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Datasheet for the decision of 13 July 2023

Case Number: T 1044/21 - 3.3.08

Application Number: 15727610.6

Publication Number: 3149481

IPC: G01N33/574

Language of the proceedings: EN

Title of invention:
MULTIPLEX ASSAY FOR IMPROVED SCORING OF TUMOR TISSUES STAINED FOR PD-L1

Patent Proprietor:
Ventana Medical Systems, Inc.

Opponent:
CMS Cameron McKenna Nabarro Olswang LLP

Headword:
Multiplex assay /VENTANA

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

Keyword:
Admittance of late-filed evidence - (no)
Inventive step - all requests - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
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Office européen des brevets

Beschwerdekammern

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Case Number: T 1044/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 13 July 2023

Appellant: (Opponent)	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Representative:	Hollywood, Jane CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Respondent: (Patent Proprietor)	Ventana Medical Systems, Inc. 1910 E. Innovation Park Drive Tucson, Arizona 85755 (US)
Representative:	Teschemacher, Andrea Simmons & Simmons LLP Lehel Carré Thierschplatz 6 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 12 April 2021 rejecting the opposition filed against European patent No. 3149481 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Claes
Members:	D. Pilat
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 149 481 was granted for European patent application No. 15 727 610.6, filed as an international application published as WO 2015/181343.

Claims 1 and 8 of the patent as granted read:

"1. A method of scoring PD-L1 expression in a tumor sample, the method comprising:
• labeling the tumor tissue sample, the labeling comprising:
- contacting the tissue sample with an anti-PD-LI primary antibody; and
- contacting the same tissue sample with
- a primary antibody directed to a tumor cell-specific marker and an antibody directed to an immune cell-specific marker; and
- visualizing each of the antibodies in the tissue sample with a reagent that generates a detectable signal corresponding to each of the primary antibodies, wherein the anti-PD-LI antibody has a first detectable signal, the antibody directed to the tumor cell-specific marker has a second detectable signal distinguishable from the first detectable signal, and the antibody directed to an immune cell-specific marker has a third detectable signal distinguishable from the first detectable signal and the second detectable signal;
wherein the first, second, and third detectable signals are generated by chromogens; and
• scoring PD-L1 expression in tumor cells, immune cells, or both, wherein co-localization of the first and second detectable signals indicates the presence of

PD-L1-positive tumor cells and co-localization of the first and third detectable signals indicates the presence of PD-L1-positive immune cells."

"8. The method of any of claims 1 to 7, further comprising counterstaining the tissue sample, the counterstain producing a fourth detectable signal that is distinguishable from the first, second, and the third detectable signals, optionally wherein the counterstain comprises hematoxylin."

II. The patent was opposed on the grounds of Article 100(a) EPC in conjunction with Articles 54, 56 and 57 EPC, and of Article 100(b) and (c) EPC. The opponent (appellant) lodged an appeal against the opposition division's decision to reject the opposition.

III. With its reply to the appeal, the patent proprietor (respondent) maintained the main request (patent as granted) and submitted nine sets of claims as auxiliary requests 1 to 9. Auxiliary requests 1, 3 to 7 and 9 in appeal, corresponding to auxiliary requests 3, 4, 5, 1, 2, 7 and 6 filed in opposition proceedings respectively, and auxiliary requests 2 and 8 are new to the proceedings.

As compared with claim 1 of the patent as granted, claim 1 of auxiliary requests 1, 5 and 6 differs in that claim 1 specifies that i) the step of scoring PD-L1 expression is carried out in tumour cells and in immune cells, ii) the method is a multiplex method, or iii) the first, second, and third detectable signals are generated by chromogens and are colours, respectively.

Claim 1 of auxiliary requests 2, 3 and 4 corresponds to claim 1 of the patent as granted, except that i) the method is limited to the embodiment defined in the granted claim 8, ii) the tissue sample is limited to a formalin-fixed paraffin-embedded (FFPE) sample, or iii) the method is an automated method, respectively.

Claim 1 of auxiliary request 7 corresponds to claim 1 of the patent as granted, except that i) the method is a multiplex method, ii) the step of scoring PD-L1 expression is carried out in tumour cells and immune cells, and iii) the tumour is scored as PD-L1 positive if the score is above a threshold.

Claim 1 of auxiliary request 8 is identical to claim 1 of auxiliary request 7, but further includes the step of counterstaining the tissue sample specified in claim 1 of auxiliary request 2.

Claim 1 of auxiliary request 9 is identical to claim 1 of auxiliary request 3, but further specifies that the signals are colours and that it is an automated and multiplex method.

IV. The board summoned the parties to oral proceedings as per their requests and issued a communication pursuant to Article 15(1) RPBA.

V. In reply, the respondent submitted further arguments and submitted two new documents (D17 and D18).

VI. At the end of the oral proceedings, the Chair announced the board's decision.

VII. The following documents are cited in this decision:

D6: Ghebeh, H. *et al.*, Neoplasia, vol. 8 (3), 2006, pages 190 to 198

D12: Zhao, T. *et al.*, PLOS ONE, vol. 12 (4), e0176822, pages 1/17 to 17/17

D13: Shklovskaya, E. and Rizos, H., Int. J. Mol. Sci., vol. 21 (19), 7139, 2020, pages 1 to 23;

D14: Chris M. van der Loos, Journal of Histotechnology, vol. 33 (1), 2010, pages 31 to 40;

D17: Powles, T. *et al.*, Cancer treatment reviews, vol. 82, 101925, 2020, pages 1 to 11;

D18: Product information on VENTANA PD-L1 (SP142) Assay (https://diagnostics.roche.com/us/en/products/tests/ventana-pd-l1-_sp142-assay1.html)

VIII. The submissions made by the **appellant** relevant to this decision may be summarised as follows:

Admittance and consideration of documents D17 and D18 under Article 13(2) RPBA 2020

Documents D17 and D18 were *prima facie* not relevant because they did not address the technical difference between the claimed method and the method disclosed in document D6. Accordingly, they should not be admitted into the proceedings.

Inventive step
Main request - claim 1

The claimed invention was obvious to the skilled person in view of the combination of the PD-L1 detection method disclosed in document D6, which represented the closest prior art, with the disclosure in document D14.

Since there was no evidence of an improvement associated with the use of the claimed multiplex detection in a tumour sample over the method described in document D6, the technical problem was the provision of an alternative method for scoring PD-L1.

Inventive step
Auxiliary requests 1 to 9

The subject-matter of claim 1 of all these requests lacked inventive step for the same reasons as that of claim 1 as granted (main request).

Document D14 did not dissuade the skilled person from using a hematoxylin counterstain.

IX. The submissions made by the **respondent** relevant to this decision may be summarised as follows:

Admittance and consideration of documents D17 and D18 under Article 13(2) RPBA 2020

Documents D17 and D18, which had only been published in 2020, were submitted in reaction to the board's communication under Article 15(1) RPBA in order to provide a better understanding of the disclosures in documents D12 and D13.

Inventive step
Main request - claim 1

The claimed method differed from the method disclosed in document D6 in that it detected three markers instead of one or two, PD-L1 and/or a tumour cell-specific marker or alternatively PD-L1 and/or an immune cell-specific marker,in one chromogenic assay using the same tissue sample.

Differentiated staining, at least triplex, of a PD-L1 marker and a marker specific to tumour cells as well as a marker specific to immune cells on cells in one sample made it possible to differentiate between the PD-L1-positive tumour cells and the PD-L1-positive immune cells. The technical problem derived from this technical difference was to provide improved methods of PD-L1 scoring that were faster, more accurate, more reproducible and more sensitive than prior-art methods.

Document D6 provided neither information nor any motivation to measure the PD-L1 marker expression on tumour cells (TC) and on immune cells (IC) separately in one and the same sample.

The skilled person would not have turned to document D14, which did not relate to prognosis in cancer patients or to cancer. Even if the (sequential) triple staining had been carried out in document D14, several paragraphs taught away from triplex staining and referred to associated difficulties and the limitations of such a multiplex analysis.

Inventive step
Auxiliary requests 1 to 9 - claim 1

Document D6 did not teach that the cell-type-specific PD-L1 detection was of importance, but found only that PD-L1 presence in the tumour tissue - regardless of the

cell type in which it was expressed - was indicative for the diagnosis and treatment of cancer. By separately detecting PD-L1-positive tumour cells and PD-L1-positive immune cells, document D6 further examined the relationship between PD-L1 expression in tumour cells and in tumour-infiltrating lymphocytes. Hence the claimed subject-matter of auxiliary request 1 involved an inventive step. This document also taught away from using formalin-fixed paraffin-embedded (FFPE) samples as claimed in auxiliary request 3 (page 197, left-hand column, lines 2 to 6).

Document D14 taught away from using a hematoxylin counterstain as claimed in auxiliary request 2, even though this step increased the contrast and enhanced visibility.

Although the method disclosed in document D6 demanded human handling, it also required human judgement, which was difficult to automate (Chapter I.D.9.21.6 of Case Law of the Boards of Appeal of the European Patent Office, 10th edition, 2022, hereinafter "Case Law"). The specific detection and scoring of PD-L1 in tumour cells and immune cells in one sample using the set of markers as defined in the claims avoided the necessity of human judgement and allowed the design of an automated method according to the claims of auxiliary request 4.

The amendments to the claims of both auxiliary requests 5 and 6 were limited to a "multiplex" method, and to signals being colours.

The concept of differentiated scoring of PD-L1 expression on TC and on IC in a patient's tumour sample above a threshold for selecting responsive patients

and/or for diagnostic reasons was missing in document D6. The subject-matter of auxiliary request 7 solved this problem and improved the ability of samples to be scored more quickly, more accurately, and with a greater degree of reproducibility compared with the scoring of samples stained with PD-L1 alone.

Auxiliary request 8 corresponded to a combination of amendments introduced in auxiliary requests 2 and 7. Auxiliary request 9 corresponded to a combination of amendments introduced in auxiliary requests 1, 3 and 6. The reasons given above for considering that the claimed subject-matter involved an inventive step therefore applied.

X. The requests of the parties to the appeal proceedings relevant to this decision were:

The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked in its entirety. The appellant further requested that auxiliary request 2, filed by the respondent with the reply to the appeal, not be admitted into the proceedings and that documents D17 and D18, filed by letter of 7 July 2023, not be admitted either.

The respondent (patent proprietor) requested that the appeal be dismissed. As an auxiliary measure, the respondent requested that the decision under appeal be set aside and the patent be maintained based on the set of claims of any of auxiliary requests 1 to 9, filed with the statement of grounds of appeal.

Reasons for the Decision

Admittance and consideration of documents D17 and D18 under Article 13(2) RPBA 2020

1. Documents D17 and D18 were filed by the respondent in response to the board's communication under Article 15(1) RPBA, and their admittance is thus subject to the discretion of the board pursuant to Article 13(2) RPBA. In accordance with this provision, any amendment to a party's appeal case after notification of a summons to oral proceedings is, in principle, not to be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned. According to the case law of the boards of appeal, in addition to a justification for the late filing, one further criterion for admitting late-filed documents is their *prima facie* relevance, in the sense that they could reasonably be expected to change the outcome of the proceedings.

2. The appellant held documents D17 and D18 *prima facie* not relevant, because they provided no evidence of a technical effect of the technical difference between the claimed method and the method disclosed in document D6. The respondent submitted that they had been filed for better understanding of documents D12 and D13, previously submitted in the context of the assessment of inventive step in order to show the importance of separate detection of PD-L1 on TC and on IC for scoring PD-L1 expression in a tumour sample, and thus to show that these differentiating features of the patent vis-à-vis the prior art (document D6) lead to a technical effect.

3. First, the board cannot identify any exceptional circumstances justifying the filing of these documents after notification of the board's preliminary opinion. The formulation of the technical problem as the provision of an alternative in the discussion on inventive step had already been adopted by the opposition division and was submitted again by the appellant with its statement of grounds of appeal. Thus, regardless of whether D17 and D18 have only recently become available, as had been argued by the respondent, the board finds that the respondent had reasons to file them at an earlier stage of the appeal proceedings. Further, admittance is not justified even if the *prima facie* relevance criterion is taken into account. Even though documents D17 and D18 confirm and illustrate that a differentiated detection of PD-L1 on TC and on IC is important as a classification tool using cell-specific thresholds for diagnosis and selecting patients responsive to anti-PD-1 and anti-PD-L1 therapies, these documents however, just like documents D12 and D13 — referring to PD-L1 expression as a new biomarker for prognosing the survival of cancer patients —, provide no evidence that a differentiated detection of PD-L1 on TC and on IC in one tissue sample renders the scoring of PD-L1 expression in a tumour sample faster, more accurate and more reproducible, as was argued by the respondent. Thus it can equally not be derived from these documents that the differences between the method described in document D6 and that of claim 1 would lead to a technical effect.

4. Although some of the calculation models used in the patent were equally used in documents D17 and D18, these models do not add any information with respect to the technical effect resulting from the technical

difference between the method of claim 1 and the method described in document D6 that might render them *prima facie* relevant to the board's decision.

5. Accordingly, exercising its discretion (Article 13 RPBA 2020), the board sees no reason to admit and consider them in the appeal proceedings.

Main request - claim 1 - inventive step (Article 56 EPC)
Closest prior art

6. The claimed method aims at scoring PD-L1 expression in a tumour sample. The respondent agreed with the opposition division that the disclosure in document D6 represents the closest prior art. The board has no reason to disagree.

7. Document D6 discloses chromogenic immunohistochemical (IHC) assays wherein snap-frozen, acetone-fixed breast cancer tissue samples are double-stained in separate assays for PD-L1 and the tumour cell-specific marker cytokeratin (Figure 1F), and for PD-L1 and one of the immune cell-specific markers CD3, CD4 and CD5 (Figures 2B, 2D and 2F). Thus it discloses double staining of PD-L1 and a tumour cell marker and double staining of PD-L1 and an immune cell marker (see "Immunohistochemistry" section on pages 191 and 192, for example). The scoring of PD-L1 expression in tumour cells (TC) and of PD-L1 expression in tumour-infiltrating lymphocytes (TIL) (immune cells (IC)) is shown to correlate with clinicopathological parameters of patients. Some parameters are important prognostic factors associated with high-risk patients for breast cancer (see page 196, right-hand column, paragraph 2). It is concluded that PD-L1 expression may be an important risk factor in breast cancer patients and may

represent a potential immunotherapeutic target for monoclonal antibodies (see abstract, last sentence, and page 197, last paragraph).

Difference, technical effect and technical problem

8. It is uncontested that the claimed method differs from the method disclosed in document D6 in that it relates to triplex staining in a chromogenic assay of a tissue sample for detecting PD-L1, a tumour cell marker and an immune cell marker, i.e. detection and chromogenic staining of a tumour tissue sample with antibodies directed towards all three antigens.

9. The respondent submitted that the technical effect of this difference was that the claimed method of scoring PD-L1 expression in a tumour sample was faster, more accurate, more reproducible and more sensitive than the known methods. Since many tumour samples show PD-L1 staining on both tumour cells and on immune cells, which were difficult to differentiate, the use of PD-L1 protein expression as an accurate predictor for cancer and/or the efficacy of anti-PD-1 and anti-PD-L1 directed therapies was challenging (see paragraph [0012] of the patent). Thus differentiated staining between the PD-L1-positive tumour cells and the PD-L1-positive immune cells may improve the ability of samples to be scored (manual/visual, machine/image analysis) more quickly, more accurately, and with a greater degree of reproducibility (see paragraphs [0013] and [0029] of the patent). It was submitted in this context that post-published documents D12 and D13 proved that it was important that PD-L1 expression on immune cells be analysed independently from that on tumour cells, i.e. needed to be analysed on both the

immune cells and tumour cells in order to be predictive of cancer outcome and therapy.

10. According to established case law of the Boards of Appeal, alleged advantages to which a patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (Case Law, Chapter I.D.4.3.1).

11. Although the occurrence of PD-L1 staining in both tumour and immune cells as well as in other cells in many tumour samples may make it difficult for pathologists to distinguish between these (two) cell types, so the use of PD-L1 protein expression as an accurate predictor of cancer and/or the efficacy of anti-PD-1 and anti-PD-L1 targeted therapies may prove challenging, the board in the case at hand has not seen any comparative data of the claimed method and the method disclosed in document D6 which might support the allegation that the claimed triplex staining in a chromogenic assay of a tissue sample improved the ability of the skilled person to score samples more quickly, more accurately, and with a greater degree of reproducibility as compared with scoring samples stained with PD-L1 in combination with a differentiating marker specific for tumour cells or for immune cells (double staining) (see paragraph [0013] and Figure 1).

12. Furthermore, although the post-published documents D12 and D13 indeed disclose, as argued by the respondent, that PD-L1 expression on tumour cells and on immune cells should be analysed independently from each other when assessing tumour prognosis (see document D12,

"Abstract", last sentence, and "Conclusions", and document D13, page 2, second paragraph), the documents do not disclose, let alone demonstrate that differentiated scoring of PD-L1-positive tumour cells and PD-L1-positive immune cells in a multiplex assay allowed samples to be scored more quickly, more accurately and with a greater degree of reproducibility .

13. The board thus agrees with the opposition division and the appellant that the objective technical problem must be formulated as the provision of an alternative method for scoring PD-L1 in tumour and/or immune cells instead of an improved method as submitted by the respondent.

14. It is undisputed that the claimed invention solves this problem and the board has no reason to disagree.

Obviousness

15. Starting from the disclosure in document D6 and faced with the technical problem defined above, the claimed solution was obvious to the skilled person in view of the statement in document D14 that the desire "*for multiple antigen visualisation in one tissue specimen is almost as old as IHC itself*" (see page 31, right-hand column, lines 3 to 5) and the teaching of multiple staining as an option (see page 31, right-hand column, lines 5 to 8). Even if double immunohistochemical (IHC) staining methods played a significant role in many research projects, spectral unmixing allowed colocalisation to be demonstrated from triple or even quadruple IHC-stained tissue samples (see page 39, left-hand column, line 18). The disclosure in document D6 concerns expression of PD-L1 on tumour cells or on immune cells and the correlation between the cell-

specific PD-L1 expression and patients' clinicopathological parameters as well as the significance thereof in terms of disease manifestation in patients (see abstract, page 196, right-hand column, 2nd paragraph and Table 2), but does not, as the respondent argued, provide the skilled person with the motivation for combining the teaching of document D6 with that of document D14 to change the staining from duplex staining to triplex staining. However, the board considers that the skilled person does not need such a pointer or motivation in the underlying situation, because - given the formulation of the problem as the provision of an alternative method (see point 13. above) - the skilled person would in fact recognise and consider *any* multiple chromogenic immunohistochemical staining method described in the art, including those disclosed in document D14, as a valid alternative method to that described in document D6 and thus as a solution to the technical problem. The definition of the claimed subject-matter thus merely amounts to a selection of one method combining a number of equally-known methods.

15.1 Although, admittedly, document D14 relates to the (sequential) triple staining of *Helicobacter pylori* with two different mucins or combining three macrophage markers on atherosclerotic plaque in the human carotid artery, which are not explicitly associated with cancer patients or cancer diagnosis, this is irrelevant when assessing inventive step in the case at hand because the claimed method is a method of scoring PD-L1 expression on tumour tissue samples without any explicit cancer-diagnostic aim, such as for early detection of cancer pathologies and for assessing the efficacy and durability of investigational drugs that inhibit the binding of the PD-L1 protein. In fact,

these are aspects which are only mentioned in the description of the patent specification (see paragraphs [0003] and [0012] and Figure 1).

15.2 Furthermore, although the respondent has highlighted that some chromogen combinations in document D14 were found to be unsuitable for detecting antibodies at the site of colocalisation, as they "*do*[es] *not allow the observation of colocalization*" while "*Quantitation of the different subsets and colocalizations with the unaided eye, however, is fully impossible*" (see page 35, right-hand column, section "Chromogen Combinations for Triple Staining and Beyond"), the board cannot see why these passages in document D14, as argued by the respondent, would teach away from triplex staining, as D14 also mentions that "*Using the colocalization tool from the Nuance software, the percentage of different macrophages subsets, including colocalizations and triple-localizations, can be simply calculated*" (see page 35, right-hand column, last sentence of second complete paragraph).

15.3 In addition, the respondent's allegation that the technology was not yet mature because only a limited series of chromogens was available for IHC staining and that they needed improvement and that hardware/ software, spectral imaging played an important role in the future of multicolour microscopic imaging (see document D14, page 38, right-hand column, last paragraph, and page 39, left-hand column, lines 18 to 22) cannot be accepted by the board as an argument that the skilled person would not have arrived at the claimed subject-matter, because document D14 in fact refers to the development of spectral imaging, which brings the multiple IHC staining to a next level, i.e. a level beyond double IHC staining to a multi-marker

tissue analysis, even though it requires the development of a new generation of enzymatic chromogens (see document D14, right-hand column, last paragraph and page 39, left-hand column, lines 12 to 45), which were however available and disclosed before the priority date, in Example 2 of WO 2013/148498, published in 2013. Moreover, the "*Tips and Tricks for Adapting Single IHC Staining to Multiple IHC Staining*" section provides clear information on how to address possible challenges (see document D14, page 36, left-hand column).

16. Furthermore, even if, *arguendo*, there were difficulties associated with performing triplex IHC staining disclosed in document D14, as argued by the respondent, then the same would also apply to the claimed method, as the claim appears not to include features with the purpose of overcoming such difficulties, and the patent does not teach how these alleged difficulties should be overcome in order to perform successful triplex staining either.

17. In view of the above considerations, the board concludes that the skilled person faced with the technical problem defined in point 13. would have modified the method described in document D6 by turning to the teaching in document D14, thus combining the two double-staining assays with prognostic significance into a triplex staining assay in one single tissue specimen, instead of two assays of double staining combining PD-L1 and an immune cell marker and combining PD-L1 and a tumour cell marker, and would therefore have arrived at the claimed method in an obvious manner. Thus the method according to claim 1 of the main request lacks inventive step (Article 56 EPC).

Auxiliary requests 1 to 9 - claim 1 - inventive step

18. In the board's communication under Article 15(1) RPBA, the respondent was informed that the board considered that no particular technical effect was associated with any of the distinguishing features introduced in each amended claim 1, which appeared to be mere arbitrary modifications of the teaching of the state of the art and thus not suitable to justify an inventive step (see board's communication, point 13.).

19. Indeed, since the board has seen no evidence, let alone indications, that the additional/modified features introduced in claim 1 of these auxiliary requests further distinguishing the claimed method (see section III.) achieve a technical effect going beyond that achieved by the claimed method of the main request, the objective technical problem for assessing inventive step starting from the disclosure in document D6 representing the closest prior art is the same as for the main request (see point 13. above).

20. Considering that document D6 discloses a multiplex method which scores PD-L1 expression in tumour cells and immune cells, uses chromogens for the first, second and third detectable signals that are colours (see abstract, page 196, right-hand column and Figure 2 referring to colours), the claimed methods of auxiliary requests 1, 5, 6 and 9, directed at scoring PD-L1 expression in a tumour sample without any claimed diagnostic requirement, lack inventive step for the same reasons as the main request.

21. The counterstaining of the tissue sample according to claim 1 of auxiliary requests 2 and 8, wherein the counterstain comprises hematoxylin, is also described

and applicable in multiple IHC experiments (see document D14, page 37, left-hand column, second bullet point). Thus the skilled person seeking to provide an alternative method to that disclosed in document D6 with a view to solving the technical problem would have added a hematoxylin staining step and would have scored the tumour tissue sample to classify it as positive above a threshold. Hence the claimed methods of auxiliary requests 2 and 8 equally lack inventive step.

22. The board disagrees with the respondent's arguments that document D14 teaches away from using a hematoxylin counterstain in the "Tips and Tricks for Adapting Single IHC Staining to Multiple IHC Staining" section (see page 36, right-hand column, fifth line from the bottom), because document D14 only teaches that hematoxylin counterstaining should be avoided when primary antibodies are validated and their appropriate dilution is determined, while it explicitly specifies that two full multiple IHC experiments should be conducted with all primary antibodies, one with hematoxylin staining and one without (see page 37, second bullet point).

23. The use of a formalin-fixed paraffin-embedded (FFPE) sample according to claim 1 of auxiliary requests 3 and 9 is equally described in document D6, albeit this document warns that "*the available antibody we used to stain breast cancer sections is reliable only for immunohistochemical staining of cryogenic sections and is not functional for staining of embedded tissues*" (see page 197, left-hand column, lines 1 to 4). However, antibodies suitable for use on FFPE tissues are publicly available to the skilled person (see Example 1 of the patent applying e.g. rabbit monoclonal anti-PD-L1 clone SP142). Thus the skilled

person seeking to provide an alternative method to that disclosed in document D6 would have selected antibodies suitable for staining FFPE tissues and would have arrived at the claimed method of auxiliary request 3 without applying inventive skill. For the same reason, this step cannot, by its mere presence, confer an inventive character on a method that includes it (auxiliary request 9).

24. The automation of the method according to claim 1 of auxiliary request 4, by replacing manual operation with automatic operation, is a routine optimisation not requiring inventive skill of the skilled person and cannot confer an inventive step (see Case Law, Chapter I.D.9.21.6). For the same reason, this step cannot, by its mere presence, confer an inventive character on a method that includes it (auxiliary request 9).

25. Claim 1 of auxiliary request 9 is identical to that of auxiliary request 3 (see also point 23. above), except that the claimed method is an automated multiplex method comprising detectable signals that are generated by chromogens and are colours. Although the automation of a disclosed multiplex method is no more than a routine optimisation (see point 24. above) and document D6 mentions that "*the available antibody we used to stain breast cancer sections is reliable only for immunohistochemical staining of cryogenic sections and is not functional for staining of embedded tissues*", the board, based on this unique specific statement, cannot exclude that other known antibodies than the antibody used in document D6 and colour-generating chromogens are available and suitable for detection on an FFPE sample (see Example 1 of the patent). The claimed subject-matter therefore simply represents another alternative solution to the technical problem

set out above. Thus the skilled person seeking to provide an alternative method to that disclosed in document D6 would have arrived at the method of claim 1 of auxiliary request 9 without any inventive skill being required.

26. The respondent held that the additional feature "whereby the tumour is classified as PD-L1 positive if the value is above a threshold value" in claim 1 of auxiliary request 7 emphasised even more the importance of detecting PD-L1 in different cell types, namely tumour cells and immune cells, for reliably recognising a PD-L1-positive tumour or PD-L1-negative tumour and then selecting the appropriate applicable responsive therapy (see patent, paragraph [0012]).

27. The board notes that document D6 discloses a duplex, i.e. multiplex, method which scores the PD-L1 expression in tumour cells and immune cells. The assignment of a correlation between the PD-L1 expression on specific cells and the large tumour size, among all the recited clinicopathological parameters, involved the application of a threshold above which the correlation was considered significant (abstract, page 196, right-hand column, first full paragraph).

28. The claimed method only requires a step of scoring PD-L1 expression in tumour cells and immune cells wherein the tumour is scored as PD-L1 positive if the score is above a threshold. However, since neither the equation nor the threshold value nor any consequence of a positive or negative score above a threshold value is set out in the claim, the board can only conclude that the step of scoring does not bring about any selection of patients or group of patients and of a therapy, and thus any technical effect going beyond the technical

effect of the granted claim 1. Since the technical effect of the subject-matter of this claim is thus identical to the technical effect of the granted claim 1, the objective technical problem must also be identical (see point 13. above).

29. Thus the skilled person in an attempt to determine a correlation which is of significance between the PD-L1 expression on specific cells and the large tumour size, would have scored the tumour tissue sample and would have classified it as positive when the score was above a selected threshold. Hence the claimed method lacks inventive step.

30. Thus the subject-matter of claim 1 of none of auxiliary requests 1 to 9 involves an inventive step (Article 56 EPC). Consequently and in conclusion, neither the main request nor any of auxiliary requests 1 to 9 meet the requirements of Article 56 EPC.

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:

L. Malécot-Grob B. Claes

Decision electronically authenticated