0390/07, T 0544/12

Catchword:

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Case Number: T 0923/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 June 2015

Appellant I: (Patent Proprietor)	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB)
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Appellant II: (Opponent)	Micromet AG Staffelseestrasse 2 81477 München (DE)
Representative:	Schiweck, Weinzierl & Koch European Patent Attorneys Landsberger Straße 98 80339 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 March 2010 concerning maintenance of the European Patent No. 1198251 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M. Blasi

Summary of Facts and Submissions

I. The appeals were lodged by the patent proprietor (hereinafter "appellant I") and by the opponent (hereinafter "appellant II") against the decision of the opposition division to maintain European patent No. 1 198 251 in amended form. The patent has the title "*Combination of an anti-Ep-CAM antibody with a chemotherapeutic agent*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), and under Article 100(b) EPC.

III. In its decision the opposition division held *inter alia* that the subject-matter of claim 1 of the main request lacked novelty (Article 54 EPC) over the disclosure of document D2, that the subject-matter of claim 1 of the first auxiliary request added matter contrary to the requirements of Article 123(2) EPC and that the subject-matter of claim 1 of the second auxiliary request lacked inventive step (Article 56 EPC).

Regarding the latter issue, the opposition division took the view that it was not credible that the technical effect ascribed to the chemotherapeutic agents claimed, namely the increase of the Ep-CAM expression on the surface of tumour cells by arresting the cell cycle in either the S or G2/M phase, was achieved by all of them. Data disclosing such an increase were only presented in the application for Navelbine and Taxol (paclitaxel), both acting on microtubuli. The other compounds referred to in the

claim belonged to different chemical families and had modes of action completely unrelated to the exemplified ones.

The claims of the third auxiliary request were considered to meet the requirements of the EPC.

IV. With its statement of grounds of appeal appellant I submitted a main request and eight auxiliary requests. None of these requests, with the exception of the seventh auxiliary request which is identical to the third auxiliary request dealt with in the decision under appeal, were part of the first instance proceedings.

In the following recitation of the claims the term "disclaimer" stands for "wherein the anti-Ep-CAM antibody is not conjugated to other molecules such as radionuclides or enzymes" of claim 1 of the main request.

Claim 1 of the main request reads:

"1. A kit-of-parts of an anti-Ep-CAM antibody with one or more chemotherapeutic agents that is capable of arresting Ep-CAM antigen expressing cells in S or G_2/M which chemotherapeutic agent is selected from the group consisting of:

camptothecin, oxaliplatin, paclitaxel, docetaxel, cyclophosphamide, vinorelbine, epirubicin, mitoxantrone, tomudex, cisplatin, carboplatinum, etoposide and topotecan,

wherein the anti-Ep-CAM antibody is not conjugated to other molecules such as radionuclides or enzymes."

Claim 1 of the first auxiliary request differs from the main request in that the disclaimer is replaced by "is a lytic antibody capable of antibody-dependent cytolytic functions when administered to a human".

Claim 1 of the second auxiliary request differs from the main request in that the disclaimer is replaced by "is a lytic antibody capable of antibody-dependent cytolytic functions when administered to a human" and in that the formulation "for co-administration in the treatment of primary or metastatic cancers expressing Ep-CAM, comprising" is added after "A kit-of-parts".

Claim 1 of the third auxiliary request differs from the main request in that the disclaimer and "cisplatin" are deleted.

Claim 1 of the fourth auxiliary request differs from the main request in that the disclaimer and "cisplatin" are deleted and the formulation "for co-administration in the treatment of primary or metastatic cancers expressing Ep-CAM, comprising" is added after "A kit-of-parts".

Claim 1 of the fifth auxiliary request differs from the main request in that the disclaimer is replaced by "is a lytic antibody capable of antibody-dependent cytolytic functions when administered to a human" and that "camptothecin, cyclophosphamide, epirubicin, mitoxantrone, tomudex, etoposide and topotecan" are deleted.

Claim 1 of the sixth auxiliary request differs from the main request in that the disclaimer is replaced by "is a lytic antibody capable of antibody-dependent cytolytic functions when administered to a human", in

that the formulation "for co-administration in the treatment of primary or metastatic cancers expressing Ep-CAM, comprising" is added after "A kit-of-parts" and in that "camptothecin, cyclophosphamide, epirubicin, mitoxantrone, tomudex, etoposide and topotecan" are deleted.

Claim 1 of the seventh auxiliary request reads:

"1. A kit-of-parts of an anti-Ep-CAM antibody with one or more chemotherapeutic agents that is capable of arresting Ep-CAM antigen expressing cells in S or G_2/M wherein the chemotherapeutic agent is selected from paclitaxel, docetaxel and vinorelbine."

V. With its statement of grounds of appeal appellant II *inter alia* argued that the subject-matter of the claims found allowable by the opposition division lacked inventive step in view of either documents D3, D6, D18 or D39 as closest prior art (the respective documents are identified in section IX below).

VI. In its reply to the statement of grounds of appeal of appellant I, appellant II *inter alia* argued that the main request and auxiliary requests 1 to 3, 5 and 6 lacked inventive step in view of document D2 as closest prior art (the respective document is identified in section IX below).

VII. Third party observations pursuant to Article 115 EPC were received on 27 June 2012.

VIII. With letters dated 18 March 2015 and 5 May 2015 the appellants announced that they would not attending the

oral proceedings scheduled for 16 June 2015. Appellant I in addition withdrew its request for oral proceedings.

IX. The following documents are cited in this decision:

D2: Kievit et al., Int. J. Radiation Oncology, 38, 419-428, (1997)

D3: Schneider-Gädicke et al., European Journal of Cancer, 31A, 1326-1330, (1995)

D4: Riethmüller et al., J. Clin. Oncol., 16, 1788-1794, (1998)

D6: Schwartzberg et al., Cancer Investigation, 17, 32-34, (1999)

D8: Inaba et al., Oncology Res., 6(7), 303-309, (1994)

D18: Tankanow et al., Am. J. Health-Syst. Pharm., 55, 1777-1791, (1998)

D20: Caputo et al. (eds.), Cancer - Principles & Practice of Oncology, Lippincott-Raven Publishers, Philadelphia, 375-498, (1997)

D37: Thurmond et al., Cancer Immunol. Immunother., 52, 429-437, (2003)

D38: Packeisen et al., Hybridoma, 18, p. 37-40, (1999)

D39: Perez et al., The Oncologist, 3, 373-389, (1998)

X. Oral proceedings before the board took place on 16 June 2015 in the absence of both parties as announced. At the end of the oral proceedings, the chairwoman announced the decision of the board.

XI. Appellant I's arguments may be summarised as follows:

Inventive step (Article 56 EPC)

Main request and auxiliary requests 1 to 6

The invention was based on the observation that the Ep-CAM surface expression largely specifically increased on tumour cells when the cells were pretreated with certain chemotherapeutic agents that blocked the cell cycle progression at the S or G2/M phase. This resulted in an improved targeting of the arrested tumour cells by an anti-Ep-CAM antibody. The invention thus provided a combination of immunotherapy and chemotherapy that resulted in an improved targeting of cancer cells expressing Ep-CAM when compared to a monotherapy based on the use of the antibody alone.

There was no evidence on file suggesting that not all of the chemotherapeutic agents claimed that arrested Ep-CAM-bearing tumour cells in either the S or G2/M phase were at the same time also able to increase the amount of Ep-CAM.

This was also not questionable in view of the data of the patent concerning 5-fluorouracil (5-FU) and its inability to arrest the cell cycle of Ep-CAM expressing tumour cells and to increase the concentration of Ep-CAM (see example 2). 5-FU has a known unique and complex mechanism of action in arresting the cell cycle (see document D8 and document D20, figure 19.6-3) and

the fact that it did not arrest the cell cycle of the cells tested in the patent merely indicated that its effectiveness depended on the conditions applied.

The correctness of the general teaching of the patent was confirmed by post-published document D37 that reported "*the data from this study suggest that agents that block the cell cycle in G2/M can significantly increase the cell surface expression of Ep-CAM*" (cf. page 436, column 1, second paragraph).

Auxiliary request 7

All of the chemotherapeutic agents according to claim 1 arrested the cell cycle of the tumour cells in the S or G2/M phase and specifically increased the amount of Ep-CAM on the surface of tumour cells versus normal cells (see examples 2 and 5, figures 2, 3a, 5 of the patent). This pre-treatment resulted in an improved targeting of the tumour cells by an anti-Ep-CAM antibody and in an increased level of antibody-dependent tumour cell cytotoxicity (see figure 5). The invention thus provided a combination of agents with a novel and synergistic mechanism of action. The effect attained was surprising and rendered the subject-matter of claim 1 inventive over the cited prior art.

Third party observations (Article 115 EPC)

Appellant I did not comment on the third party observations.

XII. Appellant II's arguments may be summarised as follows:

Inventive step (Article 56 EPC)

Main request and auxiliary requests 1 to 6

Claim 1 concerned a kit-of-parts of an anti-Ep-CAM antibody and chemotherapeutic agents. The claim underlying decision T 9/81 was formulated such that the two compounds achieved a functional amalgamation through a purpose-directed application according to Article 54(5) EPC 1973. In accordance with the reasoning applied in that decision, the term "kit-of-parts" alone did not imply such an amalgamation. In the absence of any other feature that did, the subject-matter of the "kit-of-parts claims" was to be regarded as a mere juxtaposition of at least two known compounds, an anti-Ep-CAM antibody and one or more chemotherapeutic agents.

Document D2 represented the closest prior art for the subject-matter of claim 1. It disclosed a study assessing cisplatin's ability to improve the efficacy of an anti-Ep-CAM antibody for tumour treatment. The chemotherapeutic agents of claim 1 were different but this difference was not associated with any technical effect since neither the data of the patent nor that of the prior art rendered a generalised concept credible that any of the listed chemotherapeutic agents arresting Ep-CAM-expressing tumour cells in the S or G2/M phase also increased Ep-CAM surface-expression. This concept was also not supported by the teaching of post-published document D37, which reported that the mere arresting of cells in either the S or G2/M phase of the cell cycle was not sufficient for an increased Ep-CAM surface concentration but also required an

interference with the microtubules to block Ep-CAM internalisation (see document D37, page 436, column 2, first paragraph).

The technical problem was the provision of an alternative combination of an anti-Ep-CAM antibody with a chemotherapeutic agent.

The solution comprising an anti-Ep-CAM antibody with one or more of the chemotherapeutic agents claimed was obvious for the skilled person, since the agents were arbitrarily selected and commonly known in tumour therapy, e.g. from document D18 (see page 1778, column 1, third paragraph).

Auxiliary request 7

The disclosure of any of documents D3, D6, D18 or D39 represented the closest prior art for the subject-matter of claim 1. The term "kit-of-parts" of claim 1 merely meant that the claim concerned an anti-Ep-CAM antibody and one or more chemotherapeutic agents in a physical juxtaposition.

Document D3 disclosed a clinical trial with a combination of an anti-Ep-CAM antibody and the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of cancer. The subject-matter of claim 1 differed therefrom in the provision of a further chemotherapeutic agent juxtaposed to an anti-Ep-CAM antibody. The technical problem was the provision of a further or alternative juxtaposed anti-Ep-CAM antibody and a chemotherapeutic agent. The solution was obvious since the specific chemotherapeutic anti-tumour agents claimed were known and would have been randomly chosen by the skilled

person since there was no reason to adopt a sceptical attitude towards their choice. The skilled person had also some expectation of success or no particular expectations of any sort, but only adopted a "try and see" attitude in solving the problem (cf. decision T 1396/06). A further reason for the skilled person to select paclitaxel in particular was its successful use in the treatment of breast cancer for which it was a standard-of-care medicament (see documents D18 and D39).

Document D6 disclosed a combination of an anti-Ep-CAM antibody with the chemotherapeutic agents 5-FU or 5-FU and leucovorin. The subject-matter of claim 1 concerned paclitaxel or docetaxel as chemotherapeutic agents juxtaposed to an anti-Ep-CAM antibody. The skilled person would have selected paclitaxel or docetaxel because both chemotherapeutic drugs had been used for the treatment of breast cancer (see documents D18 and D39).

Document D18 disclosed the FDA-approved chemotherapeutic agent docetaxel for the treatment of breast cancer which might be administered in combination with a further agent. The technical problem was the provision of a combination of docetaxel with another agent. The solution, namely the combination of docetaxel with an anti-Ep-CAM antibody, was obvious in the light of the teaching of document D38 which reported the expression of Ep-CAM in breast and colorectal cancer cells and suggested an immunotherapy for their treatment.

Document D39 disclosed the combination of paclitaxel with an anti-Her2 antibody for the treatment of breast cancer. The subject-matter of claim 1 differed

therefrom in that it concerned an anti-Ep-CAM antibody instead. The technical problem was the provision of a juxtaposition of an alternative to the anti-Her2 antibody in combination with paclitaxel. The combination of paclitaxel with an anti-Ep-CAM antibody was obvious for the skilled person because this antibody was used for the treatment of tumours originating from epithelial cells, such as breast cancer, and the skilled person was inclined to try out another therapeutic combination, in particular in view of the low toxicity of the anti-Ep-CAM antibody (see document D3).

Third party observations (Article 115 EPC)

Appellant II did not comment on the third party observations.

XIII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, or alternatively on one of auxiliary requests 1 to 6, or alternatively that appellant II's appeal be dismissed (auxiliary request 7), or alternatively that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 8.

Appellant II requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. As announced the appellants did not attend the oral proceedings. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, these took place as scheduled and the appellants were treated as relying on their written case.

Third party observations (Article 115 EPC)

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

3. The boards have discretion to take such observations into consideration or to disregard them. When exercising their discretion the boards normally take criteria into account which they consider when they decide about the admissibility of submissions by parties to the proceedings that are considered "late-filed" in view of Article 114(2) EPC and Articles 12(1), (2), (4) and 13(1), (3) RPBA. These criteria include the relevance of the submissions filed (see for example decisions T 1137/98, point 6 of the reasons; T 390/07, point 4 of the reasons; T 544/12, point 11 of the reasons).

4. In the present case the board considers that the observations filed by the third party are less relevant than the submissions made by the parties to the proceedings.

5. Also, none of the parties took up any of the arguments or evidence of the third party. The board therefore decided to disregard the observations of the third party.

The invention

6. The invention concerns, as a kit-of-parts, an antibody against the human pan-carcinoma antigen (Ep-CAM) expressed on the surface of tumour cells and one or more chemotherapeutic agents capable of arresting Ep-CAM expressing cells in the DNA synthesis (S) phase and/or during the phase of cell enlargement and mitosis (G_2/M) of the cell cycle, i.e. in specific phases that characterise a sequence of events between one mitotic cell division and another (see paragraph [0004] of the patent).

The Ep-CAM density on the surface of tumour cells naturally varies depending on the phase of the cell cycle. Its homogeneity and concentration are higher in the S or G_2/M phase than in the quiescent resting phase (G_0) or growth phase (G_1) (see figure 1 of the patent).

The invention infers a central mechanism from this natural Ep-CAM variation and postulates that any of the chemotherapeutic agents claimed that arrest Ep-CAM-bearing tumour cells in the S and/or G_2/M phase automatically increase the amount of surface expressed Ep-CAM.

This increase of Ep-CAM is largely tumour cell specific (see figure 3) and thus allows the anti-Ep-CAM antibodies to target the tumour cells with increased efficiency and specificity (see paragraphs [0003] and [0006] of the patent). The achievement of an enhanced targeting of Ep-CAM expressing tumour cells results in an improved treatment of the tumour which requires the combined action of a chemotherapeutic agent and an antibody and cannot be attained by each of the two compounds alone.

Claim interpretation - all requests

7. Claim 1 of all requests relates to a product designated as "kit-of-parts".

The board interprets the term "kit-of-parts" to mean that the different compounds referred to in claim 1, i.e. the anti-Ep-CAM antibody and the at least one chemotherapeutic agent, represent a combination of individual components which are kept physically separate but adjacent. In the board's view, an additional functional property, such as a synergism between the adjacent compounds cannot be inferred from the term as such - in accordance with the reasoning in decision T 9/81, where a functional property was accorded to the subject-matter of the claim, not because it is inherent in the term "kit-of-parts" but because this property was an explicit feature of the claim (see decision T 9/81, points 6 and 7 of the reasons).

Inventive step (Article 56 EPC)

Main request - Claim 1

Closest prior art

8. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal of the EPO generally apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

The closest prior art is generally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed

invention and having the most technical features in common, *i.e.* requiring the minimum of structural modifications (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.3.1).

9. The purpose underlying the present invention is the treatment of Ep-CAM-expressing tumours (see point 5 above).

10. The parties considered the teaching of documents D2 to D4 and D6 to represent the closest prior art.

10.1 Document D2 discloses a study assessing the ability of the radiosensitising chemotherapeutic agent cisplatin to improve the radiotherapeutic efficacy of the ^{131}I-labelled anti-Ep-CAM antibody 323/A3 in the treatment of ovarian cancer (see page 419, abstract).

10.2 Document D3 reports on a study assessing *inter alia* the efficiency of a combination therapy based on an anti-Ep-CAM antibody and the cytokine granulocyte macrophage colony stimulating factor (GM-CSF) in tumour treatment. GM-CSF is known to stimulate the antibody-dependent cytotoxic activity (ADCC) of effector cells of the immune system, e.g. natural killer cells or macrophages (see abstract; page 1328, column 2, second paragraph and page 1329, column 1, second paragraph).

10.3 Document D4 discloses a monotherapy based on an anti-Ep-CAM antibody for the treatment of colon cancer (see abstract).

10.4 Document D6 reports on an ongoing study of an anti-Ep-CAM antibody in combination with either the chemotherapeutic agent 5-fluorouracil (5-FU) or a mixture of 5-FU and leucovorin in the treatment of Ep-

CAM-expressing cancer to assess their potential synergistic effect, as compared to a monotherapy (see abstract, page 33, column 1, third paragraph to column 2, second paragraph).

11. The board considers that all of the cited documents relate to the same technical purpose, i.e. the treatment of Ep-CAM-expressing tumours.

Concerning the structural commonality, the board considers that document D6 shares the highest number of relevant technical features because it discloses the combination of an unconjugated anti-Ep-CAM antibody - unlike the antibody of document D2 - with a classical chemotherapeutic agent, 5-FU - unlike the cytokine GM-CSF of document D3. Document D4 discloses no combination therapy at all.

Thus, the disclosure of document D6 represents the closest prior art for the subject-matter of claim 1.

Technical problem and solution

12. The technical problem to be solved is to be formulated in the light of the technical effects achieved by those features distinguishing the claimed invention from the closest prior art (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.4.3.1, second paragraph).

13. The invention defined in claim 1 is directed to several alternative embodiments. Two of them relate to a kit-of-parts of an anti-Ep-CAM antibody and at least the chemotherapeutic agents tomudex or carboplatinum, respectively. In the following these two embodiments will be considered.

14. The difference between the disclosure of document D6 and the embodiments considered here is that tomudex or carboplatinum instead of 5-FU are part of the kit-of-parts.

15. Appellant I argued that **all** chemotherapeutic agents referred to in claim 1 arrested the Ep-CAM-bearing cells in the S and/or G_2/M phase of the cell cycle **and thereby** increased the surface concentration of Ep-CAM on tumour cells versus normal cells (see paragraphs [0003] and [0006] of the patent). Accordingly, this includes explicitly tomudex and carboplatinum.

16. The board notes that the patent discloses no experimental evidence that either tomudex or carboplatinum alone arrests the cell cycle and increases the Ep-CAM concentration on tumour cells.

17. Regarding tomudex it is known from the prior art that this compound inhibits the activity of thymidylate synthase (TS), an enzyme required for the preparation of deoxythymidine triphosphate (dTTP), a nucleoside essential for DNA *de-novo* synthesis (see document D20, page 436, column 2, second paragraph). Tomudex is also believed to arrest the cell cycle in either the S or the G_2 phase (see appellant I's statement of grounds of appeal, page 7 and paragraph [0020] of the patent).

17.1 Also the chemotherapeutic agent 5-FU inhibits TS as one of its principle cytotoxic activities and thus shares a mechanism of action with tomudex (see document D20, page 438, column 1, fourth paragraph). The patent discloses however that, under the conditions applied, 5-FU neither significantly arrests tumour cells in either the S or G_2/M phase nor increases the Ep-CAM concentration on tumour cells, although it normally

arrests the cell cycle in the S phase (see document D8, abstract).

17.2 Thus, from the evidence on file, it can be inferred from the failure of 5-FU to increase the Ep-CAM surface concentration that the same holds true for tomudex, since both agents inhibit the activity of TS.

18. Regarding carboplatinum, the patent discloses that a mixture of carboplatinum and taxol induces an increase in Ep-CAM surface expression (see figure 2, example 2). However, this increase is also observed in the presence of taxol alone (see example 2a and figure 3a), but the patent is silent regarding this effect for carboplatinum alone.

18.1 Therefore, in the board's view, the disclosure of the patent for a mixture of carboplatinum and taxol allows no conclusions to be drawn for carboplatinum's individual ability to increase Ep-CAM on the cell surface.

19. The prior art discloses that carboplatinum is a DNA alkylating agent that after modifying nucleotides in the DNA strand introduces intra- and interstrand cross-links that inhibit DNA synthesis, distort cell signaling pathways and result in an arrest of the cell cycle in the G_2 phase (see document D20, page 421, column 1, second paragraph to page 422, column 1, third paragraph). However, the available prior art is silent regarding carboplatinum's individual ability to affect the concentration of surface-exposed Ep-CAM.

20. Regarding the mechanism of action underlying the increase of surface-exposed Ep-CAM, the patent discloses that two specific chemotherapeutic agents are

successful. These agents are taxol, i.e. paclitaxel (see paragraph [0016]; example 2a and figure 3a), and navelbine, i.e. vinorelbine (see paragraph [0013], example 5 and figure 5), and they arrest the cell cycle in the mitotic (M) phase accompanied by an increase of the surface concentration of Ep-CAM on tumour cells.

Both agents act on microtubules, a polymeric structure composed of tubulin proteins that are *inter alia* an integral part of the mitotic spindle (see document D20, page 467, column 1, second paragraph to page 468, column 2, third paragraph; page 473, column 2, first and second paragraph).

20.1 Accordingly, both taxol and navelbine rely on a mechanism of action that is separate from and unrelated to those of either carboplatinum or tomudex. Therefore, the effect of carboplatinum and tomudex to increase surface-exposed Ep-CAM cannot be inferred from the ability of taxol or navelbine to achieve this effect either.

21. Finally, the inability of tomudex and carboplatinum to increase the Ep-CAM surface concentration on tumour cells seems to be inferable from the teaching of post-published document D37, which reports that "*We have shown that antigen density is increased during G2/M phase of the cell cycle, but the changes are small compared to the two- to ten-fold changes we saw following drug treatment. It appears that the significant increases in surface antigen density cannot be accounted for solely by cell cycle block or receptor internalization, but appear to be a combination of both*" (see page 436, column 2, lines 4 to 11) (emphasis added by the board).

This document thus seems to suggest that only anti-microtubule agents that arrest the cell cycle and at the same time inhibit the microtubule-dependent internalisation of surface-exposed Ep-CAM achieve a significant increase of Ep-CAM (see document D37, page 434, column 2, fourth paragraph to page 435, column 1, first paragraph, figure 7). However, neither tomudex nor carboplatinum belongs to this functional group of chemotherapeutic agents.

22. Consequently, in view of the evidence before it, the board is not convinced that tomudex and carboplatinum achieve the technical effects ascribed to them, i.e. an arrest of the cell cycle accompanied by an increase of the Ep-CAM concentration on tumour cells. Hence, these effects cannot be considered for the formulation of the technical problem in relation to the two embodiments considered.

23. In view of the above considerations, the board formulates the technical problem to be solved in relation to a kit-of-parts of an anti-Ep-CAM antibody and the at least one chemotherapeutic agent tomudex or carboplatinum as the provision of an alternative chemotherapeutic agent suitable for arresting Ep-CAM expressing cells in the S or G_2/M phase.

24. The board is satisfied that this technical problem is solved by the subject-matter of claim 1, because tomudex and carboplatinum are standard prior art chemotherapeutic agents either known to arrest the cell cycle (see for carboplatinum: document D20, page 422, column 1, second and third paragraphs) or credible to do so in view of a common mechanism of action with 5-FU (see point 17.1 above).

Obviousness

25. The question to be assessed is whether the skilled person starting from document D6 and faced with the technical problem identified in point 23 above would have arrived in an obvious manner at replacing 5-FU with tomudex or carboplatinum.

26. As noted above, tomudex and carboplatinum are either known or credible to arrest the cell cycle in the S and/or G_2/M phase (see point 24 above). Therefore, in the board's view, the skilled person would consider either tomudex or carboplatinum as obvious alternatives to the chemotherapeutic agent 5-FU in a kit-of-parts with an anti-Ep-CAM antibody.

Consequently, at least these two embodiments of claim 1 of the main request - and hence claim 1 as a whole - cannot be considered to involve an inventive step (Article 56 EPC).

Auxiliary requests 1 to 6 - claim 1

27. Tomudex as a chemotherapeutic agent in a kit-of-parts with an anti-Ep-CAM antibody is an embodiment of claim 1 of auxiliary requests 1 to 4. Carboplatinum as a chemotherapeutic agent in a kit-of-parts with an anti-Ep-CAM antibody is an embodiment of claim 1 of auxiliary requests 1 to 6.

The subject-matter of claim 1 of auxiliary requests 1 to 6 differs from the main request only in that it is not defined by the disclaimer (see section IV above) but by the feature "is a lytic antibody capable of antibody-dependent cytolytic functions when administered to a human" (auxiliary requests 1, 2, 5

and 6) or in that it is not defined by this feature (auxiliary requests 3 and 4) but by the feature "for co-administration in the treatment of primary or metastatic cancers expressing Ep-CAM, comprising" (auxiliary request 4) or in that it is additionally defined by the feature "for co-administration in the treatment of primary or metastatic cancers expressing Ep-CAM, comprising" (auxiliary request 2).

28. However, these differences in the definition of the subject-matter claimed do not affect the definition of tomudex or carboplatinum. Hence, the board arrives at the same conclusion as for the subject-matter of claim 1 of the main request. Therefore, none of auxiliary requests 1 to 6 fulfil the requirements of Article 56 EPC.

Auxiliary request 7 - claim 1

29. The list of chemotherapeutic agents referred to in claim 1 is reduced to paclitaxel, docetaxel and vinorelbine.

Closest prior art

30. The parties considered the disclosure of documents D3, D6, D18 or D39 to represent the closest prior art for the subject-matter of claim 1.

30.1 The relevant disclosure of documents D3 and D6 is summarised in points 10.2 and 10.4 above.

30.2 Document D18 reports on the use of docetaxel either alone or in combination with other chemotherapeutic agents - and not antibodies - in the treatment of cancer (see abstract, page 1782, column 2, fourth paragraph to page 1783, column 2, fifth paragraph).

30.3 Document D39 discloses a clinical trial of paclitaxel combined with the anti-Her2 receptor monoclonal antibody trastuzumab (Herceptin^{TM}) in patients with metastatic breast cancer overexpressing Her2 (see page 381, column 2, fifth paragraph). The purpose of document 39 thus aims at a treatment of Her2-expressing cancer which is different from the treatment of Ep-CAM-expressing cancer underlying the present invention.

31. Hence, the disclosure of document D6 represents the closest prior art also for the subject-matter of claim 1 of auxiliary request 7, since documents D18 and D39 relate to the treatment of cancer which is not an Ep-CAM-expressing cancer and for the reasons outlined above (see point 11).

Technical problem and solution

32. The subject-matter of claim 1 differs from the disclosure of document D6 in that it relates to the chemotherapeutic agents paclitaxel (i.e. taxol), docetaxel and vinorelbine (i.e. navelbine).

33. Regarding the technical effect achieved by these three chemotherapeutic agents, all of them are commonly known to arrest the cell cycle in the M-phase by the same mechanism of action, i.e. the interference with or the disruption of microtubules (see document D20, page 468, column 2, third paragraph and page 473, column 2, first and second paragraphs). Moreover, the patent discloses

that the administration of taxol or navelbine increases the Ep-CAM surface concentration on tumour cells (see figures 3a and 5 of the patent). In view of their common mechanism of action, the board considers it credible that also docetaxel has this effect on Ep-CAM. Tumour cells expressing an increased surface concentration of Ep-CAM can be more efficiently and specifically targeted by an anti-Ep-CAM antibody.

34. Accordingly, the technical problem to be solved may be formulated as the provision of a kit-of-parts whose components allow an improved targeting of Ep-CAM-expressing tumour cells.

35. The board is satisfied that this problem is credibly solved by the kit-of-parts of claim 1 in view of the experimental data disclosed in figures 2, 3, 3a and 5 of the patent and the common mechanism of action of the chemotherapeutic agents claimed (see point 33 above).

Obviousness

36. The question to be assessed here is whether the skilled person starting from the anti-Ep-CAM antibody/5-FU combination of document D6 and faced with the technical problem identified in point 34 above would have modified the teaching of the closest prior art so as to arrive at the invention in an obvious manner.

37. None of the available prior art documents discloses that the administration of a chemotherapeutic agent, let alone one that interferes with microtubules, such as paclitaxel, docetaxel and vinorelbine, results in an increased concentration of surface-exposed Ep-CAM. Moreover, none of these documents suggests that the targeting of Ep-CAM-bearing tumour cells by an anti-Ep-

CAM antibody could be improved by exploiting this technical effect. The skilled person thus had no motivation to replace 5-FU with any of the three chemotherapeutic agents referred to in claim 1.

38. Appellant II argued that the skilled person would have randomly selected these agents because they were standard medicaments for the treatment of tumours and the skilled person had either an expectation of success or would at least have adopted a "try and see" attitude in line with the decision T 1396/06, point 7 of the reasons.

38.1 The board is not convinced by this. The skilled person seeking to provide means for an improved targeting of Ep-CAM-expressing tumour cells is faced with a plethora of available chemotherapeutic anti-tumour agents (see document D20, page 385, column 1, first paragraph). Under these circumstances, in the absence of any pointer in the prior art to suggest that the three particular chemotherapeutic agents of claim 1 specifically increase the Ep-CAM concentration on tumour cells and thus improve the targeting of these cells by a respective antibody, the skilled person would have neither an expectation of success nor a reason to select any of these agents, irrespective of whether they are standard therapeutics in the field.

38.2 The skilled person is for the same reasons also not in a "try and see" situation. According to the established jurisprudence of the Board of Appeal this presupposes that the skilled person already envisages a particular group of compounds in view of the effect to be achieved and only then determines by routine tests whether a member of this group in fact achieves this effect (see Case Law of the Boards of Appeal, 7th edition 2013,

I.D.7.2). However in the present situation, the skilled person, without knowing that a tumour-specific Ep-CAM surface expression can be increased - let alone of ways attaining such an increase - is incapable of envisaging a particular group of suitable compounds that could be tested for this purpose.

39. For these reasons the board concludes that the subject-matter of claim 1 is not obvious. This conclusion also applies to the subject-matter of dependent claims 2 and 3 and to the subject-matter of claim 4 relating to a second medical use of the subject-matter of claim 1. Hence, the claims of auxiliary request 7 fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated