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Datasheet for the decision of 12 August 2025

Case Number: T 0694/23 - 3.3.08

Application Number: 11773381.6

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IPC: G01N33/50, G01N33/574, G01N33/68

Language of the proceedings: EN

Title of invention:
MEANS AND METHODS FOR THE PREDICTION OF TREATMENT RESPONSE OF A CANCER PATIENT

Patent Proprietor:
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Jäger, Dirk
Zörnig, Inka

Opponent:
Plougmann Vingtoft a/s

Headword:
Predicting treatment response in cancer patients/GRABE HALAMA JÄGER ZÖRNIG

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

Keyword:
Main request and auxiliary requests 1 to 5 - inventive step (no)

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Catchword:

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Beschwerdekammern

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Case Number: T 0694/23 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 12 August 2025

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Appellant I: (Patent Proprietor 2)	Halama, Niels, Dr. Im Neuenheimer Feld 350 69120 Heidelberg (DE)
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Appellant II: (Opponent)	Plougmann Vingtoft a/s Strandvejen 70 2900 Hellerup (DK)
Representative:	Plougmann Vingtoft a/s Strandvejen 70 2900 Hellerup (DK)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 March 2023 concerning maintenance of the European Patent No. 2619576 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 2 619 576 is based on European patent application No. 11 773 381.6, filed as an international application published as WO 2012/038068. The patent was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Article 100(b) and (c) EPC. In an interlocutory decision, the opposition division held that the claims as granted (main request) as well as those of auxiliary requests 1 and 2 were not allowable for lack of novelty, but that the claims of auxiliary request 3, filed on 1 September 2022, fulfilled the requirements of the EPC.

II. Both the patent proprietors (appellant I) and the opponent (appellant II) filed an appeal against this decision. With the statement of grounds of appeal, appellant I requested that the patent be maintained as granted (main request) or, alternatively, on the basis of the claims of auxiliary requests 1 to 4, all filed with the grounds of appeal.

III. In a communication under Article 15(1) RPBA, the parties were informed of the board's provisional opinion on the issues of the case.

IV. With letter dated 25 July 2025, submitted in reaction to the board's communication, appellant I submitted auxiliary request 5, consisting of a set of claims identical to that of auxiliary request 3 and an amended description wherein paragraph [0125] was deleted.

V. Claim 1 of **the main request** (claims as granted) read as follows:

"1. A method for predicting whether a cancer patient with a solid tumor is responsive to treatment with chemotherapy comprising the steps:

• providing a tumor sample previously taken from said patient, wherein the tumor sample is a tumor section and comprises the invasive margin; and
• determining in the tumor section the number of CD3-positive cells per squaremillimeter and either the number of CD8-positive cells per squaremillimeter or the number of Granzyme B-positive or both, wherein the number of cells is determined with immunohistochemistry and/or immunofluorescence using whole slide imaging technology on the whole tissue section; wherein microscopically digitized slides resulting from whole slide imaging are subject to automatic image processing; wherein the biological markers are assessed automatically and; wherein the sample of the patient is classified by algorithms towards their response to the treatment with chemotherapy wherein a number of CD3-positive cells per mm^2 and CD8-positive cells/mm^2 and/or Granzyme B-positive cells/mm^2 above a threshold predefined for each of CD3, CD8 and Granzyme B is indicative that said patient is responsive to said chemotherapy."

VI. In auxiliary requests 1 to 5, claim 1 is identical to claim 1 of the main request.

VII. The documents cited in this decision include the following:

D1 Halama N. *et al.*, Cancer Res., 2011 vol.71 (17), pages 5670 to 5677, & supplementary material pages 1 to 6
D2 Halama N. *et al.*, Cancer Immunity, 2009, vol.9, pages 1 to 6
D8 EP 10010537 (patent's priority document)

VIII. The parties' submissions, insofar as they are relevant to the decision, are discussed in the Reasons for the Decision, below.

IX. The parties' final requests, in so far as relevant for the present decision, were the following:

Appellant I requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or alternatively that the patent be maintained based on the claims of one of auxiliary requests 1 to 5.

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

Reasons for the Decision

Admittance of new evidence and arguments

Evidence submitted with appellant I's letters of 25 July 2025 and of 7 August 2025

1. In reaction to the board's communication under Article 15(1) RPBA, appellant I submitted new evidence in the form of figures and a corresponding internet link, arguing that they refined the arguments presented previously in the context of claim interpretation and inventive step and did not represent a fresh case. In

an even later letter, appellant I referred to several new documents and provided links to webpages where these documents could be retrieved.

1.1 The board notes that the interpretation of the claim and the inventive step objection starting from document D2 were raised and already addressed in opposition proceedings. This objection was maintained by appellant II in its statement of grounds of appeal. Thus, appellant I's documents and arguments, which were submitted after the notification of a communication under Article 15(1) RPBA, could and should have been submitted earlier. The same is true for the reformulation of the technical problem proposed by appellant I in the letter of 25 July 2025. In the absence of exceptional circumstances justified with cogent reasons, the board considers that this evidence and arguments constitute a very late amendment to the appellant I's appeal case and decides not to admit them under Article 13(2) RPBA.

Main request and auxiliary requests 1 to 5
Claim interpretation

2. Claim 1 is identical in all of the main request and auxiliary requests 1 to 5. It is directed to a method for predicting whether a cancer patient with a solid tumor is responsive to treatment with chemotherapy comprising the steps of

- providing a tumor sample from said patient, wherein the tumor sample is a tumor section and comprises the invasive margin;
- determining in the tumor section the densities of tumor infiltrating lymphocytes (TILs), i.e. the number of CD3+, CD8+ and Granzyme B+ cells per squaremillimeter, wherein the number of cells is

determined ... using whole slide imaging technology on the whole tissue section ... (for the whole wording of the claim see section V.).

3. There was disagreement as regards the interpretation of a number of features in the claim, such as "tumor sample", "whole tissue section" and the sampling and quantitative assessments.

"tumor sample"

3.1 The board considers that the term "tumor sample" is clear and well understood by the skilled person. It is a broad term that may encompass different embodiments, as is also apparent from paragraph [0125] of the patent: *"A tumor sample, thus, also includes a tumor, parts of a tumor, tumor cells derived from a tumor (including tumor cell lines which may be derived from a tumor and which are grown in cell culture),..."*. There is no requirement in the claims that the tumor sample must include the center of the tumor, nor is this derivable from the patent description. The wording of the claim only requires that the tumor sample comprises the invasive margin and accordingly may consist of the invasive margin only.

"the whole tissue section"

3.2 There is no definition of a "whole tissue section" in the claims or in the description. Since the claim equates "tumor sample" with "tumor section" and then refers to "whole tissue section", the whole tumour section must logically correspond to the whole tissue section of the tumor sample, which necessarily includes the invasive margin, but may also include the centre of the tumour, and the surrounding tissue (patent,

paragraphs [0041], [0053], [0054] [0090] and Figure 6). This interpretation is supported by the description, including the experimental data of the patent (paragraphs [0073], [0074], [0089], Figure 4 third panel), in accordance with G1/24. Hence, the claim requires that the whole tissue section is digitized, so that every pixel of the tumour section is analysed and captured. Whilst the subsequent quantification of each CD3, CD8 and Granzyme B-positive cells over the entire tissue section is possible, it is not required, as entire (sub)regions - spatially connected - of the whole tissue section may also be evaluated (e.g. the invasive margin). Based on these arguments, the board concludes that the entire "whole tissue section" is digitised, while the relevant tumor-infiltrating immune cells/lymphocytes (TIL) density may be quantified and determined (counted) only in - biologically coherent - compartments or subregions, such as the invasive margin or a portion thereof.

3.3 The board hence disagrees with appellant I that the whole tissue section must comprise both the invasive margin and the tumor center and rather considers that the whole tissue section can be the invasive margin only. Appellant I's arguments that it would not be technically possible to obtain a section of invasive margin from a histological tumour section are not convincing because the claimed method does not exclude the quantification of biomarkers in a tumour section consisting of an invasive margin obtained by e.g. laser capture microdissection (patent, paragraph [0038]). Thus, the "whole tissue section" covers also an invasive margin from a microdissected histological section.

Sampling and quantitative assessments

3.4 The board cannot share appellant I's view that the method according to claim 1 requires counting of stained cells over an entire biologically coherent compartment and that the resulting absolute densities of CD3 together with either CD8 or Granzyme B must be fed into a recursive-partitioning algorithm with fixed cut-off values. As already set out above, it suffices when the counting of stained marker cells is performed in a portion of a biologically coherent compartment. Furthermore, it is not required from the wording of claim 1 to perform a multivariate analysis to classify the samples. The algorithm-based classification according to claim 1 also namely includes the use of two independent density comparisons of separate and individual stained marker cells on a whole tissue sample with its threshold value, above which said cancer patient is predicted to be responsive to chemotherapy.

3.5 In the decision under appeal, it was decided that the claimed method required that the numbers of relevant cells were determined in all subsections, such as the centre and the invasive margins, and then added up to give the total number of cells in the whole tissue section, which included both the centre and the invasive margin. The claims are the starting point and the basis for assessing the patentability of an invention. The description and any figures are to be consulted in order to interpret the claims. Following this approach the Board considers that the claim is clear, albeit not limited. Hence, the tumour sample being a tumour section, it is not excluded that it is an invasive margin or more, such as an invasive margin and the centre of the tumour. The counting and determining according to the claim cannot be seen to be

limited to any region of the digitized tumour section or compartment or subpart thereof.

Inventive step (Article 56 EPC)

4. Document D2 represents the closest prior art as regards the subject-matter of claim 1. This was not contested.

5. Document D2 is directed at predicting whether a cancer patient is responsive to treatment with chemotherapy, based on the observation that immune infiltrates at the invasive margin of liver metastases could be predictive of the response to chemotherapy treatment. For each tumour sample, the number of stained tumor-infiltrating immune cells/lymphocytes (TILs) in selected regions at the invasive margin was counted. The TIL densities at the invasive margin of the metastasis was then determined by a software program that was developed to reassess the manual counts and to measure TIL densities across a given region of interest (page 6, left-hand column, first and fourth paragraphs). The cell densities and counts obtained by computer or manually were found to be highly coherent (page 6, left-hand column, third paragraph).

6. The sole distinguishing feature between the method described in D2 and the one being claimed is that D2 only suggests that a correlation exists between TIL densities at the invasive margin of liver metastasis and the time to progression under chemotherapy, but considers that, due to the small patient cohorts in the study, these conclusions are not statistically significant. In contrast, the patent shows that the correlation underlying the method as claimed is statistically significant, at least for colorectal cancer, which is what is assessed in the Examples of

the patent. The technical effect underlying this difference is that the (statistical) robustness of the method for predicting whether a cancer patient is responsive to chemotherapy treatment is achieved.

7. The objective technical problem may be formulated as the provision of a robust method of predicting whether a cancer patient with a solid tumour is responsive to treatment with chemotherapy. This is in agreement with appellant I's formulation of the technical problem in the reply to appellant II's appeal.

8. Starting from the disclosure of document D2 and faced with the technical problem identified above, the skilled person would have been motivated to confirm D2's prediction and the correlation between the cell densities and the response to chemotherapy. For this, it had simply to follow D2's explicit suggestion and increase the number of samples in order to arrive, with a reasonable expectation of success, at a statistically significant correlation and thus at the method of claim 1.

9. The claimed subject-matter thus lacks an inventive step from D2 alone.

10. Appellant I essentially argued that a further distinguishing feature between the claimed method and that of D2 was the sampling and quantitative assessments and that, starting from document D2, the skilled person had no motivation to arrive at the method according to claim 1. The board disagrees.

11. It is true that the sampling according to the method of claim 1 relies on at least two cell markers and on the selection of a biologically coherent compartment,

whereas the method described in D2 is based on individual cell markers, such as CD3, CD8 and Granzyme B, and on a random selection of up to eight individual 1 mm² windows. However, the board notes that document D2 describes a marked variability in the density of the inflammatory infiltrate at the invasive margin between normal and metastatic liver tissue, in particular for CD3, CD8 and Granzyme B positive cells (D2, page 3 right-hand column, lines 1 to 6). This demonstrates that each of the aforementioned individual cell densities and the resulting correlation with regard to the response to chemotherapy in cancer patients can be used either individually or in any appropriate combination. Furthermore, the board observes that the sampling of D2, i.e. selection of up to 8 individual separate windows, 1 mm^2 in size, is not excluded from the wording of claim 1, since, according to the claim construction above (points 3.2 last sentence and 3.4), such windows constitute a portion or a compartment of the whole tissue section. Nor is the selection of a specific biologically coherent compartment required in claim 1 (see claim construction, point 3.5).

12. As regards the quantitative assessment, appellant I argued that the method described in D2 relied on manual counting of single cell markers, whereas the quantitative assessment of the claimed method relied on an automatic counting of a biologically coherent compartment and a comparison between relevant cell densities to predefined density thresholds using an algorithm, i.e. a multivariate analysis and a decision tree, to predict whether a cancer patient is responsive to chemotherapy. This argument is not persuasive for the following reasons. The method of claim 1 is open-ended and does not exclude the method according to D2 applying a manual and then a subsequent automated

computer-assisted cell counting, regardless of the purpose assigned to the automated counting step. The automated counting does not play a role in the claimed prediction statistics, as long as other (manual) cell counts take up this role. Although, according to appellant I, the automated counting tends to underestimate the number of cells due to cell agglomeration in areas of high cell density, the board notes that the ratios obtained through manual and automated counting were found to be highly consistent. Therefore, there is no reason for the skilled person to avoid using automated counting, especially when it is preceded by manual counting (see D2, page 6, left column, second paragraph).

13. The board cannot share appellant I's point of view that D2's assessment of selected biological markers CD3, CD8 and Granzyme B in the invasive margin of the metastatic tumour tissue is based on a sparse, univariate, tile level counting. Firstly, a sparse and tile-level counting in document D2 falls under the method according to claim 1 (see claim construction, points 3.2 and 3.4 above). Even if it were not the case, an increase in the sampling area is explicitly suggested in D2 (12 mm^2 instead of maximum 8 mm^2 on page 6, left-hand column, third paragraph and page 4, left-hand column, lines 5 to 9; page 5, right-hand column, lines 3 to 8 from the bottom). This results in more accurate stained cell densities leading to a more reliable correlation and, in turn, a more robust method for predicting and classifying each individual cancer patient as likely responder or non-responder to chemotherapy. Secondly, the wording of claim 1 does not require any predefined density threshold or a combination of specific cell markers, which must exceed their own thresholds simultaneously, going beyond what

is already disclosed in D2. These features are thus already part of D2's disclosure.

14. The board also disagrees that the marked difference in cell densities in different patients, referred to in the last paragraph of D2's Discussion section, could refer to a correlation other than the correlation between the absolute density of each immune marker CD3, CD8, Granzyme B and the response of cancer patient to chemotherapy. In D2, no correlation could be established either on the basis of the ratios of selected marker pairs or on the basis of the ratio of epithelial cells to the total number of cells (stromal and epithelial) (Ei) from primary tumours, whilst a correlation could be established for the invasive margin of liver metastases. As a result, the suggested correlation between the absolute density of each immune marker CD3, CD8, Granzyme B staining cells and the response to chemotherapy in cancer patients can only refer to cell densities in the invasive margin of liver metastases, for which a larger cohort must be analysed to achieve statistical significance.

15. The classification of whether a cancer patient is responsive to chemotherapy is based on cell counts and densities in both the claimed method and the method of D2. Although D2 does not explicitly disclose a comparison of cell densities with threshold values, such a comparison is implicit and inevitable, otherwise the suggested correlation between cell count and patient response to chemotherapy in document D2 could not have been established. For this correlation, the skilled person had to at least operate a binary classification of CD3, CD8 and Granzyme B positive cell densities in different patients, which were mentioned to show marked differences at the invasive margin of

the liver metastases. The use of thresholds or cut-off density values for each of the stained marker cells is therefore imperative for establishing a reliable classification and prediction.

16. As to appellant I's argument that the skilled person, starting from D2, would have had no motivation to arrive at the method of claim 1, the following is noted. The skilled person does not need a pointer or motivation in the underlying situation, because - given the formulation of the problem as the provision of a (statistically) robust prediction method (see point 7. above) - the skilled person would simply have increased the number of samples assessed in order to confirm the correlation between cell densities and the response to chemotherapy in cancer patients, thus establishing a statistically significant correlation for each of CD3, CD8 and Granzyme B positive cells, and would have used them in any combination to achieve an even more robust method than that described in D2. In doing so, it would inevitably have arrived at a method according to claim 1.

17. With regard to auxiliary request 5, the board notes that it comprises the claims of auxiliary request 3 but with an amended description. Specifically, paragraph [0125] of the description of auxiliary request 5 has been deleted. This amendment intends to remove embodiments that fall under a more general definition of "tumor sample" and to address the board's interpretation of the claims. The board considers that, since the term "tumour sample" is interpreted based on how the skilled person would have understood it in the art and since this term is not otherwise restricted in claim 1, the presence or absence of such a confirmatory paragraph in the description does not affect this

interpretation (see point 3.1. above). It remains the same.

18. Hence, claim 1 of all claim requests on file lacks inventive step.

19. The ground of opposition under Article 100(a) EPC in conjunction with Article 56 EPC, inventive step, therefore prevents the maintenance of the patent as granted (main request) and auxiliary requests 1 to 5 are not allowable for lack of compliance with 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 Chairwoman:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated