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Datasheet for the decision of 14 January 2022

Case Number: T 1403/19 - 3.3.08

Application Number: 06720702.7

Publication Number: 1851339

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Language of the proceedings: EN

Title of invention:
Methods and compositions for detecting a drug resistant EGFR mutant

Patent Proprietor:
Memorial Sloan-Kettering Cancer Center

Opponents:
Hoffmann Eitle
Roche Diagnostics GmbH
König Szynka Tilmann von Renesse

Headword:
Method for detecting acquired drug resistance/MEMORIAL SLOAN-KETTERING CANCER CENTER

Relevant legal provisions:
EPC Art. 54, 87(1), 123(3)

Keyword:
Main request - Priority - (no)
Main request and auxiliary request 3 - Novelty - (no)
Auxilliary requests 1, 2 and 4 to 7 - Amendments - Extension beyond the content of the application as filed - (yes)

Decisions cited:
G 0002/98, G 0002/10, G 0001/16, T 0307/05, T 2285/09

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1403/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 14 January 2022

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 4 March 2019 revoking European patent No. 1851339 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman B. Stolz
Members: M. Montrone
A. Bacchin

Summary of Facts and Submissions

I. The appeal lies against the decision of an opposition division to revoke the European patent No. 1 851 339. This patent is based on European patent application No. 06720702.7 published as international patent application WO 2006/086777 (the "patent application").

II. The opposition division was of the view that the main request, and auxiliary requests 2 to 7 were not entitled to priority, and hence, lacked novelty over the disclosure of at least document D22. Furthermore, claim 1 of auxiliary request 1 was held to lack clarity.

III. With their statement of grounds of appeal, the patent proprietor ("appellant") relied on a main request and auxiliary requests 1 to 7, that were all filed during the first instance proceedings. Accordingly, the set of claims in appeal is identical to that dealt with in the decision under appeal.

IV. All three opponents ("respondents I to III", respectively) replied to the appellant's statement of grounds of appeal. The respondents submitted objections under added subject-matter, non-entitlement to priority, and lack of novelty over the disclosure of several documents, including document D22 against the main request. Further objections were submitted against the auxiliary requests under added subject-matter, extension of scope of protection, lack of clarity, insufficiency of disclosure, non-entitlement to priority, lack of novelty and inventive step.

V. In reply, the appellant submitted counter arguments.

VI. In a communication in preparation of the oral proceedings, the parties were informed of the board's provisional, non-binding opinion.

VII. In reply, the appellant submitted further arguments.

VIII. Oral proceedings before the board were held on 14 January 2022 by video conference.

IX. Claim 1 of the main request reads:

"1. An *in vitro* method for detection of an acquired resistance to the therapeutic effects of gefitinib or erlotinib in a subject that is suffering from non-small cell lung cancer, wherein the method comprises the steps of:

a) providing a sample that has been obtained from the subject, and

b) probing the sample with a means for selectively detecting a nucleotide sequence comprising a mutant T at the position corresponding to base 2369 of EGFR cDNA (SEQ ID No: 1);

c) identifying that the base at said position is T;

wherein finding that the mutant form is present indicates that the non-small cell lung cancer is developing acquired resistance to the therapeutic effects of gefitinib or erlotinib, wherein the patient has been treated with gefitinib or erlotinib before the sample has been obtained from the patient, and the patient was responsive to gefitinib or erlotinib when it is first administered".

X. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the feature "*is developing acquired resistance*" has been replaced by "*has developed acquired resistance*".

XI. Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that the feature "*is developing acquired resistance*" has been replaced by "*has an acquired resistance*".

XII. Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the feature "*wherein the non-small cell lung cancer harbors a somatic gain-of-function mutation in the tyrosine kinase domain of EGFR that renders the non-small cell lung cancer sensitive to gefitinib or erlotinib*" has been added.

XIII. Claim 1 of auxiliary request 4 differs from claim 1 of the main request in that the features "*a sample*" and "*is developing acquired resistance*" have been replaced by "*a cancer sample*" and "*has an acquired resistance*", respectively. Furthermore, step c) has been reworded from "*identifying that the base at said position is T*" to "*identifying the presence of the base T at said position*".

XIV. Claim 1 of auxiliary request 5 differs from claim 1 of the main request in that the features "*subject*", "*a sample*", "*finding that the mutant form is present*", and "*is developing acquired resistance*" have been replaced by "*patient*", "*a cancer nucleic acid sample*", "*the presence of the mutant T*", and "*has acquired resistance*", respectively.

XV. Claim 1 of auxiliary request 6 differs from claim 1 of the main request in that the features "*a sample*", "*finding*", and "*is developing acquired resistance*" have been replaced by "*a cancer sample*", "*observing*", and "*has an acquired resistance*", respectively. Furthermore, step c) has been reworded from "*identifying that the base at said position is T*" to "*identifying the presence of the base T at said position*". Lastly, the feature "*wherein the non-small cell lung cancer harbors a somatic gain-of-function mutation in the tyrosine kinase domain of EGFR that renders the non-small cell lung cancer sensitive to gefitinib or erlotinib*" has been added.

XVI. Claim 1 of auxiliary request 7 differs from claim 1 of auxiliary request 6 in that the feature "*non-small cell lung cancer*" has been replaced by "*lung adenocarcinoma or bronchioloalveolar carcinoma*".

XVII. The following document is referred to in this decision:

D22: WO 2006/084058 (published 10 August 2006).

XVIII. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request

Claim construction - claim 1

The claimed method was directed to the determination of an acquired resistance of a non-small cell lung cancer ("NSCLC"), i.e. the detection of at least one cancer cell that was resistant to erlotinib or gefitinib if a specific mutation was present. This mutation was located in the cDNA sequence of the epidermal growth

factor receptor ("EGFR") at a particular position (2369 C → T, "C2369T"). Thus the claimed method provided information at a molecular/cellular level, on whether the tumour comprised cells that "*have developed acquired resistance*" at the molecular level, which indicated inherently that the overall tumour was "*further developing acquired resistance*". This ongoing process of developing drug resistance necessarily resulted in a further tumour growth which was diagnosed. In other words, the method detected acquired resistance before and after the cancer established drug resistance.

Thus, acquired drug resistance of the cancer was a continuum/continuous process that developed in the presence of the C2369T mutation. The term described not a macroscopically observable time point of the cancer, i.e. when tumour progression (relapse) was clinically visible. Rather the method detected acquired drug resistance in NSCLC as such, irrespective of the cancer's state of responsiveness as a whole, based on the detection of the C2369T mutation in the EGFR gene in at least a single cancer cell.

The claimed method aimed at a diagnostic purpose since it screened for the C2369T mutation in cancer samples irrespective of the cancer's response status, while the information provided by the method to the skilled person included prognostic aspects too. Thus the claimed method served a diagnostic and a prognostic purpose.

The method was not directed to the diagnosis of a NSCLC patient's (future) status, but to the current status of a cancer sample at the molecular/cellular level. This sample was defined in that it was obtained from NSCLC

patients that were treated with gefitinib or erlotinib, and were initially responsive to these drugs.

The sample cited in claim 1 in which the C2369T mutation was detected was necessarily a tumour sample. The use of non-cancer samples in the claimed method was excluded because that was not a sensible claim interpretation.

Priority entitlement

The priority document (US 60/652488) disclosed the predictive character of the claimed method in the title which read "*Cancer Relapse Prognosis by Detection of an EGFR Mutant Resistant to Certain Therapies and Methods for Designing New Therapies*". A title of a document referred to the document as a whole. Thus the title of the priority document was not isolated from the remaining content of the document. The priority document disclosed in the summary of the invention (see page 1, last paragraph) that the C2369T mutation (i.e. the T790M mutation in the corresponding amino acid sequence of EGFR) was responsible for causing the drug resistance. This mutation emerged during the treatment with the two drugs cited in claim 1 and enabled a search for a more effective therapy. The finding that the cancer was no longer responsive against the drugs implied that a relapse emerged, i.e. an event that was predictable. The detection of therapy resistant mutants as cited in the title allowed an intervention before a relapse occurred which improved the patient's therapy.

The priority document further disclosed the diagnostic purpose of the claimed method, i.e. the identification of the C2369T mutation as the underlying cause for detecting cancer resistance to the therapeutic agents

referred to in claim 1 (see page 1, first paragraph, and page 2, first paragraph). The terms "*diagnostic kit*" or "*diagnosing*" were explicitly mentioned (see e.g. priority document, page 5, line 6, and page 7, second and third paragraphs). The C2369T mutation was detected by "*methods known per se*" or "*various methods*" as indicated on page 2, second paragraph, and page 4, third paragraph of the priority document, i.e. by any means/methods suitable for this purpose.

A further indication that the patent and the priority document related to the same invention was that the objective problem and its solution were identical in both documents.

The problem to be solved by the claimed invention was the provision of a diagnostic method for identifying the cause of an acquired resistance in cancer treated with gefitinib or erlotinib, which allowed the therapy's optimisation.

The priority document disclosed that the C2369T mutation that emerged during drug treatment (i.e. the T790M mutation in the corresponding amino acid sequence of EGFR) was responsible for causing the drug resistance (see page 1, last paragraph, and page 18, fifth paragraph). Furthermore, the priority document disclosed that resistant tumours exhibited a selective advantage over non-mutated tumour cells. This at least implicitly disclosed that resistance formation and relapse was correlated, which necessarily allowed an early identification of patients becoming resistant to the treatment (see page 4, second paragraph).

The formation of resistance as an ongoing process, i.e. a continuum, was derivable from page 4, second

paragraph and page 18, fifth paragraph of the priority document that disclosed the use of the present tense in the expressions "*cancer that acquire clinical resistance*", and "*the T790M mutation is associated with lesions that progress*" (emphasis added).

Further evidence that the C2369T mutation indicated that the cancer was developing acquired resistance was derivable from the patients' case reports disclosed on pages 16 to 18 of the priority document (see Example 5). The patients were screened for this mutation before and during the therapy. It was found that the copy number of the C2369T mutated allele increased over time, in particular in patient 1, who further showed a fairly low copy number of the mutation (see page 18, second and fifth paragraph, Figure 2A). This observation directly and unambiguously disclosed the skilled person that a finding of the C2369T mutation indicated that the cancer was developing drug acquired resistance.

Novelty

Since the method of claim 1 was entitled to priority, document D22 was no prior art and had to be disregarded for assessing novelty of the claimed subject-matter.

Auxiliary request 1

Extent of protection

Claim 1 of auxiliary request 1 differed from claim 1 as granted in that the feature "*the non-small cell lung cancer is developing acquired resistance*" was replaced by "*the non-small cell lung cancer has developed acquired resistance*".

Claim 1 as granted was directed to a diagnostic and a prognostic method that detected acquired resistance before and after a cancer's drug resistance was established. This was implied by the term "*is developing acquired resistance*" which indicated that drug resistance has developed in a cancer because a single mutated cell was found, and that this process continued until the whole tumour was drug resistant.

The feature "*has developed acquired resistance*" in claim 1 of auxiliary request 1 implied that the cancer's drug resistance has developed, a process which likewise continued into the future. The term "*has developed*" in this context did not mean that the cancer was fully resistant, since drug resistance was an ongoing process that lasted until all cells of the tumour proliferated in the presence of the therapeutic agents.

The method of claim 1 of auxiliary request 1 thus related to the detection of a subset of drug resistant cancers that were fully encompassed by the cancers cited in claim 1 as granted that were "*developing acquired resistance*". Amended claim 1 did not encompass subject-matter that was not encompassed by claim 1 as granted, because the claimed method was limited compared to that of claim 1 as granted.

XIX. The respondents' submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request

Claim construction - claim 1

The claimed method related to a method of predicting tumour resistance to the therapeutic effects of gefitinib or erlotinib by identifying the C2369T mutation. This construction of claim 1 was derivable from the functional feature wherein "*the cancer is developing acquired resistance*", in line with claim 20 as filed. A prediction related to a future event. Thus claim 1 related to the detection of a patient/cancer developing acquired resistance, i.e. of a not yet established drug resistant state.

It was incorrect that the claimed method related to the detection of acquired resistance as such, i.e. irrespective of the cancer's drug responsiveness, once sub-clones of cells carrying the C2369T mutation emerged. Such an interpretation had no basis in claim 1, since (single) drug resistant cell(s) were not mentioned in claim 1, but NSCLC, i.e. cancer as such. Moreover, if the sample mentioned in claim 1 comprised a single cancer cell only, it was technically not feasible to detect a "*developing acquired resistance*", because a single cancer cell was either drug resistant or not, depending on the presence/absence of the C2369T mutation in the EGFR gene. Thus, the sample cited in claim 1 had to be a bulk tumour.

According to the appellant's interpretation there was no difference between an acquired resistance, and a developing acquired resistance, with the consequence

that the term "*developing*" in the claim was redundant. However, a cancer that was developing acquired resistance implied that the drugs still achieved a therapeutic effect, i.e. the cancer was not yet drug resistant. Therefore the feature that the cancer "*is developing acquired resistance*" in claim 1 pointed to a future event, which implied that the claimed method had a predictive character. Contrary thereto, a method that detected a cancer that had developed or had an acquired resistance implied that the drugs achieved no longer a therapeutic effect, i.e. the cancer was drug resistant. Since the finding of the C2369T mutation in such a cancer sample explained retroactively the established drug resistance, a method detecting this property had a diagnostic character.

Priority entitlement

The priority document (US 60/652488) did not disclose the following features of claim 1:
(i) the patient group from where the sample was obtained,
(ii) a prognostic purpose, i.e. the detection of a developing acquired drug resistance,
(iii) a generic sample to be analysed, and
(iv) generic means for detecting the mutation.
Thus, the claimed method was not the same invention as that disclosed in the priority document within the meaning of Article 87(1) EPC. Consequently, the claimed method was not entitled to priority, and it's effective date was thus the patent's filing date, i.e. 13 February 2006. Thus the so-called "gold standard" test was not fulfilled in this case.

Novelty

The disclosure of document D22 anticipated the claimed method, for example, in paragraphs [0013], [0029], [0035] to [0037], claims 1, and 11 (Article 54(3) EPC).

Auxiliary request 1

Extent of protection

The feature "*is developing acquired resistance*" in claim 1 as granted was a technical feature that limited the claim's scope of protection. This feature implied that the method was directed to a prognostic purpose since the cancer's drug resistance was not yet established.

In claim 1 of auxiliary request 1 this feature had been replaced by "*has developed acquired resistance*". The method of amended claim 1 comprised thus the detection of drug resistant NSCLC samples, i.e. of cancers with an established drug resistance. Since the underlying cause of an established drug resistance was assessed, the method of claim 1 of auxiliary request 1 had a diagnostic purpose. Such a method was not encompassed in claim 1 as granted, which detected cancers that were developing acquired drug resistance, i.e. cancers with a not yet established drug resistance.

The amendment in claim 1 therefore shifted, and hence extended the scope of protection, contrary to Article 123(3) EPC.

XX. The appellant 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 the basis on one of auxiliary requests 1 to 7.

XXI. The respondents requested that the appeal be dismissed.

Reasons for the Decision

Main request

Claim construction - claim 1

1. Claim 1 of the main request is directed to an *in vitro* method for detection of an acquired resistance to the therapeutic effects of gefitinib or erlotinib in a subject that is suffering from non-small cell lung cancer ("NSCLC").

1.1 Thus, claim 1 defines a purpose-limited *in vitro* method aiming at the detection of a property ("*acquired resistance*") to certain therapeutic agents ("*gefitinib*" or "*erlotinib*") in individuals of a specified patient group (suffering from NSCLC).

1.2 The term "*acquired*" in connection with "*resistance*" as cited in claim 1 inherently implies that the patients are initially responsive to the treatment, but become resistant against the drugs gefitinib or erlotinib at an unknown time point during the therapy. Acquired drug resistance relates thus to a new property that describes a status.

1.3 The purpose of claim 1 is achieved by process steps (a) to (c). In particular, as set out in step (b), by probing a sample with any means for selectively detecting a mutation in the cDNA sequence (SEQ ID NO: 1) of the epidermal growth factor receptor (EGFR) at a

particular position (2369 C → T, "C2369T"). This nucleotide exchange substitutes the wild-type amino acid threonine (T) by methionine (M) at position 790 ("T790M") in the corresponding protein sequence of EGFR (see patent application, page 2, lines 11 to 14).

1.4 The term "*sample*" in steps a) and b) of claim 1 is not defined. Accordingly, the steps encompass the use of NSCLC patient-derived samples of any size and origin, including cancerous and non-cancerous material. A single cancer cell, however, is excluded from the "*sample*" of claim 1 since a single cell has an acquired drug resistance or not by either carrying the mutation or not, respectively. Consequently, a single tumour cell cannot develop drug resistance as mentioned in claim 1, since this requires a sample comprising more than one tumour cell. The appellant argued that the term "*sample*" in claim 1 did not encompass non-cancerous material, since this was not a technical sensible interpretation of the claim. The board does not agree. The term "*sample*" in the absence of any further definition encompasses any material obtained from a patient, including for example, cell-free blood plasma samples that contain DNA. Although such a cell-free sample is non-cancerous, the DNA that it contains might carry a C2369T mutation indicative of an acquired drug resistance, which makes it suitable for the claimed method.

1.5 The samples are obtained from a NSCLC patient group that is defined by (i) a treatment scheme (all pretreated with the drugs), and (ii) response characteristics (all initially drug responsive). The time point of sampling and probing is not defined in claim 1, except that the drug treatment of the patients must have started. Accordingly, the method of claim 1

encompasses sampling and probing at any time during the treatment, i.e. early or late, while the cancer in the patients is still drug responsive.

1.6 Likewise the term "*means*" in step b) of claim 1 is not further defined. Accordingly, the step comprises the use of any suitable means for probing a nucleotide sequence for the presence of the C2369T mutation. The nucleotide sequence analysed comprises DNA and RNA.

1.7 Claim 1 further states that the finding of the mutation C2369T "*indicates that the non-small cell lung cancer is developing acquired resistance to the therapeutic effects of gefitinib or erlotinib*" (emphasis added), and specifies that the method is performed on samples obtained from gefitinib or erlotinib-treated patients, that were initially responsive to these drugs.

1.8 According to the appellant, an acquired drug resistance of a cancer was a continuous process that started when in a sample in at least one cancer cell the C2369T mutation emerged. The persistent selection pressure on the cancer by the administered drugs had the effect that drug sensitive cells within a tumour died, while drug resistant tumour cells continuously propagated. At the end of this process the whole tumour was drug resistant, i.e. all tumour cells propagated in the drug's presence. Thus, the claimed method provided information on whether the tumour comprised cells that "*have developed acquired resistance*", which inherently indicated that the overall tumour was "*developing acquired resistance*". This development of a steadily increasing drug resistance was diagnosed which was accompanied by a tumour size that initially shrunk until it started to grow again. Accordingly the feature that the cancer "*is developing acquired resistance*" in

claim 1 indicated that the method had diagnostic and predictive aspects.

1.9 The board does not agree. The feature the "*cancer is developing acquired resistance*" in claim 1 is a functional feature that relates to and further specifies the method's purpose set out above in point 1.1. Thus, this feature limits the purpose of the claimed method to the detection of a developing acquired drug resistance in a sample obtained from a NSCLC patient. The detection of a tumour with a developing drug resistance implies that the tumour's acquired drug resistance is not yet established, and hence, that the tumour is still responsive to the therapeutic agents indicated in claim 1. The detection of a tumour with such a drug resistance is different from the detection of a tumour characterised by an acquired, i.e. established drug resistance, where the tumour, i.e. not only a single cell thereof, is no longer drug responsive.

1.10 It is likely that a tumour with a developing acquired drug resistance becomes drug resistant in the future. Therefore, since the method according to claim 1 is directed to the detection of a new situation which was not present *ab initio*, the board agrees with the opposition division's finding in the decision under appeal that the overall purpose of the claimed method is a predictive one.

1.11 The appellant submitted that the claimed method has a diagnostic as well as a predictive character.

1.12 The board does not agree. It is uncontested that a diagnostic test is generally used for identifying a disease/condition or its underlying cause, while a

prognostic method is generally directed to a prediction of a likely development of a disease/condition, and of a treatment's outcome. For the reasons outlined above the method of claim 1 is not directed to the detection of NSCLC with an acquired drug resistance by screening samples for the presence of the C2369T mutation as a molecular marker, but to the detection of NSCLC with a developing acquired drug resistance based on the detection of this molecular marker. Since claim 1 explicitly defines that an acquired drug resistance is developing in NSCLC, the molecular marker C2369T in the claimed method is not used for identifying the underlying cause of the acquired drug resistance in NSCLC, but to predict a likely development/outcome.

1.13 In summary, the claimed method is directed to the detection of a developing (i.e. not yet established) acquired drug resistance (to the therapeutic agents gefitinib or erlotinib) of NSCLC in samples obtained from a specific patient group (as defined in the claim) through the screening for a marker mutation (C2369T) in the gene encoding EGFR.

Substantive entitlement to priority

2. It is contested between the parties whether or not the invention as defined in claim 1 as a whole (see point 1.13 above) is the same invention as that disclosed in the priority document (US 60/652488) within the meaning of Article 87(1) EPC. It was particularly contested whether the detection of a developing acquired drug resistance is disclosed in the priority document.

3. In opinion G 02/98 (OJ 2001, 413) it was established that the "*requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC,*

means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole" (see headnote). Furthermore, with the aim to apply a uniform concept, the disclosure as the basis for the right of priority and as the basis for amendments in an application have to be interpreted in the same way (as also confirmed in decisions G 2/10, point 4.6 of the reasons, in OJ EPO 2012, 376 and G 1/16, point 17. of the reasons, in OJ EPO 2018, A70).

4. The appellant submitted that the priority document disclosed the predictive character of the claimed invention already in the title which states "*CANCER RELAPSE PROGNOSIS BY DETECTION OF AN EGFR MUTANT RESISTANT TO CERTAIN THERAPIES AND METHODS FOR DESIGNING NEW THERAPIES*", in combination with the summary of the invention (see page 1, last paragraph). A further indication that the patent and the priority document related to the same invention was that the objective problem and its solution were identical in both documents. Further support that a finding of the C2369T mutation indicated that the cancer was developing acquired resistance was derivable from the patients' case reports disclosed on pages 16 to 18 (see Example 5) of the priority document.

4.1 The board does not agree. Although the title of the priority document mentions "*CANCER RELAPSE PROGNOSIS*" that is based on the "*DETECTION OF AN EGFR MUTANT RESISTANT TO CERTAIN THERAPIES*", there is no functional link between this title, and the remaining disclosure of the priority document, which instead focuses on the

detection of an EGFR mutant "*to determine the cause for resistance to the treatment with certain EGFR inhibitors*" (see e.g. page 1, first paragraph, and page 2, line 1). In other words, the priority document relates to the provision of a diagnostic method (see e.g. page 1, fourth paragraph, page 4, last paragraph, page 7, second paragraph of the priority document). There is also no link to the specific method of claim 1. The priority document, except for the title, does not mention the term prognosis, or another related term that directly and unambiguously implies a prognostic/ predictive purpose.

4.2 Nor is a predictive/prognostic purpose of the claimed invention derivable from page 1, last paragraph of the priority document which states: "*In patients with tumors bearing gefitinib- or erlotinib-sensitive EGFR mutations, resistant subclones containing an additional EGFR mutation emerge in the presence of drug*", and from "*the T790M mutation confers resistance to EGFR mutants usually sensitive to either gefitinib or erlotinib. This new mutant guides the search for a more effective therapy against a specific subset of lung cancers or any other cancers where the T790M mutation in EGFR confers resistance to therapy*".

4.3 Contrary to the appellant's view, no prediction about a relapse is directly and unambiguously implied by the observation that resistant subclones emerge during the therapy. At best this provides the reason why these patients are drug resistant. The second statement mentioned above refers to a drug research programme (as implied by the term "*search for*") to find new drugs that are effective against drug resistant tumours due to the presence of the T790M mutation. This, however, is fundamentally different from using this mutation in

a method to identify tumours early during the therapy to identify cancers that will develop an acquired drug resistance.

4.4 As mentioned above, a diagnostic test is generally used for identifying a disease/condition or its cause, while a prognostic method is directed to a prediction of a likely development of a disease/condition, and of a treatment's outcome.

4.5 The other parts of the priority document provide ample disclosure for a diagnostic use of the C2369T mutation as molecular marker in determining the underlying cause of progressive, and hence, drug resistant lung cancer. However, the priority document is silent on any predictive use of this marker for the purpose indicated in claim 1. In particular, a direct and unambiguous disclosure is missing in the priority document for a method that identifies NSCLC in samples, for example, early during a patient's therapy, that are "*developing acquired resistance*" to gefitinib or erlotinib, i.e. a tumour stage that is still drug responsive.

4.6 Rather the priority document mentions consistently, for example, on page 1, fourth paragraph that: "*there is a need in the art for new compounds that are able to treat patients that show cancer progression or relapse despite initial response to current EGFR inhibitors. Moreover, there is a need in the art for the determining the underlying causes of such resistance so that a diagnostic test can be developed and more customized treatment can be delivered*" (emphasis added). The method disclosed in the priority document therefore determines the cause of an already established acquired drug resistance in a tumour for diagnostic purposes, i.e. the detection of a non-

responsive tumour stage usually observed later during the therapy.

4.7 The appellant referred further to Example 5 on pages 16 to 18 of the priority document. However, this working example reports on studies of "*identified secondary EGFR mutations in three of six individuals whose disease progressed on either gefitinib or erlotinib (Table 1)*" (emphasis added). Accordingly, all patients reported in Example 5 are suffering from progressing tumours, i.e. drug resistant tumours, and not tumours that are developing drug resistance.

4.8 The priority document further mentions in Example 5 on page 18, at the end of the second paragraph "*that a subclone of cells harboring these mutations emerged during drug treatment*", and on page 18, at the end of the fifth paragraph that "*at least in patients 1 and 2, the subclones of tumor cells bearing this mutation probably emerged between the time of initial treatment with a tyrosine kinase inhibitor and the appearance of drug resistance*".

4.9 While the emergence of resistant tumour subclones during the treatment in Example 5 of the priority document explains the cause of an acquired drug resistance, a disclosure is missing that necessarily implies a use of this finding in a method for detecting tumours with a not yet established acquired drug resistance.

4.10 Example 5 of the priority document further mentions that a tumour sample obtained from patient 1 having an established acquired drug resistance shows an increased copy number of mutated alleles. However, this observation does not necessarily imply that these

alleles are used for identifying tumours characterised by a developing acquired drug resistance.

4.11 Consequently, the claimed method is not entitled to priority rights, and the effective date for assessing novelty is the patent's filing date, i.e. 13 February 2006. As a consequence, document D22 is prior art for the assessment of novelty.

Novelty

5. The appellant has not contested that the method of claim 1 lacked novelty over the disclosure of document D22, if the priority of the claimed method was not valid.

6. In the absence of any arguments of the appellant, the board has no reason to overturn the opposition division's finding that the method of claim 1 lacks novelty over the disclosure of document D22. Thus, the main request contravenes Article 54 EPC.

Auxiliary requests 1 and 2

7. Claim 1 of auxiliary requests 1 and 2 differs from claim 1 of the main request in that the feature "*is developing acquired resistance*" has been replaced by "*has developed acquired resistance*" or "*has an acquired resistance*", respectively.

Claim construction - claim 1

8. The methods of claim 1 of auxiliary requests 1 and 2 are *inter alia* defined by the functional features "*has developed acquired resistance*" and "*has an acquired resistance*", respectively. In essence both of these

features have the same meaning, since they refer to the identification of tumours in NSCLC patients characterised by an established acquired drug resistance. Thus, the methods detect tumours that are no longer responsive to the therapeutic effects of gefitinib or erlotinib. Since the finding of the C2369T mutation provides the underlying reason for this drug resistance, both methods have a diagnostic character.

9. For the reasons outlined above, the method of claim 1 of the main request has a predictive character since it detects a developing acquired drug resistance in tumours, i.e. a not yet established drug resistance.

10. The appellant submitted that the process of a developing drug resistance in a tumour as referred to in claim 1 of the main request encompassed the detection of cells in a tumour that were drug resistant due to the emergence of the C2369T mutation in the past, while the tumour as a whole was still drug responsive, until the state when drug resistance of the tumour was established. In other words, the feature "*is developing acquired resistance*" in claim 1 of the main request encompassed the detection of an acquired drug resistance in a tumour based on using the C2369T mutation as molecular marker from the beginning of the resistance until it was established.

Since the methods of auxiliary requests 1 and 2 detected an established acquired drug resistance only, the amendment in fact limited the methods compared to claim 1 of the main request.

11. The board does not agree. According to the claim construction set out above for the main request, the functional feature "*the non-small cell lung cancer is*

developing acquired resistance" excludes the detection of an established acquired resistance in NSCLC, because it defines that this property is still developing. Thus, this functional feature does not encompass the whole development of a tumour's acquired drug resistance from the emergence of a C2369T mutation in at least a single cell until the tumour is no longer drug responsive.

Extent of protection

12. The appellant submitted that the functional feature "*has developed acquired resistance*" in claim 1 of auxiliary request 1 did not extend the protection conferred but rather limited it.

12.1 The board does not agree. Article 123(3) EPC requires that the claims of a patent as granted may not be amended during opposition/appeal proceedings in such a way as to extend the protection conferred. In order to assess whether an amendment of the patent satisfies that requirement, it is necessary to compare the protection conferred by the claims as granted, with that of the claims after amendment. A very rigorous standard, namely that of "beyond reasonable doubt" is to be applied when checking the allowability of amendments under Article 123(3) EPC (see e.g. T 307/05, points 3.3 and 3.4 of the reasons and T 2285/09, point 3.1 of the reasons), such that the slightest doubt that the scope of the patent as amended could cover embodiments not covered by the unamended patent would preclude the allowability of the amendment.

12.2 In the present case, in view of the construction of claim 1 of auxiliary request 1 (which equally applies to claim 1 of auxiliary request 2) for the reasons

indicated above, the claimed method defines a purpose (the detection of an established acquired drug resistance in NSCLC), which is excluded from the detection of a "*developing acquired resistance*" in NSCLC.

12.3 The method of claim 1 as granted likewise mentions that the finding of the C2369T mutation in a sample obtained from a subject having lung cancer "*indicates that the cancer is developing acquired resistance*". In other words, the method of claim 1 as granted (like that of the main request) is directed to the detection of a developing acquired drug resistance in cancer.

13. Therefore, the methods of claims 1 of auxiliary requests 1 and 2 encompass subject-matter (detection of an established acquired drug resistance) that is excluded from the method of claim 1 as granted.

14. Consequently, in applying the rigorous standards mentioned above, the board concludes that the amendments in claims 1 of auxiliary requests 1 and 2 shift, and thereby extend, the scope of protection conferred, contrary to the requirements of Article 123(3) EPC.

Auxiliary request 3

15. Claim 1 of auxiliary request 3 differs from claim 1 of the main request solely in that the feature "*wherein the non-small cell lung cancer harbors a somatic gain-of-function mutation in the tyrosine kinase domain of EGFR that renders the non-small cell lung cancer sensitive to gefitinib or erlotinib*" has been added.

16. The amendment in claim 1 only limits the method of claim 1 of the main request to the extent that the tumour of the NSCLC-type comprises explicitly a somatic gain-of-function mutation in the EGFR which renders the tumour sensitive to gefitinib or erlotinib. However, this limitation is considered implicit in the method of claim 1 of the main request since without that gain-of-function mutation patients affected by NSCLC are non-responsive to a treatment with gefitinib or erlotinib (see patent, paragraph [0002]). Therefore, the methods of claim 1 of auxiliary request 3 and of claim 1 of the main request are in fact identical.

17. Consequently, the objections under lack of priority entitlement (Article 87(1) EPC) set out above for the method of claim 1 of the main request equally apply to the method of claim 1 of auxiliary request 3.

18. Since, moreover, the appellant has not contested that the claimed method lacks novelty over the disclosure of document D22, if the priority of the claimed method is not valid, auxiliary request 3 contravenes Article 54 EPC.

Auxiliary requests 4 to 7

19. As set out above under sections XIII to XVI, the method of claim 1 of auxiliary requests 4 to 7 is *inter alia* defined by the functional features "*has an acquired resistance*" (see auxiliary request 4, 6 and 7), or "*has acquired resistance*" (see auxiliary request 5). In other words, an established acquired drug resistance.

Extent of protection

20. Since for the reasons outlined above under auxiliary requests 1 and 2, the detection of an established acquired drug resistance is excluded from the method of claim 1 as granted, the methods of claims 1 of auxiliary requests 4 to 7 likewise shift, and thereby extent the scope of protection conferred by the patent as granted, contrary to the requirements of Article 123(3) EPC.

21. In the absence of an allowable set of claims, the appeal has to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated