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Datasheet for the decision of 14 September 2023

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Language of the proceedings: EN

Title of invention:
FGFR3 fusion gene and pharmaceutical drug targeting same

Patent Proprietor:
Chugai Seiyaku Kabushiki Kaisha

Opponent:
Murphy, Colm Damien

Headword:
FGFR3 fusion gene/CHUGAI SEIYAKU KABUSHIKI

Relevant legal provisions:
EPC Art. 54, 56, 83, 89, 123(2)
RPBA 2020 Art. 12(4), 12(6), 13(2)

Keyword:
Main request - novelty (no)
Auxiliary request 1 - priority, inventive step (no)
Auxiliary request 2 - added matter (no), priority, novelty, inventive step, sufficiency of disclosure (yes)
Late-filed evidence - admitted in first-instance proceedings (no) - should have been submitted in first-instance proceedings (yes)
Amendment after summons - cogent reasons (no)

Decisions cited:
T 1063/06, T 1959/15, T 0694/16

Catchword:
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Case Number: T 3122/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 September 2023

Appellant I: (Patent Proprietor)	Chugai Seiyaku Kabushiki Kaisha 5-1, Ukima 5-chome Kita-ku Tokyo 115-8543 (JP)
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Appellant II: (Opponent)	Murphy, Colm Damien Cooley (UK) LLP Dashwood 69 Old Broad Street London EC2M 1QS (GB)
Representative:	Cooley (UK) LLP 22 Bishopsgate London EC2N 4BQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 September 2019 concerning maintenance of the European Patent No. 2902489 in amended form**

Composition of the Board:

Chair	R. Hauss
Members:	B. Claes
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 902 489 (the patent) was granted for European patent application No. 13 842 962.6 (the application) and has the title "*FGFR3 fusion gene and pharmaceutical drug targeting same*". The patent claims priority from two Japanese patent applications, JP 2012214739, which was filed on 27 September 2012 (see certified English translation of 12 February 2016, referred to herein as "PD1"), and JP 2013149217 ("PD2"), which was filed on 18 July 2013.

Independent claims 1, 4 and 6 of the patent read as follows:

"1. A compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof for use in a method of treating or preventing cancer in a patient who has been identified to express a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or to carry a polynucleotide encoding the fusion polypeptide,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8, and
wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide.

4. A method for selecting a patient, in particular a patient having bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, to which an anticancer agent comprising a compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof is applicable, which comprises the steps of:

(a) determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from a subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7, and
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and

(b) selecting a patient confirmed to have the fusion polypeptide or the polynucleotide as a patient to which the anticancer agent is applicable,
wherein the compound or a pharmaceutically acceptable salt thereof is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide.

6. A method for testing cancer susceptibility of a subject, whether a subject is affected with cancer, or whether cancer has progressed in a subject, in particular wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell

carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, by determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or determining the presence or absence of a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from the subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and
wherein the method is based on the criterion that a subject is more likely to develop cancer, is affected with cancer, or has progressed cancer when the fusion polypeptide or polynucleotide encoding the fusion polypeptide is detected."

II. The appeals lodged by both the patent proprietor (appellant I) and the opponent (appellant II) are against the interlocutory decision of the opposition division. The opposition proceedings were based on the grounds for opposition set out in Article 100(a) EPC, relating to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

III. Reference is made to the following documents:

D1: Wu *et al.*, Cancer Discov. 3(6), 2013, pages 636-647

D2: Williams *et al.*, Human Molecular Genetics 22(4), 2012, pages 795-803

D4: Lamont *et al.*, British J. Cancer 104, 2011, pages 75-82

D6: Guangnano *et al.*, J. Med. Chem. 54, 2011, pages 7066-7083

D11: EP-A-3 339 305

D12: WO 2007/144893

D14: Turner & Grose, Nature Reviews Cancer 10, Feb. 2010, pages 116-129

D15: Gozgit *et al.*, Mol. Cancer Ther. 11(3), January 2012, pages 690-699, and supplemental material

IV. The opposition division decided that while claim 1 of the patent as granted (main request) did not contain added subject-matter (Article 100(c) EPC) and the patent did sufficiently disclose the claimed invention (Article 100(b) EPC), the subject-matter of claim 1 lacked novelty (Articles 54 and 100(a) EPC). However, this objection was overcome by the claimed subject-matter in auxiliary request 1, which was also deemed to involve an inventive step (Article 56 EPC). The opposition division also decided not to admit document D12 into the proceedings (Article 114(2) and Rule 116(1) EPC).

As compared with claim 1 of the patent as granted (see section I.), claim 1 of auxiliary request 1 has the additional wording "and wherein said patient is a human patient" appended at the end. Claims 4 and 6 of

auxiliary request 1 are identical to claims 4 and 6 as granted (see section I.).

V. With its statement of grounds of appeal, appellant I re-submitted the sets of claims of its main request and of auxiliary requests 1 to 5, and provided arguments as to why the subject-matter of claim 1 of the patent as granted (main request) was novel.

Claims 1 and 4 of auxiliary request 4 are identical to claims 1 and 4 of auxiliary request 1 as dealt with by the opposition division (see section IV.). Independent claim 6 of auxiliary request 4 reads as follows (with deletions compared with claim 6 of the main request and auxiliary request 1 shown by strike-through):

"6. A method for testing cancer susceptibility of a subject~~, whether a subject is affected with cancer, or whether cancer has progressed in a subject~~, in particular wherein the cancer is bladder cancer, brain tumor, head and neck squamous cell carcinoma, lung cancer, lung adenocarcinoma, lung squamous cell carcinoma, skin melanoma, esophageal cancer, gastric cancer, or liver cancer, by determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide or determining the presence or absence of a polynucleotide encoding a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide in a sample isolated from the subject,
wherein the FGFR3 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 6 or 7,
wherein the BAIAP2L1 polypeptide is the whole or a part of a wild-type polypeptide consisting of the amino acid sequence of SEQ ID NO: 8; and

wherein the method is based on the criterion that a subject is more likely to develop cancer~~, is affected with cancer, or has progressed cancer~~ when the fusion polypeptide or polynucleotide encoding the fusion polypeptide is detected."

VI. With its statement of grounds of appeal, appellant II submitted new documents D13 and D14 and provided arguments in relation to auxiliary request 1, which had been held allowable in the decision under appeal. Appellant II pursued the following objections in respect of this auxiliary request.

i) Claim 1 contained added subject-matter.
ii) The invention of claim 1 was not sufficiently disclosed in the patent.
iii) The subject-matter of claim 1 lacked novelty over the disclosure in document D4.
iv) The subject-matter of claims 1 to 10 lacked an inventive step over the disclosure in document D4.
v) Claims 1, 2, 4 and 6 could not validly claim priority from the first priority document (PD1).
vi) Since the priority had not been validly claimed, documents D1 to D3 were state of the art that could be taken into account in the assessment of novelty and inventive step.

VII. With its reply to the appeal of appellant II dated 12 June 2020, appellant I filed auxiliary requests 6 to 9.

VIII. With its reply to the appeal of appellant I dated 15 June 2020, appellant II filed, *inter alia*, new document D15.

IX. In preparation for oral proceedings, the board issued a communication under Article 15(1) RPBA, setting out

its preliminary opinion on substantive and legal matters concerning the appeal.

X. With a letter dated 7 August 2023, appellant I referred to some of its arguments relating to sufficiency of disclosure in reply to points 26 and 27 of the board's communication.

XI. Oral proceedings before the board were held on 14 September 2023. During the oral proceedings, appellant I renumbered auxiliary request 4 (see section V.) as auxiliary request 2.

XII. The arguments of appellant I, where relevant to the decision, can be summarised as follows:

Main request

Claim 1 - novelty

The patient group identified in claim 1 was particularly susceptible to treatment and conferred novelty to the claimed subject-matter over the disclosure in document D4. The actual "identification step" (in the form of a method step) did not have to be a claim feature in order to define this particular patient group.

In decision T 694/16, the expression of two CSF markers identified a particular subgroup of dementia patients who were "prodromal" and could benefit from a particular therapy, whereas non-prodromal subjects were spared the unnecessary intervention (therapy) and possible side effects. The selection of these patients was thus purposive and not arbitrary and the patient

group expressing the CSF markers was novel (Reasons 5.3 to 5.21). The same logic applied to the case at hand.

For assessing novelty, it was important to determine whether the selection of patients bearing the marker had been made available to the public, not whether the treatment of a patient inherently bearing the marker was known. Since document D4 was silent on the FGFR3-BAIAP2L1 fusion polypeptide, it did not make available to the public the fact that the patient group that should be treated was one that had been identified as expressing the FGFR3-BAIAP2L1 polypeptide.

In the *in vivo* experiment in document D4, three different cell lines overexpressing FGFR3 (MGH-U3, RT112 and SW780) were transplanted in mice, and were tested and shown to be susceptible to an FGFR inhibitor (see the last paragraph of the 'Results' section, on page 78). SW780 was only one of these cell lines and the xenograft patient group treated in this example thus consisted of three "subjects" overexpressing FGFR3. Accordingly, there was not a 100% overlap between the patient group treated in document D4 and that in the claim. The partial overlap was in fact accidental, as it was not known that the SW780 cells expressed the FGFR3-BAIAP2L1 polypeptide. Nothing in document D4 pointed to an individualisation of the xenograft mice bearing the SW780 cell line.

Document D4 only referred to the overexpression of FGFR3 wild-type in the three tested cell lines and the technical teaching of the document was thus at most that FGFR inhibitors could treat FGFR3-overexpressing patients but not the presence of any fusion protein in the studied cell lines. This was a further difference which conferred novelty on the claimed subject-matter.

Auxiliary request 1

Claim 6 - entitlement to the priority date of PD1

The skilled person would readily derive healthy subjects, subjects affected with cancer and subjects with progressed cancer from the disclosure in PD1 as a whole.

PD1 was in the field of personalised medicine, which clearly and unambiguously included all possible types of subjects, namely healthy subjects, i.e. subjects who were more likely to develop cancer, subjects who were already affected with cancer, and subjects who had been affected with cancer for a longer period of time, i.e. a progressed cancer, e.g. a metastatic cancer.

Claim 6 - inventive step (Article 56 EPC)

No arguments were submitted as to why the claimed subject-matter involved an inventive step over the disclosure in document D1.

Auxiliary request 2

Claim 1 - amendments (Article 123(2) EPC)

The application as filed provided a direct basis for the amendments in claims 1, 38 and 52 of auxiliary request 2.

The clarifying phrase ("*wherein the compound ... is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide ...* ") was disclosed in the paragraph bridging pages 37 and 38, in

particular by the sentence "*The proliferation of cells expressing such fusion polypeptides is significantly inhibited by compounds having FGFR inhibitory activity*".

The feature did not result in the definition of a particular "subgroup" of active agents (FGFR inhibitors) being referred to in the claim as compared with those in the application as filed. Even without the clarifying phrase, claim 1 related to FGFR inhibitors for use in the inhibition of cancer in the defined patient group of claim 1, i.e. in patients expressing the fusion polypeptide. It was self-evident that a further medical use of a compound in the treatment/prevention of cancer "*in a patient who has been identified to express a* [particular] *fusion polypeptide*" inevitably involved the inhibition of the "growth of a cancer cell expressing the fusion polypeptide". The notion that the compound "significantly" inhibited proliferation of cells from the disclosure on page 37 was implicit in the medical use recited *per se* in the claim.

Document D14 - admittance (Article 13(2) RPBA)

Appellant II had filed D14 with its statement of grounds of appeal in the context of inventive step and had referred to it (and thus submitted it) in the context of sufficiency of disclosure only during the oral proceedings before the board.

This new line of argument should have been filed at the latest in response to the statement of grounds of appeal of appellant I. In fact, point 27 of the board's preliminary opinion did not provide or give rise to any new arguments. There were therefore no exceptional

circumstances justifying the admittance of D14 in relation to the issue of sufficiency of disclosure at this advanced stage of the proceedings.

Document D15 - admittance (Article 12(4),(6) RPBA)

Any arguments to which document D15 was allegedly responsive had already been made during the opposition proceedings. The document should therefore have been submitted at that time. The fact that document D15 had allegedly only recently been identified was not a sufficient justification.
Moreover, document D15 was not *prima facie* relevant.

Claim 1 - sufficiency of disclosure (Article 83 EPC)

The invention resided in the identification of a subgroup of cancer patients that was particularly susceptible to treatment with FGFR inhibitors.

FGFR inhibitors useful in the context of the claimed invention inhibited cell proliferation in patients expressing the fusion protein recited in the claim. If required, this activity could be tested, as disclosed in Example 3 of the patent. FGFR inhibitors were generally suitable for the claimed medical use and met the definition of the active agent in claim 1.

Appellant II had failed to identify any FGFR inhibitor that did not inhibit cancer cells in the claimed medical use, despite carrying the burden of proof in this respect. Appellant II had not presented any serious doubts, substantiated by verifiable facts, that the invention could not be put into practice.

The principles of decision T 1063/06, as cited by appellant II, were not applicable to the case at hand because the underlying cases differed.

FGFR inhibitors were well known in the art and the patent disclosed numerous examples in paragraphs [0211] to [0295]. Documents D4 and D6 also disclosed FGFR inhibitors. The person skilled in the art could thus readily carry out the invention on the basis of the disclosures therein and their common general knowledge, without undue burden.

The argument that specific inhibitors were unable to inhibit FGFR3 or the newly discovered biomarker (fusion polypeptide) was not pertinent. Document D11 did not prove that identifying further FGFR inhibitors suitable for the claimed use would constitute an undue burden.

In the patent, six kinds of FGFR inhibitors had been shown or made credible, respectively, to be suitable in the claimed medical use. Identifying further compounds having the required properties did not constitute an undue burden for the skilled person.

Suitable FGFR inhibitors would not need to be specific inhibitors of the present biomarker (the fusion polypeptide) rather than "regular" FGFR inhibitors. Thus, testing or screening of such compounds was not required.

The claimed medical use was made credible in the application as filed. Determining which FGFR inhibitors were sufficiently potent in the treatment of human patients did not constitute an undue burden, and appellant II had not provided any example of a non-working embodiment.

It was established jurisprudence that a certain (accidental) failure should not be confused with insufficiency of disclosure. Accordingly, it was of no harm if there were an FGFR inhibitor that was not suitable for the claimed medical use (i.e. if a claim comprised non-working embodiments), as long as sufficient information was available on the relevant criteria for finding appropriate alternatives over the scope of the claim with reasonable effort (see decision G1/03, Reasons 2.5.2). This was the case for the patent here.

Entitlement to the priority date of PD1 (Article 89 EPC)

The priority documents and the application as filed were largely identical. PD1 contained all of the passages of the application as filed up to Example 4.

Based on these passages, essentially the same reasoning applied analogously in support of priority entitlement as that already set out in the context of added subject-matter and of sufficiency of disclosure.

Inventive step (Article 56 EPC)

The claimed subject-matter differed from the disclosure in document D4 by the identification of, and limitation to, a particular patient group expressing the FGFR3-BAIAP2L1 fusion polypeptide. The effect of these differences included the fact that it was possible to identify and treat this particular patient group using FGFR inhibitors. The objective technical problem could thus be formulated as in the words of the opposition

division, i.e. the "provision of an effective cancer treatment for specific patients".

Document D4 described the nature of the SW780 FGFR3 polypeptide explicitly as "wild-type" and provided no indication that it could be a fusion polypeptide rather than wild-type FGFR3. Even if document D4 did demonstrate that the cell line SW780 was highly sensitive to a known FGFR inhibitor, PD173074, this was in the context of a respective overexpression of wild-type FGFR3 rather than any mutation of FGFR3 or the like. Moreover, the comments in the background section of document D4 on particular findings in a small percentage of certain malignancies (see the bottom of page 75 and the top of page 76) did not distract from the understanding in document D4 that the SW780 cell line overexpressed wild-type FGFR3. Document D4 therefore did not provide any motivation to further analyse this cell line and any argument to the contrary involved hindsight.

Document D4 explicitly mentioned overexpression of wild-type FGFR3 in SW780 cells and thus actually taught away from any mutant FGFR3, and particularly from any FGFR3 fusion polypeptide.

Even if there had been a motivation to doubt this teaching with respect to the explanation of the mechanism, it was not inevitable that the fusion biomarker in SW780 would have been identified.

Document D2 (which was also relied on by appellant II) was post-published and therefore not relevant to the assessment of inventive step.

The medical use identified in the claims would not have been obvious to the skilled person as there was no pointer in document D4 to the particular fusion peptide and there was no motivation to particularly turn to SW780 for further analysis.

XIII. The arguments of appellant II, where relevant to the decision, can be summarised as follows:

Main request

Claim 1 - novelty

The patients of claim 1 were defined as having been identified as expressing an FGFR3-BAIAP2L1 fusion polypeptide. However, the claim itself did not require testing of subjects for the FGFR3-BAIAP2L1 fusion polypeptide or selecting subjects for treatment as active steps of the claimed therapeutic use of the FGFR inhibitory compound. The identification feature did not distinguish a subject from other subjects having the same biomarker.

Document D4 disclosed the use of a known FGFR3 inhibitor compound (PD173074) to treat cancer in xenograft mice bearing tumours established using the human bladder cancer cell line SW780 (see page 78, right-hand column, and the results shown in Figure 3A, third panel). The SW780 xenograft mice expressed an FGFR3-BAIAP2L1 fusion polypeptide as defined in the claim.

The SW780 xenograft mice were treated as a distinct and separate treatment group of cancer subjects (see "Materials and Methods", "Animals" heading, page 76). The treatment group of eight xenograft mice carrying

tumours derived from the human bladder cancer cell line SW780 were treated with PD173074 and was distinct from the treatment groups of mice carrying MGH-U3 or RT112-derived tumours. Document D4 thus disclosed the treatment of three distinct and separate patient groups and Figure 3A reported on the results for each different tumour type in different graphs.

Although document D4 did not disclose selecting tumours expressing the FGFR3-BAIAP2L1 fusion polypeptide for treatment with FGFR inhibitors, in the *in vivo* experiments the subgroup of SW780 xenograft mice was selected for treatment with the known FGFR inhibitor PD173074, based on the sensitivity of SW780 cells to several known FGFR inhibitors. The later characterisation of the SW780 tumours as expressing an FGFR3-BAIAP2L1 fusion polypeptide merely provided more information regarding this tumour type, i.e. the underlying genetic make-up of the tumour, and was of no consequence for the treatment of the tumours, and hence the patient group, using PD173074.

Since each of the individuals in the distinct group of subjects carrying tumours derived from the human bladder cancer cell line SW780 treated in document D4 inherently carried a tumour that expressed an FGFR3-BAIAP2L1 fusion polypeptide, the mice group bearing the SW780 cell line was individualised and had a 100% overlap with the "patient group" defined in claim 1. Given this situation, the claim did not define a new therapeutic use of a compound but merely provided more information about an already known therapeutic use. The claimed subject-matter thus lacked novelty.

The reasoning of decision T 694/16, as relied on by appellant I, did not apply because there was a 100%

overlap between the SW780 xenograft population treated in D4 and the patient group defined in the claim. When there was a 100% overlap, there could be no purposive selection of a particular group of patients.

Auxiliary request 1

Claim 6 - entitlement to the priority date of PD1 (Article 89 EPC)

The embodiments of claim 6 relating to testing whether a subject was affected with cancer and testing whether cancer had progressed in a subject were not entitled to priority based on PD1 as they were not directly and unambiguously derivable from PD1.

Claim 6 - inventive step (Article 56 EPC)

Document D1 characterised the cell line SW780 as expressing an FGFR3-BAIAP2L1 fusion polypeptide and identified a bladder cancer patient carrying an FGFR3-BAIAP2L1 fusion gene, i.e. the fusion according to claim 6. Document D1 also taught the fusion's tumourigenic effect. On this basis, it would have been obvious to the skilled person that the fusion was a marker for cancer and could be used in a method for testing whether a subject was affected with cancer.

Auxiliary request 2

Claim 1 - amendments (Article 123(2) EPC)

Compared with claim 52 of the application as filed, claim 1 additionally specified that the compound having FGFR inhibitory activity for use in the method of treating or preventing cancer was a compound capable of

inhibiting the growth of a cancer cell expressing the fusion polypeptide. The additional feature changed the functional definition of the compound and presented the skilled person with new technical information extending beyond the content of the application as filed.

Compounds having "FGFR inhibitory activity" as referred to in the claim were defined rather broadly in the application (see page 70, line 23, to page 71, line 6). However, not all of these compounds would be expected to be capable of inhibiting the growth of cancer cells expressing an FGFR3-BAIAP2L1 fusion polypeptide. The dual-functional properties of the claimed compound thus restricted the compounds and hence defined a new, undisclosed group of compounds in claim 1 as compared with the former group in claim 52 that included any FGFR inhibitor. The passage on page 37, lines 32 to 33, of the application as filed did not provide a clear and unambiguous basis for the new subgroup of FGFR inhibitor compounds capable of inhibiting the growth of cancer cells expressing a FGFR3-BAIAP2L1 fusion polypeptide. The passage referred neither to a FGFR3-BAIAP2L1 fusion polypeptide nor to treating human cancer patients identified as expressing specifically a FGFR3-BAIAP2L1 fusion polypeptide.

Furthermore, inhibiting cell proliferation according to page 37 was not the same as inhibiting the growth of a cancer cell in claim 1. Moreover, claim 1 did not require that the claimed compounds "*significantly*" inhibited the proliferation of cells expressing the fusion polypeptide (as formulated in the passage on page 37).

The combination of features in claim 1 involved at least a four-fold selection of 1) FGFR3-BAIAP2L1 as the

fusion polypeptide; 2) human cancer patients; 3) human cancer patients identified as expressing the fusion polypeptide; and 4) a subgroup of compounds that had FGFR inhibitory activity and were capable of inhibiting the growth of cancer cells expressing a FGFR3-BAIAP2L1 fusion polypeptide.

Document D14 - admittance (Article 13(2) RPBA)

The reliance on document D14 in the context of sufficiency of disclosure during the oral proceedings before the board had been prompted by the submission filed by appellant I in response to point 27 of the board's communication. It was thus a timely response, and the reference to the document and the related arguments in the context of sufficiency of disclosure should be admitted.

Document D15 - admittance (Article 12(4),(6) RPBA)

Document D15 had been filed with the reply to the appeal of appellant I, in response to the submission that every FGFR inhibitor known in the art was suitable for the treatment and, hence, screening for compounds which met the requirements of claim 1 was not necessary. Appellant II had only recently become aware that document D15 reported data relevant to the issue of sufficiency of disclosure, namely in relation to an inactive compound which was a "FGFR inhibitor" and which was specifically named in the patent (brivanib). The document was thus highly relevant and should be admitted.

Sufficiency of disclosure (Article 83 EPC)

Claim 1 sought to monopolise the therapeutic use of *any* compound which dually qualified as a "compound having FGFR inhibitory activity", as broadly defined in the patent (see paragraphs [0208] to [0212]), and as being capable of inhibiting the growth of a cancer cell expressing a FGFR3-BAIAP2L1 fusion polypeptide composed of "the whole or a part" of wild-type FGFR3 and "the whole or a part" of wild-type BAIAP2L1 polypeptide.

In a first aspect, the definition of the FGFR inhibitor in the patent was broad both structurally and mechanistically. The patent did not enable the skilled person to obtain all substances falling within the broad dual-function definition in claim 1 without undue burden. Accordingly, not all of the alternatives falling within the dual-function definition were available to the skilled person on the basis of the disclosure in the patent.

Although paragraph [0212] of the patent provided the structure of six exemplary low molecular weight compounds with FGFR inhibiting activity, in accordance with paragraph [0210] an "FGFR inhibitor" could equally be, for example, an antibody, siRNA, antisense nucleic acids or ribozymes. Further, besides inhibitors of FGFR kinase activity, compounds with different mechanisms of action were also encompassed, such as compounds which inhibited dimerisation between FGFR, TACC3 and BAIAP2L1 or FGFR-mediated signalling via the MAPK pathway and P13K/AKT pathway, or inhibited FGFR expression.

However, the patent provided no guidance as to the structure of FGFR inhibitors that acted downstream in the FGF signalling pathway, nor did it provide a

suitable screening method to enable those skilled in the art to test candidate compounds for these properties.

The skilled person thus did not know the structure of all FGFR inhibitors as the term also encompassed FGFR inhibitors yet to be discovered. There was no evidence that clear structural selection rules for compounds with "FGFR inhibitory activity" were part of common general knowledge on the priority date of the patent or would even be possible, especially given the diversity of compound structures and the diversity of mechanisms of action encompassed. Therefore, the requirement of sufficient disclosure was not fulfilled for this additional reason. A "compound having FGFR inhibitory activity" was thus a "reach-through" functional definition of the compound.

As in the case at hand, decision T 1063/06 (OJ EPO 2009, 516) was concerned with a claim relating to a medical use, in which the compounds to be used for the claimed therapeutic treatment were defined only in functional terms. The decision established, *inter alia*, that the need to perform screening assays in order to obtain all compounds encompassed by the claim constituted an undue burden for the skilled person.

The case at hand was also similar to that underlying decision T 1959/15, where the claims at issue were directed to the second medical use of an inhibitor of soluble epoxide hydrolase (sEH) for inhibiting cardiomyopathy. The therapeutic agent for use in the claim was defined solely on the basis of a functional definition: inhibition of sEH, a known target. The patent provided a list of known sEH inhibitors and data for two of them tested in an animal model. The

competent board held that even if the patent provided a list of known compounds allegedly meeting the required functional definition, and assays for providing more compounds that exhibited this function, the requirements of Article 83 EPC were not met because the skilled person would have had to resort to trial-and-error experimentation in order to identify further (unknown) compounds that met the functional definition (see Reasons 4.3 to 4.5).

Claim 1 of auxiliary request 2 likewise encompassed a myriad of structurally diverse known and unknown compounds which needed not have more in common than the dual function. The skilled person thus had to resort to trial-and-error experimentation on arbitrarily selected compounds to establish whether they possessed the functions required by claim 1. Thus, following T 1959/15, the patent did not sufficiently disclose the claimed invention for this reason alone.

In a second aspect, it was not credible that all FGFR inhibitors were also capable of inhibiting the growth of cancer cells expressing a fusion polypeptide comprising "*all or part*" of FGFR3 and "*all or part*" of BAIAP2L1.

This applied in particular because it depended on which downstream signalling pathways were driving oncogenesis in cells expressing the FGFR3-BAIAP2L1 fusion, as opposed to cells carrying any other type of abnormality in FGFR3. In fact, the statement in paragraph [0010] of the patent that signals transmitted via FGFR were conveyed to the MAPK pathway and PI3K/AKT pathway was made in the context of a wild-type situation, whereas in the case of a FGFR3-BAIAP2L1 fusion the situation was not wild-type but disregulated.

Further, according to paragraph [0208] of the patent FGFR kinase activity inhibitors also encompassed pan-FGFR inhibitors as inhibitors having specificity for one (or more) FGFRs, e.g. specific FGFR2 inhibitors or specific FGFR4 inhibitors. It was not plausible that all compounds falling within this definition - such as selective inhibitors of FGFR2 or FGFR4 lacking activity against FGFR3, for example - would also be capable of inhibiting the growth of cancer cells expressing a FGFR3-BAIAP2L1 fusion polypeptide.

Document D11 demonstrated that not all compounds that were FGFR inhibitors inhibited FGFR3. This confirmed the necessity of performing a screening assay in cells expressing a FGFR3-BAIAP2L1 fusion polypeptide in order to determine whether a candidate FGFR inhibitor had the capability of inhibiting the growth of cells expressing a FGFR3-BAIAP2L1 fusion polypeptide.

According to Example 3 of the patent, the *in vitro* antiproliferative effect on cells expressing a FGFR3-BAIAP2L1 fusion polypeptide of only six FGFR3 kinase inhibitors had been tested. However, claim 1 extended this to all FGFR inhibitors falling within the broad definition given in paragraphs [0208] to [0212] of the patent and the skilled person thus had to screen all possible FGFR inhibitors - be they small molecules, antibodies, FGFR1, FGFR2, FGFR3, or FGFR4 inhibitors, MEK inhibitors, RAF inhibitors, ERK inhibitors or any yet to be discovered FGFR inhibitors - by performing functional assays to test for their capability of inhibiting the growth of a cancer cell expressing a FGFR3-BAIAP2L1 fusion polypeptide. This amounted to an undue burden, and the availability of proliferation

assays using SW780 cells did not remedy this deficiency.

In addition, for any newly discovered compound capable of inhibiting the growth of a cancer cell expressing a FGFR3-BAIAP2L1 fusion polypeptide, it would be necessary to determine whether the compound met the broad definition of the FGFR inhibitor in the patent because such compounds did not necessarily act via inhibition of FGFR (e.g. generally cytotoxic compounds).

In a third aspect, there were serious doubts that all of the FGFR inhibitors falling within the dual-function definition in claim 1 had a sufficiently potent antiproliferative effect on cells expressing a FGFR3-BAIAP2L1 fusion polypeptide to be effective in the *in vivo* treatment of cancer in human patients identified as expressing the fusion, as required by the claim.

Document D4 disclosed significant differences in the potency of FGFR inhibitors tested *in vitro* on SW780 cells: PD173074 was very potent, whereas SU5402 was 120-fold less potent (see Table I). PD173074 could suppress tumour growth *in vivo* in an SW780 xenograft mouse tumour model. However, although not tested, it was doubtful that SU5402 (120-fold less potent *in vitro)* would also be active *in vivo*. Accordingly, identifying such compounds was also an undue burden for the skilled person.

Similarly, in the sole *in vivo* example of the patent only compound A had been successfully tested *in vivo* in a SW780 mouse xenograft model (see Example 6(3)). Compound D was, however, 10-fold less potent than compound A *in vitro* and compounds E and F were 5-fold

less potent than compound A (see Table 3). The patent did not disclose that compounds D, E and F were also capable of inhibiting tumour growth *in vivo*, and one could not just assume that these less potent and structurally unrelated compounds would also inhibit tumour growth in the *in vivo* SW780 mouse model.

Furthermore, since only a single compound was tested in the xenograft model, the patent did not demonstrate that the results of *in vitro* cell proliferation assays were predictive of efficacy *in vivo*. Indeed, it was not plausible that all FGFR inhibitors, irrespective of their potency *in vitro*, would be suitable for the claimed therapeutic use. Thus, the fact that FGFR inhibitors displayed a broad range of potencies in the SW780 proliferation assay raised serious doubts that all compounds falling within the functional definition would be therapeutically effective in the treatment of cancer in human patients identified as expressing FGFR3-BAIAP2L1. The *in vitro* testing (Example 3) and expression study (Example 4) were not sufficient to render the therapeutic effect for *any* FGFR inhibitor plausible for the treatment of human patients expressing an FGFR3-BAIAP2L1 fusion polypeptide.

In addition, the patent contained no evidence that compound A could be used to treat cancer in a human patient identified as expressing an FGFR3-BAIAP2L1 fusion and merely relied on the assumption that a compound capable of inhibiting tumour growth in a mouse model constructed from the SW780 cell line could be used to treat human patients with any type of cancer who were identified as carrying any type of FGFR3-BAIAP2L1 fusion polypeptide.

Entitlement to the priority date of PD1 (Article 89 EPC)

PD1 did not disclose the group of compounds recited in claims 1, 2 and 4, i.e. compounds defined based on the dual-functional properties of (i) FGFR inhibitory activity, and (ii) an ability to inhibit the growth of a cancer cell expressing a FGFR3-BAIAP2L1 fusion polypeptide. Further, PD1 did not provide an enabling disclosure to support the claimed medical use, for analogous reasons as those submitted in the context of sufficiency of disclosure.

Inventive step (Article 56 EPC)

The sole feature distinguishing the subject-matter of claim 1 from the disclosure of D4 was the requirement that the patients be human. Accordingly, the objective technical problem was the provision of an alternative group of patients having a FGFR3-BAIAP2L1 fusion polypeptide. Applying the therapy to human patients having this characteristic would have been obvious in view of the fact that SW780 originated in human bladder cancer.

In an alternative approach, the technical differences over the teaching of document D4 were both the characterisation of the SW780 cell line as expressing an FGFR3-BAIAP2L1 fusion and the identification of human cancer patients expressing an FGFR3-BAIAP2L1 fusion polypeptide that could be treated using FGFR inhibitors.

The patent demonstrated that certain FGFR inhibitor compounds had the capability of inhibiting growth of the cell line SW780 (Example 3) and that SW780 cells

expressed a FGFR3-BAIAP2L1 fusion polypeptide (Example 1), with the inference that FGFR3-BAIAP2L1 provided a biomarker for human cancers that could be treated using the same FGFR inhibitors that were shown to inhibit proliferation of SW780 cells.

The problem to be solved in view of the disclosure in document D4 was thus the provision of a biomarker for human cancer patients that could potentially be treated with certain FGFR inhibitors.

The solution, i.e. the identification of FGFR3-BAIAP2L1 as a suitable biomarker, would, however, have been obvious to a skilled person based on the disclosure in document D4.

Since document D4 demonstrated that SW780 cells were useful in *in vitro* assays testing the antiproliferative effects of FGFR inhibitors and *in vivo* mouse xenograft model studies, it would have been obvious for the skilled person to further characterise this cell line, and in particular to determine the form of FGFR3 reportedly overexpressed in SW780.

Document D4, establishing a connection between sensitivity to the inhibitor PD173074 and overexpression of wild-type FGFR3 in cell lines such as SW780 (see Table 1, and page 80, right-hand column, first and second sentences) and disclosing the need for biomarkers for patient selection that were related to FGFR dependence rather than mutation status (page 81, left-hand column, lines 14 to 22, and page 81, right-hand column, last sentence), provided a pointer to examine FGFR3 in cell lines overexpressing wild-type (i.e. non-mutant) FGFR3 and investigate the underlying genetic make-up of FGFR3 in the overexpressing cell

lines sensitive to FGFR3 inhibitors, and hence an incentive for the skilled person to further characterise the SW780 model used in document D4. This would inevitably have led to the FGFR3-BAIAP2L1 fusion gene, and the FGFR3-BAIAP2L1 fusion polypeptide encoded thereby.

Post-published document D2 demonstrated that it was obvious to further characterise the SW780 cell line in view of the disclosure in document D4 because the authors of document D2 were directly motivated by the results reported in document D4 to further investigate the FGFR3 expressed in (non-mutant) cell lines exhibiting high sensitivity to FGFR3 inhibitors, including SW780. This led directly to the identification of the fusion polypeptides.

Since document D4 taught that different bladder tumour cell lines were likely to reflect the distinct tumour make-up and FGFR3 dependence of individual tumours (page 81, left-hand column), the skilled person would have expected genetic differences between the two cell lines RT112 and SW780, which were both known to overexpress wild-type (i.e. non-mutant) FGFR3. The skilled person would have sought to characterise both as sources of potential biomarkers of FGFR sensitivity.

Having identified a FGFR3-BAIAP2L1 fusion gene in SW780, and also in view of the state-of-the-art knowledge regarding the role of FGFR3 abnormalities as "drivers" for the development of cancer, it would have been obvious to look for an expression of FGFR3-BAIAP2L1 fusions in cancer patients, particularly bladder cancer patients, certainly in view of the fact that the SW780 cell line is a human bladder cell line,

and in patients with other cancers known to be sensitive to FGFR inhibitors.

XIV. Appellant I (the patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted; or, in the alternative, that the opponent's appeal be dismissed and that the patent be maintained in amended form in the version of auxiliary request 1 held allowable by the opposition division; or, in the further alternative, that the patent be maintained in amended form on the basis of the claims of one of the following auxiliary requests:
- auxiliary request 2, filed as auxiliary request 4 with the statement setting out the grounds of appeal,
- auxiliary request 3, filed with the statement setting out the grounds of appeal,
- auxiliary request 4, filed as auxiliary request 2 with the statement setting out the grounds of appeal,
- auxiliary request 5, filed with the statement of grounds of appeal, or on the basis of the claims of one of auxiliary requests 6 to 9, all filed with the reply to the opponent's grounds of appeal.

XV. Appellant II (the opponent) requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Main request - claim 1 - novelty (Articles 54 and 100(a) EPC)

1. The invention disclosed in the patent aims *inter alia* at identifying cancer cell-specific biomarkers enabling personalised FGFR inhibitor-based cancer therapy (see paragraph [0014]). In particular, fusion polypeptide genes between an FGFR3 polypeptide gene and, *inter alia*, a BAIAP2L1 polypeptide gene were identified in multiple bladder and lung cancer cells (see patent, paragraph [0016]).

2. Claim 1 (see section I.) is a purpose-restricted product claim directed to a compound having "FGFR inhibitory activity" for use in a method of treating or preventing cancer in a patient who has been identified as expressing a particular biomarker or as carrying a polynucleotide encoding it. This biomarker is a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide, each polypeptide being defined by particular sequences. The claim further specifies that the claimed compound is capable of inhibiting the growth of a cancer cell expressing this fusion polypeptide or having a nucleotide encoding it.

3. The wording of claim 1 does not require that testing or screening subjects for the FGFR3-BAIAP2L1 fusion polypeptide and selecting subjects for treatment should be active steps of the claimed therapeutic use of the FGFR inhibitory compound. A subject who "has been identified" as expressing the relevant biomarker or as carrying a polynucleotide encoding does not differ from

a subject who expresses the relevant biomarker or carries a polynucleotide encoding it.

4. The board agrees with the opposition division's finding that the claimed subject-matter lacks novelty over the disclosure in document D4 relating to FGFR inhibitor compound PD173074 (identical to compound 2 of the patent and capable of inhibiting proliferation of SW780 cells). Specifically, PD173074 inhibited tumour growth in a xenograft mouse model established using the human bladder cancer cell line SW780 (see page 78, right-hand column, and the results shown in Figure 3A, third panel).

5. Document D4 does not disclose that the SW780 cell xenografts on which the compound was tested expressed a FGFR3-BAIAP2L1 fusion polypeptide.

6. The opposition division held that the individualised patient group consisting of the mice of the SW780 cells xenograft model treated by PD173074 disclosed in document D4 (see page 76, "Animals", and the results provided in Figure 3) fell squarely within the patient group defined in claim 1 (100% overlap), given that all SW780 xenograft mice inherently fulfilled the claimed expression profile. Thus, merely specifying in the claim that the patient to be treated had been identified as expressing the FGFR3-BAIAP2L1 fusion polypeptide did not confer novelty over the patient group disclosed in document D4. The patient identification step was not part of the medical use in the claim, because this step was supposed to have been carried out before said medical use and had no effect on the patients that would allow them to be distinguished from patients who had not undergone the identification process.

7. It is an established principle in the case law of the boards of appeal that the use of the same compound in the treatment of the same disease for a particular group of subjects can be recognised as being novel only if it is carried out on a new group of subjects which is distinguished from the former by its physiological or pathological status (see Case Law of the Boards of Appeal, 10th ed., 2022, "CLBA", I.C.7.2.4 (b)).

8. In the *in vivo* experiments disclosed in document D4 (see "Materials and Methods", "Animals" heading, page 76) xenografts were established by subcutaneous inoculation of male Balb/c immunodeficient nude mice with MGH-U3, SW780 or RT112 human bladder cancer cells. In each case, the tumour from a donor animal was excised and fragmented, and single fragments were implanted into the abdominal flanks of recipient mice. The xenograft mice were allocated into groups of eight (for each tumour type and condition). Treatment groups consisted of an untreated control group (eight mice) and a PD173074-treated group (eight mice). The results shown in Figure 3A demonstrate that PD173074 delays tumour growth in all three xenograft groups *in vivo* (see also page 78, right-hand column, second paragraph).

9. The SW780 xenograft mice are treated in document D4 as a distinct and separate individualised treatment group of cancer subjects, in parallel to the distinct and separate MGH-U3 and RT112 xenograft treatment groups. In the context of the disclosed *in vivo* experiments, the subgroup of SW780 xenograft mice was singled out and selected for treatment with the known FGFR inhibitor PD173074 based on the *in vitro* sensitivity of SW780 cells to this inhibitor (see Table I). Since each

of the individuals in the SW780 xenograft treatment group according to document D4 carried a tumour that expressed an FGFR3-BAIAP2L1 fusion polypeptide, 100% of the individuals in this treatment group fall within the patient group defined in claim 1.

10. The board holds that given this situation the claim does not define a new therapeutic use of a compound based on a new patient group, but merely provides more information about the known therapeutic use in the same patient group. In fact, in the specific situation of the case at hand, the later characterisation of the SW780 tumours as expressing an FGFR3-BAIAP2L1 fusion polypeptide as disclosed in the patent merely provides more information regarding the underlying genetic make-up of the tumour, but is of no consequence for the treatment of the tumours, and hence the patient group, with PD173074.

11. With reference to decision T 694/16 (Reasons 5.3 to 5.21), appellant I submitted that claim 1 provided a purposive selection of a particular group of patients.

12. This argument must fail, however, since all individuals of the SW780 xenograft treatment group disclosed (as a distinct and separate group) in document D4 had the same marker as the patients according to claim 1. Hence, there can be no question of claim 1 providing a selection from among the patient group in document D4, and the situation underlying T 694/16 does not apply to the case at hand.

13. That document D4 refers - erroneously - in Table 1 to SW780 cells as overexpressing FGFR3 wild-type does not alter the nature of the treated patient group, which

the board considers to anticipate the patient group of claim 1.

14. Having regard to the above considerations, the board concludes that the subject-matter of claim 1 of the main request lacks novelty over the disclosure in document D4.

Auxiliary request 1

Claim 1 - novelty over disclosure in document D4

15. As compared with claim 1 of the patent as granted, claim 1 of auxiliary request 1 defines the patient as human (see section IV.). The board agrees with the opposition division that this amendment results in subject-matter which is novel over the disclosure in document D4 by virtue of the patient group treated, and appellant II has not contested this.

Claim 6 - entitlement to the priority date of PD1 (Article 89 EPC)

16. Claim 6 of auxiliary request 1 is identical to claim 6 of the main request (see section I.) and relates to three alternative embodiments:
i) a method for testing cancer susceptibility of a subject,
ii) a method for testing whether a subject is affected with cancer, or
iii) a method for testing whether cancer has progressed in a subject,
each characterised by determining the presence or absence of a fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide and
wherein the method is based on the criterion that

i) a subject is more likely to develop cancer,
ii) is affected with cancer, or
iii) has progressed cancer
when the fusion polypeptide (or a polynucleotide encoding it) is detected.

17. Appellant II pursued the argument that claim 6 was not entitled to priority based on PD1 in respect of aspects ii) and iii). As a consequence, the claimed subject-matter lacked an inventive step in view of the disclosure in document D1.

18. According to the opposition division, paragraph [0175] of PD1, in particular, disclosed aspect ii) of claim 6 and, in view of the disclosure in paragraph [0150], also aspect iii) of the claimed method. These paragraphs read as follows (emphasis added by the board):

"*[0150]*
In the present invention, "cancer" generally refers to malignant neoplasm which may be metastatic or non-metastatic. For instance, non-limiting examples of cancer that develops from epithelial tissues such as gastrointestinal tract and skin include ... Meanwhile, non-limiting examples of sarcoma that develops from non-epithelial tissues (stroma) such as muscles include [...] *Furthermore, non-limiting examples of hematological cancer derived from hematopoietic organs include* [...]."

"[0175]
Specifically, the methods of the present invention include methods for testing cancer susceptibility of a subject by testing/determining the presence or absence of a fusion polypeptide of the present invention in a

sample (tumor tissue, normal tissue, and various body fluid specimens containing cancer or normal cells (blood, serum, urine, saliva, etc.) collected from the subject (cancer patient, person who may be affected with cancer, person with the risk of getting cancer, or healthy person; however it is not limited to human) using the above-described methods and kits for detecting the fusion polypeptide of the present invention, wherein the method is based on the criterion that a subject is more likely to develop cancer when the fusion polypeptide is detected."

19. Paragraph [0175] refers solely to a predictive method, i.e. testing cancer susceptibility based on the criterion that the subject is more likely to develop cancer when the fusion polypeptide is detected. However, both the aspects, i.e. aspect ii) (a method of testing whether a subject is affected with cancer) and aspect iii) (a method of testing whether cancer has progressed in a subject), are diagnostic methods, which, contrary to the predictive method, are not directly and unambiguously derivable from paragraph [0175].

20. Contrary to the decision under appeal, the board also considers that the reference to a "cancer patient" in the same paragraph, paragraph [0175] (and thus in the context of the predictive methods), would not allow the skilled person to derive diagnostic aspect ii) (a method of testing whether a subject is affected with cancer) of the claimed subject matter.

21. Further contrary to the decision under appeal, the skilled person would not directly derive aspect iii) (a method for testing whether cancer has progressed in a subject) from the references in paragraph [0150] to

cancer being generally defined as "malignant neoplasm which may be metastatic or non-metastatic" or to examples of cancer that "develop[s] from" certain tissues. Although these references might be understood to include elements of progressive cancer they do not, however, allow the skilled person to derive diagnostic aspect iii) (a method of testing whether a subject is affected with cancer). Paragraph [0150] simply provides a definition of what is intended to be covered by the term "cancer" and contains no information about the nature of the method.

22. In conclusion, claim 6 of auxiliary request 1 is not entitled to the first priority date in relation to aspects ii) and iii).

Claim 6 - inventive step (Article 56 EPC)

23. As a consequence of the conclusion reached in point 22., document D1 is part of the state of the art for the embodiments of claim 6, i.e. the methods, that do not enjoy priority under aspects ii) and iii) (see point 16.).

24. Document D1 is generally concerned with the identification of targetable FGFR fusion proteins in diverse types of cancers, in the knowledge that recurrent gene fusions are an important class of "driver mutation" in cancer (see page 2, Introduction, first paragraph). It discloses the results of a clinical sequencing program to identify additional fusions in patients with advanced cancers.

25. Amongst other things, the study characterises the human bladder cancer cell line SW780 as expressing an FGFR3-BAIAP2L1 fusion polypeptide (page 5, first paragraph)

and identifies a bladder cancer patient carrying an FGFR3-BAIAP2L1 fusion gene (Figure 2). Document D1 also reports that further experiments demonstrated the central role of FGFR3-BAIAP2L1 fusion in SW780 cell proliferation (page 5, second paragraph, and page 4, last paragraph).

26. Claim 6 differs from the disclosure in document D1 by formulating a method for testing whether a subject is affected with cancer or has progressed cancer. Accordingly, the objective technical problem can be formulated as the provision of a further application of of the finding in document D1 that the fusion polypeptides are responsible for tumour proliferation.

27. Given that document D1 characterises the fusion polypeptide of claim 6 as a driver mutation for bladder cancer, the use of this fusion peptide as a marker for cancer is readily apparent to the skilled person. Therefore, testing for the fusion polypeptide to determine whether a person is affected with cancer would have been obvious to the skilled person.

28. As a consequence, the subject-matter of claim 6 of auxiliary request 1 lacks an inventive step (Article 56 EPC).

Auxiliary request 2

29. Claim 1 of auxiliary request 2 is identical to claim 1 of auxiliary request 1 (see section IV.). As compared to claim 6 of auxiliary request 1, the subject-matter of claim 6 of auxiliary request 2 no longer relates to the embodiments for which priority from PD1 was denied (see sections V. and XI. and point 22.).

Claim 1 - amendments (Article 123(2) EPC)

30. Claim 1 as filed is directed to the fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide as also defined in claim 1 as granted.

Claims 38 and 52 as filed read as follows:

"38. A method for treating or preventing cancer, comprising the step of administering an effective amount of a compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof to a cancer patient expressing the fusion polypeptide of any one of claims 1 to 7 or carrying a polynucleotide encoding the fusion polypeptide."

"52. A compound having FGFR inhibitory activity or a pharmaceutically acceptable salt thereof for therapeutic or prophylactic use in a cancer patient expressing the fusion polypeptide of any one of claims 1 to 7 or carrying a polynucleotide encoding the fusion polypeptide."

31. Apart from the restriction of the medical use to human patients and the additional functional feature *"wherein the compound is capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide*", the subject-matter of claim 1 can be derived directly and unambiguously from combining claim 1 with claim 52 or 38 of the application as filed. Claim 1 as filed already contains a restriction to the relevant FGFR3-BAIAP2L1 fusion polypeptide.

32. Support for the additional functional feature is found in the paragraph bridging pages 37 and 38 of the

original application. This section explains that various types of cancer cells express the fusion polypeptides of the invention and that the proliferation of such cells can be inhibited by compounds having FGFR inhibitory activity, thus enabling personalised medicine. The sentence "*The proliferation of cells expressing such fusion polypeptides is significantly inhibited by compounds having FGFR inhibitory activity*" (page 37, lines 32 to 33) outlines a general therapeutic principle that applies to any fusion polypeptide, including those with FGFR3 and BAIAP2L1. The feature "capable of inhibiting a growth of a cancer cell expressing the fusion polypeptide or having a nucleotide encoding the fusion polypeptide" therefore does not add subject-matter.

33. With regard to the argument of appellant II that claim 1 does not require "significant" inhibition, in contrast to the statement on page 37 as filed, the board agrees with appellant I that this is an implicit functional requirement of the medical use in the claim ("for use in a method of treating or preventing cancer in a patient who has been identified to express a fusion polypeptide ..."). Thus, this argument of appellant II does not support the conclusion that claim 1 contains added subject-matter either.

34. Regarding the restriction of the medical use to *human* patients, the board considers that the skilled person would directly and unambiguously derive from the passages on page 70 of the application as filed, referring to patient selection (page 70, lines 6 to 13, refers to *"the subject (cancer patient or person who may be affected with cancer; however it is not limited to human)"*, for example), that the invention was intended for, and applicable to, human patients.

Therefore, this feature does not introduce added subject-matter either.

35. In light of these considerations, the board concludes that claim 1 of auxiliary request 2 complies with the requirements of Article 123(2) EPC.

Document D12

36. In its statement of grounds of appeal, appellant II requested the board to overrule the opposition division's decision not to admit document D12 into the opposition proceedings and submitted arguments based on the disclosure in this document.

37. In its communication under Article 15(1) RPBA, the board noted that it was not persuaded by the submissions of appellant II, and took the view that the opposition division had exercised its discretion correctly in not admitting the document. The board was also not convinced that the circumstances of the appeal justified the admittance of document D12.

38. During the oral proceedings before the board, appellant II no longer relied on document D12 and neither reiterated the arguments based thereon nor rebutted the board's preliminary opinion.

39. For the present decision, the board has accordingly considered neither document D12 nor the arguments based on the disclosure in this document. Therefore, it has not been necessary for the board to decide on the admittance of this document or the related arguments.

Document D14 - admittance (Article 13(2) RPBA)

40. Appellant II filed document D14 with its statement of grounds of appeal to support its arguments on inventive step. The document is intended to provide evidence of the knowledge of the skilled person regarding mechanisms of FGFR activation.

41. However, at the oral proceedings before the board, appellant II sought to use document D14 in the context of sufficiency of disclosure, prompted by the submission of appellant I in response to point 27 of the board's communication under Article 15(1) RPBA (see section X.).

42. The board concurs with appellant I that points 26 and 27 of the board's communication merely reiterated arguments the parties made in the appeal proceedings, without introducing new ones. The submission by appellant I that replied to points 26 and 27 of the board's communication referred to arguments that the appellant had presented previously. As a result, the board found no exceptional circumstances justifying the admittance of D14 or the related arguments for sufficiency of disclosure.

43. The board thus decided not to admit document D14 or the related arguments for consideration in the context of sufficiency of disclosure (Article 13(2) RPBA).

Document D15 - admittance (Article 12(6) RPBA)

44. Appellant II filed document D15 for the first time with its reply to the appeal of appellant I, in the context of sufficiency of disclosure: *"responsive to the Proprietor's continued insistence that 'all known*

FGFR inhibitors' will be effective for the claimed therapeutic treatment" (see point 6.6 of its reply to the statement of grounds of appeal of appellant I).

45. As new evidence, document D15 and the submissions based thereon are to be regarded as an amendment to the appeal case of appellant II (Article 12(2) and 12(4) RPBA).

46. Appellant II did not argue that the filing of D15 was occasioned by a new argument, but referred instead to an argument which was already known by "continued insistence". This argument (that the treatment is carried out on patients expressing the relevant fusion polypeptide or carrying a polynucleotide encoding it, and can be performed generally with every FGFR inhibitor known in the art) was on file in the proceedings before the opposition division, as shown by point 3.7 of appellant I's reply to the opposition or points II.3 and II.4 of its submission dated 10 May 2019.

47. The board was not made aware of any valid reason why appellant II could not already have filed document D15 in the proceedings before the opposition division. The argument that appellant II had only recently become aware of document D15 and its potential relevance is not persuasive. The document was published before the first priority date of the patent and was discoverable in a literature search at the time. Furthermore, no reason was provided as to why the circumstances of the appeal case might have justified admitting D15 at the appeal stage.

48. On the basis of the above considerations, the board decided not to admit document D15 (Article 12(6) RPBA).

Sufficiency of disclosure (Article 83 EPC)

49. The requirement of sufficiency of disclosure must be satisfied on the effective filing date of the patent, i.e. on the basis of the information provided in the patent application as filed, together with the common general knowledge of the person skilled in the art at that time.

50. Article 83 EPC requires the patent application to disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. With respect to the invention as defined in claim 1 of auxiliary request 2, two issues need to be established:

(1) whether the skilled person would have been able, based on the disclosure in the application as filed and/or on their common general knowledge, to obtain compounds as defined in claim 1 without undue burden. These compounds are defined by two functional features, namely that (i) they have FGFR inhibitory activity and that (ii) they are capable of inhibiting the growth of a cancer cell expressing the fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide.

(2) whether, on the basis of the information provided in the patent application as filed, together with the common general knowledge of the person skilled in the art at that time, it was credible that the compound defined in the claim is suitable for the claimed therapeutic application.

51. The board considers that both criteria are met.

52. In the context of sufficiency of disclosure, the board refers to numbered paragraphs of the patent for which equivalent passages are present in the application (see point 49. above).

53. As concerns issue (1) the board agrees with the opposition division (see point 16.1 of the decision under appeal) that FGFR inhibitors, including FGFR3 inhibitors, were well known in the art (see also document D4, page 77, left-hand column, line 36). The patent provides numerous examples of FGFR inhibitors (see, for example, paragraphs [0211] to [0296], Tables 1 and 2, and Example 1) and numerous such inhibitors were also published (see, for example, documents D4 and D6). The skilled person was therefore able to choose from a considerable number of suitable compounds.

Furthermore, the patent and the application as filed disclose *in vitro* data (Example 3, Figure 7) relating to the assessment of six structurally different compounds which suppress the kinase activity of FGFR (FGFR inhibitors, compounds A to F; Tables 2-1 and 2-2) for their effect on cell proliferation on six types of human bladder cancer-derived cell lines, including cell line SW780 which expressed the fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide. All tested inhibitors demonstrated an antiproliferative effect on SW780 cells *in vitro* (see Example 3 and Table 3). No evidence was provided to the contrary.

54. Appellant II, in addressing issue (1), referred to the approach developed in particular in decision T 1063/06 (OJ EPO 2009, 516) in the context of so-called "reach-through" claims. The appellant argued that the patent

did not enable the skilled person to identify all compounds falling within the broad dual-function definition of the claim without undue burden and, accordingly, such alternatives were not available to the skilled person.

55. The board is of the opinion that the situation underlying decision T 1063/06 is not the same as that in the case at hand. The invention at stake in T 1063/06 was based on the discovery that a known illness (in this case cardiovascular disease) could be treated by compounds having the capability of stimulating the soluble guanylate cyclase enzyme independently of the heme group in the enzyme, i.e. the compounds stimulated both the heme-containing soluble guanylate cyclase enzyme and the heme-free soluble guanylate cyclase enzyme. No compounds having this capability were known in the art and such compounds could only be identified by means of a newly disclosed screening method as a new research tool. The claim under consideration in that decision was thus for the use of (hitherto unidentified and thus unknown) compounds, which were defined solely in terms of the specific new capability (function), for the manufacture of a medicament to treat a known illness.

56. By contrast, the invention underlying the case at hand relates to the identification of a subgroup of cancer patients which is susceptible to treatment with FGFR inhibitors. The inventors found that a known human cancer cell line (SW780), which was known to be susceptible to the antiproliferative effect of known FGFR inhibitors, expresses a fusion polypeptide of the FGFR3 polypeptide and the BAIAP2L1 polypeptide which was also identified in various other types of human-derived cancer cells. The claim under consideration is

for FGFR inhibitors which have the capability of inhibiting the growth of cancer cells expressing a FGFR3-BAIAP2L1 fusion polypeptide for use in a method of treating cancer in patients who express a FGFR3-BAIAP2L1 fusion polypeptide. This is not the same situation as in T 1063/06, in which any kind of compound (without guidance in terms of chemical structure or other selection rules) would have to be screened for the desired enzyme-stimulating activity.

57. In the case at hand, the functional definition has two levels, the first one being the required FGFR inhibitory activity and the second being the compound's ability to inhibit the growth of cancer cells having the relevant biomarker. Numerous FGFR inhibitors were known from and made available in the art, and are also identified by their chemical names or structures in the application as filed. These constitute a large pool of candidates. Together with the general structural and functional requirements mentioned in the application as filed, this information would, moreover, have provided some orientation to the person skilled in the art for identifying further FGFR inhibitors, if required (see paragraphs [0208] to [0297] of the patent). Testing for the second level activity against cancer cells (as described in the application as filed) would not have had to be carried out by trial and error on randomly selected compounds, but only on a limited selection of compounds, i.e. compounds chosen from the class of FGFR inhibitors. No evidence was provided to show that a large proportion of FGFR inhibitors would fail this test (in which case identifying active compounds would be an undue burden on the skilled person). While document D11, as mentioned by appellant II, used tests for the biological evaluation of compounds, this does not amount to evidence of undue burden. The argument of

appellant II that the compounds tested in the application as filed cover only a limited range of FGFR inhibitors is by itself not sufficient to raise serious doubts about other subgroups of FGFR inhibitors.

58. Appellant II also considered decision T 1959/15 to be relevant to the case at hand. The claim at issue in the case underlying decision T 1959/15 was directed to the further medical use of an inhibitor of soluble epoxide hydrolase (sEH), as such known in the art, for inhibiting cardiomyopathy. Again, the therapeutic agent was defined only functionally. The patent provided a list of known sEH inhibitors and data for two of them tested in an animal model for cardiomyopathy. The competent board held that although the patent provided a list of known compounds allegedly meeting the required functional definition, and assays for providing more compounds that exhibited this function, the requirements of Article 83 EPC were not met because the skilled person would have to resort to trial-and-error experimentation in order to identify further (unknown) compounds that met the functional definition. This represented an invitation to perform a research project and was thus an undue burden on the skilled person (see Reasons 4.3 to 4.5, 4.7 and 4.8).

59. In T 1959/15, the invention was based on the discovery that inhibitors of sEH could treat cardiomyopathy. The claim at issue was thus for inhibitors of sEH for use in inhibiting myocardiopathy. By contrast, the invention underlying the case at hand is based on the discovery that a known human cancer cell line (SW780), already known to be susceptible to the antiproliferative effect of known FGFR inhibitors, expresses a specific fusion polypeptide of the FGFR3 polypeptide and the BAIAP2L1 polypeptide. This fusion

was also identified in various types of human-derived cancer cells. The claim under consideration is thus for FGFR inhibitors which have the capability of inhibiting the growth of cancer cells expressing a FGFR3-BAIAP2L1 fusion polypeptide for use in a method of treating cancer in patients who express a FGFR3-BAIAP2L1 fusion polypeptide.

60. In the case underlying T 1959/15, the invention resided in providing a further class of compounds for treating the disease; in the present case, the invention resides in the identification of the specific genetic make-up of a subgroup of patients who are particularly susceptible to treatment with a known class of compounds. For this reason alone, the findings in decision T 1959/15 do not directly apply to the facts and circumstances of the case at hand.

61. Additionally, unlike the conclusion in T 1959/15 for the claim at stake therein, for the reasons already set out in point 57. above this board takes the view that under the circumstances of the case at hand, the mere fact that claim 1 also covers compounds beyond those shown to be suitable for the therapeutic use does not automatically equate to an undue burden of screening arbitrary compounds. Moreover, this does not result in the claim being able to be classified as a "reach-through" claim.

62. In view of these considerations, the board is of the opinion that the findings in decision T 1959/15 do not directly apply to the facts and circumstances of the case at hand.

63. Based on the above facts and considerations, the board concludes that the skilled person would have been

enabled to identify, without undue burden, the claimed compounds defined by the two functional features, namely FGFR inhibitory activity and the ability to inhibit the growth of a cancer cell expressing the fusion polypeptide comprising an FGFR3 polypeptide and a BAIAP2L1 polypeptide (see point 50., issue (1)).

64. As concerns issue (2) (see point 50.), in Example 3 of the application as filed a number of structurally different FGFR kinase-inhibiting compounds were tested *in vitro* for their effect on cell proliferation in a total of six types of human bladder cancer-derived cell lines (see Table 3), *inter alia* cell line SW780 bearing the fusion protein according to the claims. Furthermore, the fusion protein according to the claims was identified in numerous cancer cells obtained from patient samples. Based on the *in vitro* data on cells in Example 3, which were shown to be relevant *in vivo* in E xample 4, the claimed therapeutic effect is made credible. For the fusion in the claim this was indeed confirmed by the *in vivo* xenograft example (Example 6).

65. Appellant II argued - in essence based on principles developed in decision T 1063/06 - that there was serious doubt that all of the FGFR inhibitors falling within the definition in claim 1 had a sufficiently potent antiproliferative effect on cells expressing a FGFR3-BAIAP2L1 fusion polypeptide to be effective in the *in vivo* treatment of cancer in human patients according to claim 1. In particular, the patent did not demonstrate that the results of *in vitro* cell proliferation assays were predictive of *in vivo* efficacy, and FGFR inhibitors displayed a broad range of potencies in the SW780 proliferation assay. In addition, the patent contained no evidence that compound A could be used to treat cancer in a human

patient identified as expressing an FGFR3-BAIAP2L1 fusion, and merely relied on the assumption that a compound capable of inhibiting tumour growth in a mouse model constructed from the SW780 cell line could be used to treat human patients with any type of cancer who had been identified as carrying any type of FGFR3-BAIAP2L1 fusion polypeptide.

66. According to the case law of the boards of appeal, the mere fact that a claim is broad is not in itself a ground for holding that the application does not comply with the requirement for sufficiency of disclosure under Article 83 EPC. In the case at hand, appellant II expressed doubt that *all* FGFR inhibitors falling within the dual definition can be used to treat cancer in a human patient identified as expressing an FGFR3-BAIAP2L1 fusion. The experimental data in Examples 3 and 4 render such use credible at least for compound A in bladder cancer expressing the FGFR3-BAIAP2L1 fusion present in cell line SW780 (see point 64.)

67. In such a situation, the onus is on appellant II to demonstrate that there are serious doubts, substantiated by verifiable facts, that the skilled person cannot identify further claimed compounds suitable for the claimed therapeutic application.

68. Appellant II submitted in this context that FGFR inhibitors displayed a broad range of *in vitro* potencies in the SW780 proliferation assay (see document D4, Table I; Example 3 and Table 3 of the application as filed); although the compounds with the highest *in vitro* potency had been shown to be capable of suppressing tumour growth in an *in vivo* SW780 xenograft mouse tumour model (compound PD173074 in the case of document D4 and compound A in the case of

Example 6(3) of the application as filed), it was doubtful that less potent and structurally unrelated FGFR inhibitors would also inhibit tumour growth in the *in vivo* SW780 mouse model. In fact, the patent did not demonstrate that the results of *in vitro* cell proliferation assays were predictive of efficacy *in vivo*. According to appellant II, these facts raised serious doubts that *all* compounds falling within the functional definition of the claim would be therapeutically effective in the treatment of cancer in human patients identified as expressing FGFR3-BAIAP2L1. The *in vitro* testing (Example 3) and expression study (Example 4) were thus not sufficient to render the therapeutic effect for *any* FGFR inhibitor plausible for the treatment of human patients expressing an FGFR3-BAIAP2L1 fusion polypeptide.

69. However, appellant II did not provide verifiable facts to show that, under the circumstances of the case at hand, the skilled person is unable to identify, without undue burden, further compounds conforming to the definition in claim 1 that are suitable for the claimed therapeutic application, i.e. the treatment of human patients expressing an FGFR3-BAIAP2L1 fusion polypeptide. The argument questions the capability of the skilled person rather than proving an actual inability. The argument must accordingly fail.

70. Appellant II further submitted that there was no evidence that compound A could be used to treat cancer in a human patient identified as expressing an FGFR3-BAIAP2L1 fusion. It contended that the application merely relied on the *assumption* that a compound capable of inhibiting tumour growth in a mouse model constructed from the SW780 cell line could be used to treat human patients with any type of cancer who were

identified as carrying any type of FGFR3-BAIAP2L1 fusion polypeptide.

71. Also in this case, however, the board considers the argument of appellant II to merely amount to questioning the *in vivo* applicability of the invention to human patients, without providing supporting evidence. This does not amount to serious reasons on which a finding of a lack of sufficiency of disclosure of the claimed invention can be based.

72. In view of the above considerations, the board concludes that it has not been provided with convincing reasons from appellant II that the decision of the opposition division on sufficiency of disclosure was wrong.

Entitlement to the priority date of PD1 (Article 89 EPC) - claims 1, 2 and 4

73. The arguments of appellant II on the lack of priority for claims 1, 2 and 4 in essence mirrored the arguments submitted in the context of added-subject-matter and sufficiency of disclosure. In both these contexts, the board was not convinced by the arguments of appellant II and held that in relation to claim 1 the requirements of both Article 123(2) and Article 83 were fulfilled (see points 30. to 35. and 49. to 72. above, respectively).

74. In particular, as to sufficiency of disclosure, the board concluded (see point 64.) that the experimental data in Examples 3 and 4 render the claimed use credible at least for compound A in bladder cancer expressing the FGFR3-BAIAP2L1 fusion present in cell line SW780. Since PD1 contains all of the passages of

the application as filed up to Example 4, this must also apply, *mutatis mutandis*, to PD1.

75. Likewise, since the board referred only to passages that are also contained in PD1 when coming to the conclusion that claim 1 does find a basis in the application as filed, appellant II's case for a lack of disclosure of the definition of the compound in PD1 must also fail.

76. Accordingly, claims 1, 2 and 4, which were all attacked for similar reasons, can enjoy priority from PD1.

Inventive step - claim 1 (Article 56 EPC)

Closest prior art, objective technical problem

77. Document D4 (see also points 4. to 11. above in the context of the novelty of the subject-matter of claim 1 of the main request) relates to the use of FGFR inhibitors for the treatment of cancers and was used as the starting point for the assessment of inventive step.

78. Document D4 validates wild-type and mutant FGFR3 as a therapeutic target in bladder cancer by investigating the effects of known FGFR inhibitors, both *in vitro* and *in vivo*, to confirm that results of these culture models can be translated into therapeutic efficacy (see page 76, left-hand column, lines 13 to 24; page 81, right-hand column, last paragraph). Three known FGFR inhibitors were tested in cell proliferation assays against a panel of bladder cancer cell lines (Table 1) containing either FGFR3 point mutations or (reportedly) overexpressing a wild-type (i.e. non-point mutant) FGFR3 (SW780 cells). All three compounds exhibited

dose-dependent inhibition of FGFR3 in *in vitro* kinase assays (Supplemental Figure 1) and inhibited proliferation of SW780 cells. The most potent and selective FGFR inhibitor (PD173074) was successfully further tested *in vivo* in murine xenograft models derived from three different cell lines, including SW780 (see Figure 3*)*, which at the time, was believed to overexpress wild-type FGFR3.

79. Document D4 does not report that the SW780 xenograft mice expressed an FGFR3-BAIAP2L1 fusion polypeptide, nor does it describe the treatment of human cancer patients.

80. Appellant II submitted that since the subject-matter of claim 1 of the main request lacked novelty over the disclosure in document D4 (see point 14.), the difference between this disclosure and the claimed subject-matter could not be the presence in the latter of an FGFR3-BAIAP2L1 fusion polypeptide because the same fusion was present in the cell line SW780.

81. The board's conclusion that the subject-matter of claim 1 of the main request lacked novelty over the disclosure in document D4 of the treatment of SW780 xenograft mice is based on the fact that 100% of the individuals in the specifically disclosed mouse treatment group fell within the patient group defined in claim 1 of the main request (not restricted to human patients). Therefore, claim 1 did not define a new therapeutic use of a compound based on a new patient group.

82. The subject-matter of claim 1 differs from the disclosure in D4 by the patient group to be treated, namely human cancer patients expressing an FGFR3-

BAIAP2L1 fusion polypeptide or carrying a polynucleotide encoding it. The mice treated according to D4 have no overlap with this group, which, furthermore, is not restricted to the SW780 cell line.

83. The subject-matter of claim 1 also differs from the disclosure in document D4 by the characterisation of the patient group as expressing an FGFR3-BAIAP2L1 fusion, i.e. by the identification of this particular fusion as a general biomarker that is not restricted to the SW780 cell line.

84. The board thus agrees with appellant I that the objective technical problem to be solved in view of document D4 is the provision of a biomarker for targeted therapy of human cancer patients with FGFR inhibitors.

Obviousness

85. Document D4 describes the nature of the SW780 FGFR3 polypeptide explicitly as an overexpressed "wild-type" FGFR3 polypeptide (see Table 1 and page 80, right-hand column, first and second sentences) and provides no reason for the skilled person to doubt that something other than wild-type FGFR3 would be present in SW780. Indeed, the sensitivity of SW780 to the FGFR inhibitor PD173074 was demonstrated in the presumed context of wild-type FGFR3 overexpression.

86. Accordingly, the argument of appellant II that it would have been obvious for the skilled person to further characterise this cell line, and in particular to determine the form of FGFR3 which was reported, as being overexpressed in SW780 and thus arrive at the claimed subject-matter, is unpersuasive. Rather,

document D4 demonstrated that SW780 cells were useful in *in vitro* assays testing the antiproliferative effects of FGFR inhibitors and *in vivo* mouse xenograft model studies.

87. Appellant II further submitted that document D4 also stated the need for biomarkers for patient selection that were related to FGFR dependence rather than mutation status, as could be taken from the following passages on page 81:

"*Clinically, FGFR-targeted therapies are likely to be suitable only for patients whose tumours are still driven by FGFR3 and/or FGFR1 kinase activity. Our finding of resistance to targeted agents in the presence of FGFR3 mutation underscores the need to use biomarkers of FGFR dependence rather than mutation status when selecting patients for therapy in future. Our present findings indicate that upregulated expression with or without mutation may be a useful indicator*" (left-hand column, lines 14 to 22)

"*Additional investigations are required to determine suitable predictive biomarkers to identify subgroups of patients for whom such therapies may be beneficial, for example according to FGFR1/3 expression levels and FGFR3 and RAS mutation status*" (right-hand column, last sentence)

88. According to appellant II, document D4 thus provided a pointer to examine FGFR3 in cell lines overexpressing wild-type (i.e. non-mutant) FGFR3 and investigate the underlying genetic make-up of FGFR3 in the overexpressing cell lines identified in document D4 as being sensitive to FGFR3 inhibitors. This would have provided an incentive to the skilled person to further

characterise the SW780 model used in document D4, which would inevitably have resulted in the discovery of the FGFR3-BAIAP2L1 fusion gene and the FGFR3-BAIAP2L1 fusion polypeptide encoded thereby.

89. The board disagrees. While document D4 may suggest further investigations into biomarkers, in the passages referred to by appellant II, these suggestions relate, however, in the first passage to "biomarkers of FGFR dependence", as opposed to biomarkers for sensitivity to FGFR inhibitors, and, in the second passage to biomarkers in the general framework set out in document D4, namely FGFR1/3 expression levels and FGFR3 and RAS mutation status (see also the abstract). The board is thus unable to accept the assertion of appellant II that these passages suggest verifying the genetic make-up of the SW780 cell line or determining whether the cell line bears a FGFR3 fusion polypeptide. Accordingly, based on the disclosure in document D4, there is no pointer in D4 to this particular fusion polypeptide and no straightforward route leading to the fusion polypeptide of claim 1.

90. Appellant II further argued that based on document D4, it would have been obvious for a skilled person to characterise the SW780 cell line and identify the FGFR3 fusion polypeptide as demonstrated in document D2. However, since document D2 is post-published, it is not part of the state of the art relevant for the assessment of inventive step.

91. In view of the above considerations, the board concludes that starting from the disclosure of D4, identifying the FGFR3-BAIAP2L1 fusion gene and the FGFR3-BAIAP2L1 fusion polypeptide encoded thereby in the cell line SW780 would not have been obvious to a

skilled person. Therefore, the subject-matter of the claims of auxiliary request 2 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form according to the claims of auxiliary request 2, filed as auxiliary request 4 with the patent proprietor's statement setting out the grounds of appeal, and a description and drawings possibly adapted thereto.

The Registrar: The Chair:

I. Aperribay R. Hauss

Decision electronically authenticated