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Case Number: T 0208/17 - 3.3.08

Application Number: 08742061.8

Publication Number: 2121989

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Language of the proceedings: EN

Title of invention:
K-ras mutations and anti-EGFR antibody therapy

Patent Proprietor:
Amgen Inc.

Opponent:
Strawman Limited

Headword:
Prognostic method for panitumumab/AMGEN

Relevant legal provisions:
EPC Art. 56, 83, 123(2)

Keyword:
Auxiliary request 3 - requirements of the EPC met - (yes)
Disclaimer - requirements of Article 123(2) EPC met - (yes)

Decisions cited:
G 0001/03, G 0001/07, T 1599/06, T 1506/13

Catchword:

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0208/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 8 July 2021

Appellant I: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320-1799 (US)
Representative:	Wenke-Vogelsang, Heike Seisenberger, Georg Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstraße 4 80802 München (DE)
Appellant II: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe Witney, Oxfordshire OX29 8NH (GB)
Representative:	Desaix, Anne Ernest Gutmann - Yves Plasseraud S.A.S. 66, rue de la Chaussée d'Antin 75009 Paris (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 25 November 2016 concerning maintenance of the European Patent No. 2121989 in amended form.**

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 maintain the European patent No. 2 121 989 in amended form. The patent was filed under the PCT and published as international patent application WO 2008/112269 (hereinafter the "patent application").

II. The opposition division considered the main request and auxiliary request 2 to contravene Article 123(2) EPC and auxiliary request 1 to contravene Article 53(c) EPC, while auxiliary request 3 was held to fulfil the requirements of the EPC.

III. With its statement of grounds of appeal, the patent proprietor (hereinafter "appellant I") submitted auxiliary request 1 to 3 which correspond to the respective sets of claims dealt with in the decision under appeal.

IV. With its statement of grounds of appeal, the opponent (hereinafter "appellant II") submitted arguments under added subject-matter, sufficiency of disclosure and inventive step.

V. In their replies, both appellants provided counter-arguments for the arguments submitted by the other party.

VI. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's provisional, non-binding opinion.

VII. In reply, the appellant I provided further arguments on inventive step, while appellant II announced that they would not attend the oral proceedings.

VIII. Oral proceedings before the board were held on 8 July 2021, in the absence of appellant II as announced. At the end of the oral proceedings, appellant I withdrew the main request and auxiliary requests 1 and 2.

IX. Claims 1 and 4 of auxiliary request 3 read as follows:

"1. An *in vitro* method of predicting whether a patient suffering from colorectal adenocarcinoma will be nonresponsive to treatment with panitumumab, comprising determining the presence or absence of a K-ras mutation in a tumor of said patient, wherein the K-ras mutation is selected from G12S, G12V, G12D, G12A, G12C, and G13D; and wherein if a K-ras mutation is present, the patient is predicted to be nonresponsive to treatment with panitumumab.

4. A method of predicting whether a tumor from colorectal adenocarcinoma will be nonresponsive to treatment with panitumumab, comprising determining the presence or absence of a K-ras mutation in a sample of said tumor, wherein the K-ras mutation is selected from G12S, G12V, G12D, G12A, G12C, and G13D; and wherein the presence of the K-ras mutation indicates that the tumor will be nonresponsive to treatment with panitumumab."

X. The following documents are referred to in this decision:

E2: De Roock W. *et al.*, Journal of the American Medical Association, 2010, Vol. 304(16),

1812-1820;

E5: Easley C. and Kirkpatrick P., Nature Reviews Drug Discovery, 2006, Vol. 5, 987-988;

E6: Mancuso A. *et al.*, Journal of Clinical Oncology, 2010, Vol. 28(36), e756-e758;

E7: Messersmith W.A. and Hidalgo M., Clinical Cancer Research, 2007, Vol. 13(16), 4664-4666;

E9: Molinari F. *et al.*, Clinical Cancer Research, 2011, Vol. 17(14), 4901-4914;

E10: Moroni M. *et al.*, Lancet Oncology, 2005, Vol. 6, 279-286;

E14: Santini D. *et al.*, Journal of Clinical Oncology, 2011, Vol. 29(8), e206-e207;

E19: "Scientific Discussion", EMEA, 2007, Review of panitumumab;

E20: Approval letter for panitumumab (27.09.2006);

E21: FDA Medical Review, Application no. 125147/0;

E23: Eberhard D.A. *et al.*, Journal of Clinical Oncology, 2005, Vol. 23(25), 5900-5909;

E24: Pao W. *et al.*, PLoS Medicine, 2005, Vol. 2(1), e17, 0057-0061;

E25: Lièvre A. *et al.*, Cancer Research, 2006, Vol. 66(8), 3992-3995;

E27: Amado R.G. *et al.*, Journal of Clinical Oncology, 2008, Vol. 26(10), 1626-1634.

XI. Appellant I's submissions, insofar as relevant to the present decision, may be summarised as follows:

Auxiliary request 3

Added subject-matter - claims 1 and 4

The deletion of two K-ras mutations in claims 1 and 4 from a list of eighth as referred to in claim 6 of the patent application did not single-out a new sub-group, but represented a limitation of a single list. Table 2 of Example 1 provided a pointer for the six mutations cited in claims 1 and 4, because one of the deleted mutations was not disclosed in this table, while the other was shown as not being clearly relevant.

The combination of features recited in claims 1 and 4 had a basis in claims 1, 4, 6, and Example 1 (see Table 3 in paragraph [106]) of the patent application. The epidermal growth factor receptor (EGFR) status was not an essential feature missing in these claims. The patent application, including Example 1, did not disclose a link between the claimed prognostic methods and the EGFR status of the tumours.

The introduction of the term "*in vitro*" did not add subject-matter as set out in decisions G 01/07 and G 01/03, since it merely excised subject-matter excluded from patentability under Article 53(c) EPC for non-technical reasons.

Sufficiency of disclosure - claims 1 and 4

Example 1 of the patent application demonstrated that it was credible that the six K-ras mutations in claims 1 and 4 were suitable to predict (non-)responsive colorectal adenocarcinoma patients to a panitumumab treatment. This was further corroborated by the study data disclosed in the post-published document E27. No evidence to the contrary was submitted by appellant II. The subject-matter claimed was also not too broad, since in the absence of evidence that the claimed invention could not be put into practise over the whole breadth of the claim, a reasonable generalisation was allowable. The patent application disclosed the determination of K-ras mutations in tumour samples. A 100% rate in predicting (non-)responsive colorectal adenocarcinoma patients to panitumumab treatment by the claimed methods was not necessary, since it sufficed that the prediction was highly plausible.

Inventive step - claims 1 and 4

Documents E10 or E25 represented the closest prior art for the methods of claims 1 and 4.

Document E25 disclosed the six K-ras mutations cited in claims 1 and 4, but used them as prognostic markers for identifying non-responsive CRC patients treated with cetuximab only. Document E25 confirmed a trend already seen in document E10, namely that K-ras mutations were suitable for identifying CRC patients non-responding to a cetuximab therapy. Document E25 was completely silent on panitumumab, including suggestions about a molecular mechanism underlying cetuximab's activity. Moreover, since the clinical activity of both antibodies was not identical, document E25 provided no suggestions that K-

ras mutations were suitable for predicting panitumumab's response in CRC patients too. Document E25 at best suggested that modified molecules involved in EGFR-signaling affected the response to a targeted EGFR therapy.

The claimed methods differed from document E25 in that K-ras mutations were used as predictive markers for identifying (non-)responsive colorectal adenocarcinoma patients treated by panitumumab, instead of cetuximab. No particular technical effect was associated with this difference.

The technical problem was defined as the provision of further predictive methods for assessing the non-responsiveness of CRC patients/tumours.

The skilled person starting from document E25 had no motivation to investigate the responsiveness of CRC patients treated by panitumumab in relation to their K-ras mutational status. Document E25 was silent on this antibody. Even if the skilled person would have looked into the prior art there was no motivation for assessing the prognosis of a panitumumab therapy since, for example, documents E23 and E24 suggested other therapeutic agents, i.e. there was no one-way street towards panitumumab. Thus, the selection of K-ras as target for predicting the success/failure of a panitumumab treatment based on document E25 alone was obvious with hindsight knowledge of the claimed invention only.

The combination of documents E25 and E10 even taught away from selecting K-ras as predictive marker for a panitumumab therapy of CRC patients. Table 2 of document E10 showed that K-ras was not suitable for

this purpose (K-ras mutations were found in 50% of the responders and non-responders). This differed fundamentally for cetuximab, because Table 2 disclosed that 100% of the responders had a wild-type K-ras gene, while 1/3 of the non-responders carried a K-ras mutation. Thus, document E10 provided solely a motivation for the skilled person to assess K-ras mutations as predictive markers for a cetuximab therapy. This was corroborated by document E25, that as set out above, referred to document E10. Furthermore, document E10 disclosed several marker candidates for predicting a response to panitumumab, i.e. K-ras was not the only one.

Accordingly, the combined teaching of documents E25 and E10 provided no reasonable expectation of success that K-ras mutations could predict a CRC patient's non-responsiveness for a panitumumab therapy. Consequently, the skilled person looking for an alternative method to predict panitumumab's responsiveness, had to overcome a prejudice as regards K-ras. Cetuximab and panitumumab had different structural properties, but also a different clinical activity. In view thereof any conclusion based on analogy between both antibodies was impossible without hindsight. In particular, since the response profiles of both antibodies in relation to K-ras was different as shown in Table 2 of document E10. Also document E7 which stated that both antibodies had "*virtually the same mechanism of action*" provided *a priori* no incentive and an expectation of success, since clinical head-to-head comparisons between both antibodies were lacking. Thus the link between the presence of certain K-ras mutations and a non-responsiveness to panitumumab was hidden in the prior art and its finding accordingly, surprising.

Alternatively, document E10 represented the closest prior art. Even starting from there, the claimed methods were considered non-obvious and to involve an inventive step.

XII. Appellant II's written submissions, insofar as relevant to the present decision, may be summarised as follows:

Auxiliary request 3

Added subject-matter - claims 1 and 4

The six K-ras mutations in claims 1 and 4 were selected from eighth K-ras mutations disclosed in paragraphs [0021], [0074] to [0082], [0106] and claim 6 of the patent application. The deletion of two out of eighth K-ras mutations in claims 1 and 4 provided the skilled person with the information that two K-ras mutations had deviating properties. The remaining six K-ras mutations were thus singled out and formed a new subgroup that was not derivable from the patent application. Table 2 of the patent application did not point to this selection of K-ras mutations. While the deleted mutation G13A was not mentioned in Table 2, the likewise deleted T20M mutation was disclosed in combination with G12V in a panitumumab non-responder. Table 2 provided thus no reason for deleting T20M. Other indications that the G13A and T20M mutations were not suitable for the claimed purpose were not derivable from Example 1 of the patent application. Rather to the contrary, paragraph [0106] mentioned the deleted mutations together with the six K-ras mutations cited in claims 1 and 4. Thus, Example 1 as a whole disclosed that all eighth K-ras mutations were encompassed by the invention defined in the patent application (see paragraphs [0021], [0074] to [0082]). Consequently,

since the deletion of two K-ras mutations departed from the disclosure of the patent application and changed its technical content, the amendment represented an unwarranted advantage contrary to G 01/03.

Furthermore, in claims 1 and 4 the combination of the six K-ras mutations with (i) patients suffering from colorectal cancer/colorectal adenocarcinoma, (ii) the detection of K-ras mutations in a tumor of a patient, and (iii) the presence of the K-ras mutation predicting the patients' non-responsiveness to panitumumab had no basis in claims 1, 4, 6 and Example 1 of the patent application. Example 1 solely disclosed an association between the presence of K-ras mutations and colorectal adenocarcinoma, however, no association between these mutations and the response to panitumumab. A mutation associated with a disease was conceptually different from a mutation associated with a response to a treatment. Example 1 further disclosed tumour samples with a high EGFR expression status only, i.e. a subset of colorectal adenocarcinomas. Furthermore, while Example 1 mentioned partial responders, stable disease and progressive disease, non-responders were not mentioned, and hence not disclosed in the patent application. According to Example 1 the determination of the EGFR status was mandatory for selecting relevant tumours, which implied that the responsiveness to a panitumumab treatment depended on the EGFR status too. Since Example 1 disclosed tumour samples obtained from CRC patients following a particular treatment after their EGFR status has been determined, the omission of an EGFR status in claims 1 and 4 added subject-matter.

Claim 1 was further amended to recite an "*in vitro method*", instead of a "*method*". An *in vitro* method was not disclosed in the patent application, and since it

was not a "*negative*" technical feature, the "*in vitro*" did not comply with the criteria set up in decisions G 1/07 and G 1/03. Its introduction amounted to an intermediate generalisation of the subject-matter disclosed in the patent application.

Sufficiency of disclosure - claims 1 and 4

The methods as defined in claims 1 and 4 were not enabled over the whole range claimed. The patent application disclosed CRC patients with a high EGFR expression level only (see Example 1). Since the source of the tumour samples was not disclosed in Example 1, the skilled person taking into account the indications for which panitumumab has been approved (see documents E19, and E21), would have construed Example 1 to be directed to CRC patients characterised by a metastatic state and a high EGFR expression level, i.e. a subgroup of CRC patients only. The study data in Example 1 of the patent application allowed however, no conclusions about the reliability of the claimed methods. Nor did the patent application demonstrate that non-responsive tumours could be identified by the method of claim 4 at all. Lastly, the patent application did not provide information about tumour sampling, including experimental details about the detection of mutated K-ras polypeptides and polynucleotides, including the type of test to be used for this purpose. In the absence of this information, the development of a test amounted to an undue burden since suitable parameters could be found by trial and error only.

Inventive step

Document E25 represented the closest prior art. The claimed methods differed from document E25 only in that

the K-ras mutational status of colon cancer patients/ samples was used to predict their non-responsiveness to a panitumumab treatment instead of cetuximab. Panitumumab and cetuximab were both anti-EGFR antibodies and approved for the same clinical indication.
Since no technical effect was associated with this difference, the technical problem was defined as the determination of whether known K-ras mutations may be linked to non-responsiveness to a treatment by a different inhibitor of EGFR.
The issue to be assessed in the context of predicting non-responsiveness was whether the features relevant for this prediction were similar between cetuximab and panitumumab.
As set out above, document E25 disclosed the identical features relevant for the prediction, but used a different antibody. However, its teaching was not limited to cetuximab. Document E25 disclosed on page 3992, column 2 that EGFR was activated by an extracellular ligand binding which caused the activation of intracellular effector molecules, including K-ras. Accordingly, in the EGFR signaling pathway the activation of K-ras occurred after (i.e. downstream) of receptor activation. Since the binding of cetuximab blocked the ligand-induced EGFR activation, document E25 proposed as hypothesis that cell activation/proliferation caused by a mutated and permanently active K-ras was no longer significantly inhibited by an EGFR inhibitor, such as cetuximab, that acted upstream of the K-ras. Document E25 taught therefore a relationship between activating K-ras mutations and non-responsive CRC patients towards a cetuximab therapy (see page 3995, column 2, first paragraph). This teaching extended to other anti-EGFR antibodies as shown by the reference in document E25 to

document E10 (see page 3994, column 2, second paragraph), which mentioned in this context that the results were coherent with those reported in document E10. Document E10 assessed the suitability of various molecular markers, including K-ras, for predicting responsive CRC cancer patients to a cetuximab and panitumumab treatment. Thus, document E25 provided an incentive for the skilled person to repeat experiments for finding K-ras mutations that predicted a patient's response to panitumumab. Moreover, the working model in document E25 that described how EGFR controlled K-ras activation together with the known interference of panitumumab upstream of K-ras in this activation pathway provided a clear expectation of success for the skilled person. The fact that cetuximab and panitumumab were structurally different and did not have the same properties but similar ones only, did not disencourage the skilled person to follow this path. These differences affected secondary effects only, for example immunological reactions following the antibodies' administration (see document E7, page 4664, column 2, last paragraph, and document E5, page 988, column 1, last paragraph to column 2). Moreover, both antibodies were approved for treating the same colorectal cancer patients.

XIII. Appellant I requested that the appeal be dismissed.

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

Reasons for the Decision

Auxiliary request 3

Added subject-matter - claims 1 and 4

1. In order to determine whether the subject-matter of a claim extends beyond the content of the patent application against the prohibition of Article 123(2) EPC, it has to be examined whether that claim comprises technical information which a skilled person would not have clearly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, derived from the patent application as a whole (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019, hereinafter "Case Law", II.E.1.3.1).

2. Appellant II raised various objections under added subject-matter against the subject-matter of claims 1 and 4. In a first line of argument, appellant II submitted that the selection of the K-ras mutations "*G12S, G12V, G12D, G12A, G12C and G13D*" cited in these claims was an impermissible singling out of six mutations from a list of eight mutations (see e.g. claim 6 as filed), i.e. represents a specific subset of K-ras mutations, which was not directly and unambiguously derivable from the patent application.

2.1 According to the case law, (see e.g. decision T 1506/13, point 4.2 of the Reasons) a deletion of genes from a list of specific genes is allowable if two conditions are fulfilled: Firstly, the deletion must not result in singling out any hitherto not specifically mentioned individual compound or group of compounds, but maintains the remaining subject-matter as a generic group of compounds differing from the

original group only by its smaller size ("condition 1"). Secondly, the deletion does not lead to a particular combination of features having a specific meaning which was not disclosed originally, i.e. it does not generate another invention ("condition 2").

2.2 The patent application discloses a method of predicting non-responsiveness of colorectal adenocarcinoma patients to a treatment with the anti-epidermal growth factor receptor (EGFR) antibody panitumumab by determining the presence of various K-ras mutations in a tumour sample in individualised form, including the six mutations referred to in claims 1 and 4 (see paragraphs [074] to [078] and [080], claims 1, 4 and 6 as originally filed). Example 1 of the patent application further discloses that for the assessment of a potential association between K-ras mutations and "*colorectal adenocarcinoma ("CRC")*", samples were obtained from CRC patients prior to their treatment with panitumumab (see paragraphs [095] and [096]). Tumour responses in patients are classified as "*progressive disease*" ("*PD*") or "*stable disease*" ("*SD*") which indicate a non-responsive treatment, while a "*partial response*" ("*PR*") counts as a responsive treatment. The response findings are then compared with the presence of genomic K-ras mutations in tumour samples (see paragraphs [084], [102], [103] and Table 2). Table 2 of the patent application discloses that tumour samples with the six K-ras mutations referred to in claims 1 and 4 are found in non-responsive CRC tumours of patients treated with panitumumab. In other words, not the presence of a group of K-ras mutations as a whole indicates the patient's non-responsiveness to the antibody-based therapy, but each mutation independent from the other, i.e. in individualised form.

2.3 In view thereof, condition 1 of the case law (see above) is fulfilled since the deletion of two mutations from a list of eight results merely in a shorter list of equal alternatives in claims 1 and 4. Also condition 2 is fulfilled since the shorter list does not generate a new invention in the sense that the six mutations as a group have a functionality different from that of the individual mutations cited in claim 6 as filed.

3. In a second line of argument, appellant II submitted that the combination of the six K-ras mutations with the other features in claims 1 and 4 was not directly and unambiguously disclosed in the patent application, in particular in Example 1. Appellant II argued in essence in this context that the claimed combination of features has no basis in Example 1 of the patent application, because claims 1 and 4 lack as a feature the specific EGFR status of the tumor patients.

3.1 The board does not agree. In line with the decision under appeal, the combination of features in claims 1 and 4 has a basis in claims 1, 4 and 6 as filed in conjunction with Example 1 of the patent application.

3.2 Example 1 of the patent application reports in paragraphs [095] and [096] that CRC tumour samples are obtained from 37 CRC patients "*prior to patient treatment with panitumumab*" (emphasis added). It is further stated that "*CRC tumor samples from thirty-seven patients were collected. A portion of each tumor sample was stained to identify the amount of EGFr expression of the tumor and rated for staining on a three-point scale (where 3 is the greatest degree of staining). At least 10% of each tumor sample demonstrated a staining level of three*" (emphasis

added). All 37 samples are analysed for the presence/ absence of K-ras mutations in exon 2 (see Tables 1 and 2).

3.3 No indications are derivable from Example 1 or any other passage of the patent application that the patients enrolled in the study, or the samples tested for their K-ras status were selected according to their EGFR status too. On the contrary, the fact that the patients in Example 1 are enrolled in the study prior to the determination of their EGFR status implies that they have been classified as suffering from CRC according to other criteria. Thus, the determination of the EGFR status reported in Example 1 rather serves the purpose of corroborating on a molecular level the prior classification of patients as "CRC". Accordingly, Example 1 of the patent application discloses that there is no inextricable link between the EGF status of a CRC patient and the prediction whether such a patient benefits from a panitumumab treatment. An omission of the EGFR status in claims 1 and 4 does therefore not add subject-matter to the patent application.

4. In a third line of argument, appellant II submitted that the term "*in vitro*" in claim 1 added subject-matter. While this term was introduced to address an objection under Article 53(c) EPC, it was not disclosed in the patent application. Furthermore, the term "*in vitro*" was not a disclaimer that incorporated a "*negative*" feature into the claimed subject-matter according to the criteria set up in decisions G 1/07 and G 1/03. For this reason alone the requirements of Article 123(2) EPC were not fulfilled. Moreover, the term "*in vitro*" resulted in an unallowable intermediate generalisation of the patent application's disclosure.

4.1 The board is not convinced by these arguments. According to G 1/07 and G 1/03, the term "*disclaimer*" describes an amendment to a claim resulting in the incorporation of a "*negative*" technical feature, typically excluding from a general feature specific embodiments or areas (see G 1/07, OJ EPO 2011, 134, point 4.2.1 of the Reasons; G 1/03, OJ EPO 2004, 413, point 2 of the Reasons). Whether this is the case, is to be decided according to the individual circumstances of the case. The term "*in vitro*" in claim 1 excludes any embodiment that might be directed at a removal by surgical means of a tumor sample from a CRC patient, i.e. an *in vivo* method, which otherwise would be encompassed by the claim due to the use of the "*comprising*" language. In other words, the term "*in vitro*", although being positively formulated, relates in fact to a negative technical feature in claim 1.

4.2 Nevertheless, it has to be assessed whether or not the subject-matter remaining in amended claim 1, after excluding a potential *in vivo* process step, complies with the requirements of the EPC, in particular Article 123(2) EPC (see G 1/07, point 4.3.3 of the Reasons). Claim 5 as originally filed is dependent on claim 1 as originally filed (which corresponds to present claim 1) and recites that the K-ras mutation is determined in "*a sample*" of the tumor. The term "*a sample*" necessarily implies that the methods as originally filed are carried out "*in vitro*", i.e. outside of the patient's body on a sample that has been obtained independent from the claimed method. Thus the subject-matter of claim 1 has a direct and unambiguous basis in the patent application.

5. In view of the considerations above, the board concludes that auxiliary request 3 complies with the requirements of Article 123(2) EPC.

Claim interpretation - claims 1 and 4

6. Claim 1 is directed to an *in vitro* method of predicting the non-responsiveness of CRC patients to a panitumumab-based therapy. This purpose is achieved by determining the presence of the K-ras mutations G12S, G12V, G12D, G12A, G12C, and G13D as markers in a tumour sample to identify non-responsive patients. Claim 4 differs therefrom in that the features "*a patient suffering from colorectal adenocarcinoma*" and "*the patient*" are replaced by "*a tumor from colorectal adenocarcinoma*" and "*the tumor*", respectively. In other words, the CRC patient as defined in claim 1 is replaced in claim 4 by the cause of the disease, i.e. the specific tumour.

7. Thus, claims 1 and 4 are directed to an *in vitro* method wherein six specific K-ras mutations in CRC samples serve as predictive markers for identifying CRC patients or CRC samples that are non-responsive to a panitumumab therapy.

8. Panitumumab prevents the binding of epidermal growth factor (EGF) to its receptor (EGFR), which blocks receptor signaling and, hence, the activation and proliferation of CRC tumour cells. Panitumumab is thus an anti-EGFR antibody (see paragraph [007] of the patent application).

Sufficiency of disclosure

9. Appellant II submitted that the methods as defined in claims 1 and 4 cannot be performed across the whole range covered by the claims, because the patent application, in particular Example 1, **did not demonstrate** that:

(i) the technical effect of the claimed methods was credibly/reliably achieved. In other words it was contested that the patent application disclosed evidence that the claimed methods were capable of reliably predicting CRC patients or tumours to be non-responsive to a panitumumab treatment.

(ii) the K-ras mutational status was suitable for predicting non-responsive CRC patients or tumours in general. Example 1 disclosed metastatic CRC patients with a high expression level of EGFR only, i.e. a sub-group of the patient group or tumours defined in claims 1 and 4.

Further, appellant II submitted that the patent application did not provide information on (iii) the detection of mutant K-ras polypeptides or polynucleotides; (iv) the sampling of tumours and their preparation; and (v) the specific detection method to be used. In the absence of this information, the skilled person was unable to perform the claimed methods without undue burden.

10. The board is not convinced by these arguments.

11. As regards appellant II's first line of argument, the case law has established that attaining a claimed technical effect, here the prediction of non-responsive patients/tumours within a group of these patients/ tumours to a particular treatment, is a functional

technical feature of the claim (see Case Law, II.C. 7.2). Thus, in order to comply with the requirements of Article 83 EPC, unless this is already known at the priority date, the patent application taking the skilled person's common general knowledge into account, has to disclose the suitability of the predictive markers (here the specific K-ras mutations) for the claimed effect. This suitability may be proven by any kind of evidence which clearly and unambiguously reflects the technical effect, or at least by a plausible technical concept that allows the skilled person to conclude that the compounds (here markers) are suitable for the claimed effect.

12. Example 1 starting on page 32 of the patent application discloses a study of 37 tumour samples obtained from CRC patients prior to their treatment with panitumumab (see paragraph [095]). Example 1 further reports that a portion of each sample is analysed for EGFR expression, while the rest of the samples are purified, followed by the extraction of genomic DNA, the amplification of exon 2 of the K-ras gene, and the cloning and sequencing of the amplified fragments (see paragraphs [096] to [101]). The sequencing shows that 13 out of 37 tumour samples carry a K-ras exon 2 mutation (see Table 2), which are identical to the six mutations referred to in claims 1 and 4, except for one double mutation.

12.1 Paragraph [0095] of the patent application also mentions that the 37 CRC patients are treated with a specific dosage regimen of panitumumab until disease progression is noted. The tumour response of the patients is assessed according to "*RECIST*" criteria (Response Evaluation Criteria in Solid Tumors), which provide guidelines for classifying the response based on the tumor size. Paragraph [0102] of the patent

application describes that the response is classified as "*complete response*" (CR), "*partial response*" (PR), "*stable disease*" (SD) or "*progressive disease*" (PD) based on the tumour size in the treated patients. A stable or progressive disease implies that the tumour size remains stable or increases, respectively, which indicates that the patients are non-responsive to the panitumumab treatment. While a partial or complete response means that the tumours are smaller or no longer detectable, respectively, which indicates that the patients benefit from the therapy, i.e. are responsive.

12.2 Tables 2, 3 and paragraph [0106] of the patent application disclose *inter alia* that all of the treated CRC patients that carry one of the claimed K-ras mutations show a "*PD*" or "*SD*" tumour response, i.e. are non-responsive to a panitumumab therapy. Thus, a correlation exists between the presence of the claimed K-ras mutations in CRC patients and tumour samples, and their non-responsiveness to panitumumab.

12.3 This correlation establishes a relationship or link between the two events, which in the board's opinion, renders it sufficiently credible that the K-ras mutations cited in claims 1 and 4 are suitable as predictive markers for the claimed purpose.

12.4 Appellant II submitted that the patent application did not contain a discussion "*which would sufficiently disclose a 'fully reliable' step of predicting*" in the sense that the method "*states with certainty that a patient will be nonresponsive*" or "*a more 'weighed' step of predicting*" non-responsiveness. Reference was made to documents E2, E6, E10, E14 and E20 which *inter alia* disclose that single patients with one of the K-

ras mutations cited in claims 1 and 4 nevertheless respond to panitumumab therapy.

12.5 The methods of claims 1 and 4 do not require that the prediction is reliable to the extent of certainty. Since the term "*predicting*" is not defined in both claims, it has a relative meaning. Further, as set out above, to establish compliance with the requirements of Article 83 EPC, the case law does not require certainty either, it suffices that a claimed effect is credible/ plausible in view of the evidence/concept disclosed in the patent application/prior art. Furthermore, single failures to predict non-responsive CRC patients, as disclosed in documents E2, E6, E10, and E14, are not sufficient to establish that the six cited K-ras mutations are not suitable for the claimed purpose, since this failure is not a general observation. Rather the finding of single responders in K-ras mutated patients reflects real life because any biological test is to a certain degree error prone. Document E20 concerns the EMA's approval of treating metastatic CRC patients with panitumumab, and is thus irrelevant for the issue considered here.

12.6 Lastly, the suitability of the K-ras mutations cited in claims 1 and 4 for the claimed purpose is also corroborated by post-published evidence. Since the patent application presents no fundamental deficiency of disclosure, but rather discloses that the claimed effect is credible in view of Example 1 (see above), in line with the case law, this evidence can be taken into account (see Case Law, II.C.6.8.). Document E14 states on page e206, second paragraph: "*In the clinical setting, a consistent correlation between presence of a KRAS mutation in codon 12 or 13 and lack of response to anti-EGFR monoclonal antibody therapy in mCRC patients*

has been described.[1-3]". Further arguments in support are disclosed in the abstracts of documents E9 and E27.

13. As regards the second line of argument directed against the "broadness" of the patient or tumour group defined in claims 1 and 4, appellant II submitted that Example 1 of the patent application disclosed that the samples were taken from CRC patients with tumours expressing "*high levels of EGFr*". Moreover, since at the filing date, panitumumab was approved for treating metastatic colon cancers only, the skilled person would have concluded from Example 1 of the patent application that the CRC patients belonged to this sub-group.

13.1 As set out above under added subject-matter the 37 patients of the study disclosed in Example 1 of the patent application have been classified as CRC before becoming enrolled in the study. Accordingly, the EGFR status of tumour samples obtained from these patients was determined only after the study started (see paragraphs [0095] and [0096]). Furthermore, evidence is lacking that CRC tumours with a high EGFR expression rate respond to panitumumab treatment only, nor are indications available that the EGFR status affects the ability of the K-ras mutations cited in claims 1 and 4 in predicting non-responsive CRC patients or tumours to panitumumab.

13.2 Thus, appellant II's assertion that the skilled person "*would consider any of these features are relevant to disease and response*" and that "*it is highly likely the skilled person would further restrict any conclusion obtained from the results of Example 1 to metastatic cancer and to patients who experience disease progression following or during chemotherapy*" is

speculative, and - in the absence of facts - it is not adequate to substantiate serious doubts.

14. Appellant II has further submitted that Example 1 did not give indications "*as to results in individual tumours (the response of a patient is evaluated across all tumours and the result of an individual tumour cannot be deduced from the overall response of the patient)*".

14.1 It is undisputed that CRC tumours are the cause of patients suffering from CRC. Furthermore, it is the K-ras mutational status of such a CRC tumour that indicates with sufficient credibility whether or not CRC patients are responsive to a panitumumab therapy (see above).

14.2 Since the patent application establishes a credible relationship between the K-ras status of the CRC tumour and the responsiveness of a CRC patient to the antibody, it is likewise credible that the K-ras status of the individual CRC tumour sample determines whether or not the tumour responds to panitumumab.

15. Lastly appellant II submitted that the patent application did not provide sufficient technical information for the skilled person how to detect the mutated K-ras polypeptides/polynucleotides, and how the sampling and preparation of the tumours for analysing the K-ras status can be carried out.

15.1 The patent application discloses in paragraphs [0086] to [0093] various methods for detecting mutated K-ras polynucleotides and polypeptides. Theses methods belong to the common general knowledge of the skilled person. Moreover, evidence that the detection of mutated K-ras

polynucleotides or polypeptides by any of these methods could not be carried out by the skilled person has not been submitted by appellant II.

15.2 The board has furthermore no doubts that tumour samples can be obtained from CRC patients and prepared for methods that detect mutated K-ras polynucleotides and/or polypeptides. Paragraph [0096] of the patent application, for example, describes such preparatory steps.

16. In view of the considerations above, the board concludes that auxiliary request 3 complies with the requirements of Article 83 EPC.

Inventive step

Closest prior art and technical problem

17. Both appellants considered that document E25 represented the closest prior art.

18. Document E25 discloses that K-ras mutations predict a resistance of metastatic colorectal cancer patients to a cetuximab-based therapy (see abstract). Centuximab, like panitumumab (see paragraph [0007] of the patent application), is an anti-EGFR antibody that blocks the binding of EGF to its receptor, including receptor signaling (see document E25, page 3992, column 1, first paragraph to column 2, second paragraph). Both antibodies are used in the therapy of colorectal cancer patients (see document E25, page 3992, column 1, first paragraph to column 2, second paragraph; paragraph [0006] of the patent application). It is uncontested that the colorectal adenocarcinoma (CRC) patients of claim 1 are encompassed by the colorectal cancer

patients mentioned in document E25. Table 1 of document E25 discloses that all patients tested positive for K-ras mutations in tumour samples (eleven out of 30), are non-responsive to cetuximab (see "*SD*" and "*PD*" response, i.e. stable and progressive disease). The six K-ras mutations mentioned in Table 1 of document E25 are identical to the six K-ras mutations referred to in claims 1 and 4. Document E25 is, however, silent on panitumumab.

19. The claimed methods differ from document E25 solely in the prediction of the patients'/tumours' non-responsiveness to panitumumab instead of cetuximab, i.e. to an alternative anti-EGFR antibody. Particular effects arising from this difference are not apparent.

20. The technical problem to be solved is thus defined as the provision of further predictive methods for assessing non-responsiveness of CRC patients/CRC tumours to an alternative EGFR inhibitor.

21. This problem is solved by the subject-matter of claims 1 and 4 in view of Example 1, in particular, Table 2 of the patent.

Obviousness

22. It remains to be assessed whether or not the skilled person, starting from document E25 and faced with the problem defined above, would have arrived at the methods of claims 1 and 4 in an obvious manner.

23. Appellant II submitted that document E25 taught a clear relationship between activating K-ras mutations and the therapeutic effectiveness of the anti-EGFR antibody cetuximab based on the antibody's interaction site with

EGFR, and the downstream position of K-ras in the EGFR signaling pathway that controls the tumour's cell proliferation. Since this teaching was, moreover, coherent with the teaching of document E10 that in an earlier study assessed the same issue, i.e. the prediction of responsive colorectal cancer patients to a panitumumab and cetuximab-based treatment in relation to various molecular markers, including K-ras, the skilled person had an incentive to repeat the study of document E25 with panitumumab with a clear expectation of success.

24. The board does not agree. Document E25 formulates as working model that "*the presence of a K-ras mutation is associated with downstream activation of the Ras/MAPK pathway, leading to cell proliferation that cannot be significantly inhibited by cetuximab that acts upstream of the K-ras protein*" (see page 3995, column 2, first paragraph). In line therewith, this paragraph in document E25 further mentions that K-ras mutations are likewise "*found to be associated with resistance to EGFR kinase inhibitors gelfitinib and erlotinib in lung adenocarcinomas*", and that a "*similar trend was recently observed*" in a study of "*colorectal cancers treated with gelfitinib*", with a response rate in patients with K-ras mutations of 33% compared to 47% of patients with wild-type K-ras.

24.1 Thus, the model disclosed in document E25 provides a rationale why colorectal cancer patients are non-responsive to a treatment by various EGFR inhibitors, which interfere all, as a common mechanism of action, with the EGFR signaling pathway at sites located upstream of a permanently active mutated K-ras protein.

24.2 Document E25 is however silent on panitumumab, although the antibody is an EGFR inhibitor acting upstream of K-ras, and it is evident that the document's authors were aware of it. Document E25 explicitly refers to document E10 and states in this context on page 3994, column 2, second paragraph: "*One study had previously assessed the mutation status of the EGFR catalytic domain and its downstream intracellular effectors PIK3CA, KRAS, and BRAF and found no significant correlation with response to cetuximab (5). However, a potential trend toward higher response rates was seen in cetuximab-treated colorectal cancer patients whose tumors were of KRAS wild-type status. When our results were pooled with those of Moroni et al., the predictive value of KRAS mutation remained significant with a KRAS mutation frequency of 52.5% in nonresponders compared with 9.5% in responders (P = 0.001). When considering these pooled data, the probability to have no response to cetuximab was 91.3% in the presence of KRAS mutation. Moreover, the probability to be responder was 50% when no KRAS mutation was identified. The relative risk to obtain a response to cetuximab was 10-fold higher for nonmutated patients compared with that of patients with KRAS mutation (hazard ratio, 10.5; 95% CI, 2.1-51.1). Thus, these data suggest that the wild-type KRAS status might identify patients with metastatic colorectal cancer who are likely to respond to cetuximab and to have a longer overall survival*" (emphasis added). The reference in this passage of document E25 to "*one study*", "*(5)*", and "*Moroni et al.*", is identical to document E10 in these proceedings.

24.3 This passage above mentions a "*potential trend toward higher response rates*" for "*cetuximab-treated colorectal cancer patients whose tumors were of KRAS wild-type status*", i.e. of a trend already observed in

document E10, despite document E10's explicit statement that activating K-ras mutations "*were not associated with clinical response to monoclonal antibody*", i.e. cetuximab and panitumumab (see document E10, page 284, paragraph bridging columns 1 and 2).

24.4 In the board's opinion, document E25 refers, as regards the "*trend*", to Table 2 on page 282 of document E10. This table compares responders/non-responders to cetuximab and panitumumab with the mutational/non-mutational (wild-type) status of several molecular marker candidates, including K-ras, to find a correlation between these candidates and responsive patients, and hence, a potential suitability as predictive markers. Table 2 discloses that half of the responsive panitumumab-treated patients (two out of four, i.e. 50%) have a mutational K-ras status, while the other half have a wild-type K-ras. Contrary thereto, all responsive cetuximab-treated patients (six out of ten, 100%) have a wild-type K-ras status.

24.5 Thus, while the results in Table 2 of document E10 on responsive cetuximab-treated patients fit into the model disclosed in document E25 above, the results on panitumumab-treated patients do not fit. A 50/50 response rate based on the K-ras mutational/wild-type status as marker is unsuitable for identifying responsive colorectal patients for a panitumumab treatment, since it allows no selection. According to document E10, the suitability of K-ras mutations as predictive markers for identifying non-responsive patients to a cetuximab and panitumumab treatment are therefore fundamentally different. Neither document E10 nor document E25 provides a rational explaining these different responses to the two antibodies in relation to K-ras mutations. Both documents merely state that

the "*molecular mechanisms underlying clinical response*" of both antibodies, or of cetuximab alone, remain unknown (see documents E10 and E25, abstracts).

24.6 In the board's opinion, the skilled person starting from document E25 and faced with the problem defined above would have certainly turned to document E10, because this document is mentioned and commented therein. However, since Table 2 of document E10 (see above) demonstrates that activating K-ras mutations are not associated with a potential panitumumab responsiveness of colorectal cancer patients, contrary to cetuximab, both documents provide neither a pointer for the skilled person that activating K-ras mutations may be suitable markers for identifying non-responsive panitumumab colorectal cancer patients, nor a reasonable expectation of success that, if document E10's teaching is ignored, K-ras mutations would be obtained that are suitable for the claimed purpose.

24.7 According to the case law, a reasonable expectation of success implies that the skilled person predicts rationally, on the basis of the available facts whether or not an envisaged result can be obtained within acceptable time limits. If the evaluation of these facts provides either no confidence (see Table 2 of document E10), or only a weak one (see hypothesis/model of document E25), the reasonable expectation of success turns into a mere hope to succeed. A skilled person working on that basis follows a non-obvious course of action (see Case Law, I.D.7.1, and decision T 1599/06, Reasons, point 21.6).

25. In view of the considerations above, the board concludes that auxiliary request is neither obvious in light of the teaching of document E25 alone or when

combined with document E10. Auxiliary request 3 thus meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

A. Voyé B. Stolz

Decision electronically authenticated