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Datasheet for the decision of 9 December 2024

Case Number: T 0832/18 - 3.3.08

Application Number: 05757467.5

Publication Number: 1733056

IPC: C12Q1/68, C07H21/04

Language of the proceedings: EN

Title of invention:
METHOD TO DETERMINE RESPONSIVENESS OF CANCER TO EPIDERMAL GROWTH FACTOR RECEPTOR TARGETING TREATMENTS

Patent Proprietors:
THE GENERAL HOSPITAL CORPORATION
Dana-Farber Cancer Institute, Inc.

Opponents:
James Poole Limited
Strawman Limited

Headword:
Method for determining responsiveness of cancer to treatments targeting EGFR/GENERAL HOSPITAL CORPORATION & DANA-FARBER CANCER INSTITUTE

Relevant legal provisions:
EPC Art. 83

Keyword:
Main request and first to third auxiliary requests and P0 to P3 - sufficiency of disclosure (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0832/18 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 9 December 2024

Appellant I: (Opponent 1)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant II: (Opponent 2)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Respondents: (Patent Proprietors)	THE GENERAL HOSPITAL CORPORATION 55 Fruit Street Boston, MA 02114 (US) and Dana-Farber Cancer Institute, Inc. 450 Brookline Avenue Boston, MA 02215 (US)
Representative:	Haseltine Lake Kempner LLP One Portwall Square Portwall Lane Bristol BS1 6BH (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 January 2018 concerning maintenance of the European Patent No. 1733056 in amended form**

Composition of the Board:

Chairwoman T. Sommerfeld
Members: D. Pilat
D. Rogers
M. Montrone
M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 733 056 was granted on European patent application No. 05 757 467.5, filed as an international application published as WO 2005/094357.

II. Two oppositions were filed on the grounds set forth in Article 100(a) in conjunction with Articles 53(c), 54 and 56 EPC, and of Article 100(b) and (c) EPC. In an interlocutory decision, the opposition division held that the patent in amended form according to the main request met the requirements of the EPC.

III. Opponents 1 and 2 (appellants I and II) both lodged an appeal against the decision of the opposition division.

IV. The patent proprietors (respondents) replied to the appeals, upheld the main request and submitted sets of claims of first to third auxiliary requests as well as of auxiliary requests P0 to P3.

V. Claim 1 of the **main request** (claims as considered allowable and containing a typographical correction) reads as follows:

"1. A method for determining the likelihood of effectiveness of an EGFR tyrosine kinase inhibitor to treat cancer in a patient affected with cancer comprising: determining whether the erbBl gene obtained from a biological sample obtained from said patient comprises at least one nucleic acid variance, selected from:

a. a mutation in exon 18 that results in a substitution of cysteine for glycine at position 719 of SEQ.ID.NO:763 (G719C) or in a substitution

of serine for glycine at position 719 of SEQ.ID.NO: 763 (G719S);
b. an in-frame deletion in exon 19 that results in a deletion of at least amino acids leucine, arginine, glutamic acid and alanine at codons 747, 748, 749, and 750 of SEQ.ID.NO:763; or
c. a mutation in exon 21 that results in an amino acid substitution of arginine for leucine at position 858 of SEQ.ID.NO:763 (L858R) or of glutamine for leucine at position 861 of SEQ.ID.NO: 763 (L861Q);
wherein the biological sample is a sample of tissue or fluid isolated from the patient and wherein the presence of the at least one nucleic acid variance indicates that the EGFR tyrosine kinase inhibitor is likely to be effective; and
wherein the cancer is selected from gastrointestinal cancer, prostate cancer, ovarian cancer, breast cancer, head and neck cancer, lung cancer, non-small cell lung cancer (NSCLC), cancer of the nervous system, kidney cancer, retina cancer, skin cancer, liver cancer, pancreatic cancer, genital-urinary cancer and bladder cancer."

VI. Claim 1 of the first auxiliary request is identical to claim 1 of the main request. The second and third auxiliary requests introduce limitations regarding the mutation G719S; the third auxiliary request furthermore limits the cancer type to lung cancer. The sets of claims of auxiliary requests P0 to P3 correspond to those of the main request and first to third auxiliary requests, respectively, but in which the preamble of claim 1 further specifies "... wherein the EGFR tyrosine kinase inhibitor is effective in an EGFR targeting treatment in patients in which a nucleic acid

variance increases the kinase activity of the EGFR, ...".

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

D50 Gazdar AF, Oncogene, 2009, vol. 28, pages S24 to S31

D72 Wang Z. *et al.*, Nat. Struct. Mol. Biol., 2012, vol. 18(12), pages 1388 to 1393 & Supplementary material

D101 Affidavit of Pasi Antero Jänne, dated 28 January 2016

D108 Torti D. and Trusolino L., EMBO Mol. Med., vol. 3, 2011, pages 623 to 636

D110 Lohinai Z. *et al.*, J. Thorac. Oncol. 2015, vol. 10(5), pages 738 to 746

D132 Kumar A. *et al.*, J. Clin. Oncol., 2008, vol. 26(10), pages 1742 to 1751

D134 Sequist L.V. *et al.*, J. Clin. Oncol., 2010, DOI: 10.1200/JCO.2009.27.9414, pages 1 to 8

VIII. Furthermore, a number of documents were submitted on appeal, including new documents D158 to D160 and D165, submitted by the respondents.

IX. Oral proceedings took place as scheduled, in the absence of appellant II who had announced that it would not attend oral proceedings.

X. The parties' submissions, insofar as they are relevant to the decision, are dealt with in the Reasons for the Decision, below.

XI. The parties' requests, in so far as relevant for the decision, were:

Appellants I and II requested that the appealed decision be set aside and that the patent be revoked.

The respondents requested that the appeals be dismissed and the patent be maintained in amended form as considered allowable by the opposition division (main request), including also the correction of an obvious typographical error in claim 1 ("elected" corrected to "selected", which was requested under Rule 139 EPC). Alternatively, they requested maintenance of the patent in amended form based on one of the sets of claims of the first to third auxiliary requests or of auxiliary requests P0 to P3, all filed with the reply to the appeals.

Reasons for the Decision

Procedural issues

1. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the oral proceedings before the board took place in the absence of appellant II who had been duly summoned but decided not to attend. The present decision is based on facts and evidence put forward during the written proceedings and on which appellant II has had an opportunity to comment.

2. Appellant II requested in writing that the case be remitted to the opposition division, in view of a substantial procedural violation, and also that questions of law be referred to the Enlarged Board of Appeal.

2.1 Appellant II's allegation of a substantial procedural violation was related to the admission of documents D148 and D149 by the opposition division; these documents were submitted and used solely in the context of validity of priority, an issue which does not play a role in the present decision. Moreover, the board cannot see how appellant's right was violated when the opposition division exercised its discretion to admit these documents. It is apparent from the minutes of the oral proceedings in opposition that appellant II was indeed granted the opportunity to comment on the admissibility of documents D148 and D149 (minutes, page 6).

2.2 Since new documents D158 to D160 and D165 were likewise filed in the context of priority, they are not relevant for the present decision either and therefore there is no need to decide on their admission. The same applies to the first set of questions for referral, which also concerned the validity of the priority.

3. The text of the second question for referral is set out in the Minutes of the oral proceedings before the board. As regards the second question for referral, it is concerned with sufficiency of disclosure, thus the issue on which the present decision is based. Nevertheless, the board considers that it is not relevant to the board's decision. In view of the outcome of the present decision, there is no need to provide reasons for this conclusion.

Main request

Sufficiency of disclosure

4. Article 83 EPC stipulates that the application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. According to established case law, the subject-matter of an application must be sufficiently disclosed based on the application as filed as a whole, including examples, and taking into account the common general knowledge of the skilled person. At least one way of enabling the person skilled in the art to carry out the invention must be disclosed, but this is sufficient only if it allows the claimed invention to be performed in the whole range claimed, and the disclosure must be reproducible without undue burden.

5. Claim 1 of the main request (for the full wording of the claim see section V.) is directed to a method for determining the likelihood of effectiveness of an EGFR tyrosine kinase inhibitor (EGFR-TKi) to treat cancer, wherein the cancer is selected from a list of given cancers, the method comprising detecting the presence of specific mutations of the erbB1 gene in a sample of tissue or fluid isolated from the patient, wherein the presence of at least one of said mutations indicates that the EGFR-TKi is likely to be effective. The cancers are selected from gastrointestinal cancer, prostate cancer, ovarian cancer, breast cancer, head and neck cancer, lung cancer, non-small cell lung cancer (NSCLC), cancer of the nervous system, kidney cancer, retina cancer, skin cancer, liver cancer, pancreatic cancer, genital-urinary cancer and bladder cancer. The mutations are defined in relation to SEQ ID NO:763 and include G719C, G719S, deletions of at least leucine, arginine, glutamic acid and alanine at codons 747, 748, 749, and 750, L858R and L861Q. Hence, for this subject-matter to be sufficiently disclosed it has

to be derived from the application as filed or from common general knowledge that the presence of each of the mutations mentioned in the claim is in fact indicative of a likelihood that treatment with any EGFR-TKi for any of the claimed cancers will be effective.

6. As argued by appellant II, the application's teaching does not lead to the conclusion that each of the specified mutations are indicative of effectiveness of the therapy with any EGFR-TKi in the context of any of the claimed cancers. Examples 1 and 3 show that mutations G719C, L858R, L861Q or the deletion in any of codons 747 to 750 were found in samples of gefitinib-responsive NSCLC patients, but none of these mutations were found in other cancer types (patent application paragraph [0268], last two sentences). In Example 4, samples from NSCLC patients were tested and a number of mutations, which include some, but not all, of the claimed mutations, were found (patent application, paragraph [0322]). While Example 4 repeatedly states that "*patients harboring EGFR mutations were significantly more likely to receive recommendations for EGFR-TKI therapy than patients without mutations*" (e.g. patent application, paragraph [0331], second sentence on page 97), it fails to establish that this was due to an increased therapy responsiveness associated with the above identified mutations. It cannot be concluded from the examples that the detection of any of the claimed mutations could allow its association with a predictive value in the responsiveness to treatment with the tested EGFR-TKi (gefitinib), let alone with other EGFR-TKis, in particular types of the NSCLC, let alone in other cancer types.

7. The lack of enablement of the claimed subject-matter in the patent application is not overcome by the teachings of the prior art, and in particular common general knowledge, nor by post-published data. Contrary to the conclusions of the opposition division and in agreement with appellant I, the board considers that documents D50, D72, D132 and D134 in fact raise doubts as to the suitability of using the claimed mutations as indicators for determining the likelihood of effectiveness of a treatment of cancer with specific EGFR-TKis, in particular neratinib and lapatinib, of which neratinib is explicitly disclosed in the patent application as being a preferred TKi for the purpose of the invention (patent application, paragraphs [0016] (last full sentence), [0033] and [0233]: HKI-272 is neratinib).

8. Post-published document D134 relates to the EGFR TKi neratinib and its use in a phase II clinical trial in patients with advanced non-small-cell lung cancer (NSCLC). Of 158 patients, of which 88 harboured an EGFR mutation, only three showed a "partial response": these three patients had a G719X mutation. All the patients with an exon 19 deletion (68 patients), with a L858R point mutation (24 patients) or a L861Q point mutation (2 patients) showed less than a "partial response" to neratinib (see Table 4 (Arm A) patients without a G719X mutation; Table 5 and left half of Figure 2). The best results were seen in patients with wild type EGFR, while patients with a claimed mutation achieved poorer results. Hence, neratinib performed better in non-mutant patients than in patients having the claimed exon 19 deletion, L858R or L861Q point mutation. This is the opposite of what the method of claim 1 intends to achieve. Even if, as argued by the respondents, factors such as dosage, delivery and side effects may

play a role in neratinib's clinical efficacy, claim 1 is not limited by any of these aspects (e.g. minimum dosage per day). There is also no requirement in claim 1 that TKis, such as neratinib, must simultaneously be pharmacologically effective, i.e. achieve a therapeutic effect, and must be tolerated by patients to whatever degree, i.e. must not cause any harmful side effects. Even if the presence of side effects required the use of a lower dosage of neratinib in D134, this was true for all patients, whether or not they carried the mutation, and the effects of treatment on cancer were determined at this dosage. However, at this lower dosage, neratinib is shown to be less effective for treating cancer patients with a claimed EGFR mutation than with a wild type EGFR.

9. Post-published document D132, on the other hand, shows that lapatinib, another EGFR-TKi inhibitor, is a better inhibitor of wild type EGFR (EGFR-wt) than of EGFR-L858R mutant (page 1748, right-hand column, first paragraph). Although document D132 states that limited clinical studies with lapatinib in patients with advanced NSCLC demonstrate a low response rate of 3% in unselected patients suggestive of the low utility of this compound for this disease (see document D132, *ibidem*), the board considers that this does not detract from the fact that lapatinib has been shown to be less effective, or ineffective, in inhibiting EGFR-TK and in treating cancer in patients with a nucleic acid mutation according to claim 1(b) or (c), compared to patients who do not have such a mutation.

10. According to documents D72 and D132, lapatinib preferentially binds to an inactive rather than an active enzyme conformation (D72, page 1, first paragraph, penultimate sentence; D132, page 1748,

right-hand column, first full sentence). Moreover, the *in vitro* inhibitory results obtained for EGFR-TKis presented in D50 also cast serious doubts on the method according to claim 1 as regards lapatinib and the L858R mutation. Document D50 shows that the half maximal inhibitory concentration of lapatinib, required to inhibit the activity of EGFR by 50%, is higher for EGFR-L858R than for EGFR-wt, whereas the opposite is true for another EGFR-TKi, gefitinib (Table 3 of D50). Similar results are reported in D72 (Table 2) for lapatinib in comparison with another EFGR-TKi, erlotinib, and the authors of D72 conclude that "*[G]iven their resistance to lapatinib and Cetuximab, there appears to be little rationale for the use of these agents in non-small cell lung cancer containing L858R and Δ746-750 EGFR mutations whereas erlotinib's clinical benefit in these cases is readily understood*" (document D72, bridging paragraph, page 6 and 7).

11. The respondents' view, relying on D101, that the *in vitro* experimental data presented in documents D50 or D72 cannot be extrapolated to *in vivo* data is not shared by the board. Although documents D50 and D72, admittedly, only provide *in vitro* results concerning lapatinib and no conclusions can be drawn with certainty about *in vivo* effects, the board observes that to establish an insufficiency of disclosure the provision of serious doubts substantiated by verifiable facts suffices. No certainty is required. Hence, in the absence of evidence to the contrary, there is no reason why the *in vitro* evidence should not reflect *in vivo* situations. In fact, the *in vitro* results obtained for gefitinib are confirmed by the *in vivo* data in the patent application: see *in vitro* results in Example 1, paragraphs [0269] and [0270]; Figure 3A to 3D; Example

2, paragraph [0271] last sentence; Example 3F, paragraph [0301]; see *in vivo* results in Example 1, paragraphs [0266] and [0267] and patient 6 of Tables 1 and 2 on pages 126 and 127 (see also paragraph [0085] for Table 2). There is thus no reason to doubt that the same would apply to lapatinib too. Respondents' further argument that D50 does not demonstrate that the correlation between the claimed mutations and responsiveness to EGFR TKi treatment is generally incorrect is also not persuasive. It is sufficient that it shows that at least one embodiment falling under the scope of protection of claim 1 is not working.

12. Regarding respondents' argument that the method according to claim 1 does not require a 100% response rate and does not have to be equally effective for all responders undergoing treatment, the board observes that claim 1 allows for different degrees of enhanced sensitivity, i.e. any gradation in the amount of increased susceptibility of cancers attributable to the different claimed mutations, thereby indicating an increased likelihood of effectiveness of EGFR tyrosine kinase inhibitor for the treatment of cancer compared to cancers with wild-type EGFR. However, this increased sensitivity must be observed for each EGFR-TKi employed.

13. Hence, while there are studies showing the responsiveness of cancer patients with specific EGFR kinase domain-activating mutations to EGFR-TKi treatment (D108, page 630, right column, first full paragraph, cited in D101, section 19), there are nevertheless isolated patients or a handful of patients for which the likelihood of effectiveness of some EGFR-TKis in treating their cancer comprising the claimed mutations is not increased. These are not minor,

insignificant or marginal embodiments within the claimed scope of protection that can be disregarded. Whether other EGFR-TKis were or could be further clinically developed to treat cancer patients identified by the claimed key mutations is irrelevant, because the claim encompasses all possible EGFR-TKis, including lapatinib and neratinib. Similarly, it is immaterial whether *in vivo* experiments in both the patent application and the prior art (D110, abstract) predict that there is an increased responsiveness to EGFR-TKis in other embodiments of the claim, such as the G719X and L861Q mutations.

14. Documents D134, D132, D50 and D72 thus provide serious doubts based on verifiable facts that there is no increased therapeutic effectiveness of EGFR TKis in patients affected with cancer comprising at least one mutation as set out in claim 1. Some TKis, such as lapatinib or neratinib, do not have or have a lower effect on such patients in comparison with patients comprising a wild type EGFR. Hence, the subject-matter of claim 1 of the main request is not sufficiently disclosed (Article 83 EPC).

Auxiliary requests

15. Since the method of claim 1 of the first auxiliary request is identical to claim 1 of the main request, the same rationale and conclusions as set out above for the main request apply to the first auxiliary request as well. Although the method of claim 1 of the second and third auxiliary requests introduce limitations regarding the mutation G719S, while in the third auxiliary request the cancer type of claim 1 is further limited to lung cancer, they all still cover embodiments which, based on the teachings of documents

D134, D132, D72 and D50, cannot achieve the purpose of the method according to claim 1. Thus, for the reasons set out above for claim 1 of the main request, none of the first to third auxiliary requests fulfils the requirements of Article 83 EPC.

16. The sets of claims of auxiliary requests P0 to P3 correspond to the submitted sets of claims of the main request and first to third auxiliary requests. They further specify in claim 1 that the EGFR-TKi is effective in an EGFR targeting treatment in patients in which a nucleic acid variance increases the kinase activity of the EGFR. The board considers that claim 1 of these auxiliary requests still does not exclude non-working embodiments disclosed in document D134 combining neratinib, which is effective in an EGFR targeting treatment in patients in whom the nucleic acid variance G719X increases the kinase activity of the EGFR, with another EGFR activating mutation, such as exon 19 deletion and L858R (see point 8. above, particularly Tables 4, 5 and Figure 2 of D134). Thus, for the reasons set out above for claim 1 of the main request, none of auxiliary requests P0 to P3 fulfils the requirements of Article 83 EPC either.

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:

D. Hampe T. Sommerfeld

Decision electronically authenticated