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Datasheet for the decision of 19 October 2022

Case Number: T 0562/20 - 3.3.08

Application Number: 12150524.2

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Language of the proceedings: EN

Title of invention:
Gene defects and mutant ALK kinase in human solid tumors

Patent Proprietor:
Cell Signaling Technology, Inc.

Opponent:
F. Hoffmann-La Roche AG

Headword:
Mutant ALK kinase in human solid tumors/CELL SIGNALING TECHNOLOGY

Relevant legal provisions:
EPC Art. 84, 113(1), 123(2)
EPC R. 106
RPBA Art. 12(4), 13

Keyword:
Main request - admitted- clarity (no)
Auxiliary request 1 - admitted - added subject- matter (yes)
Auxiliary request 2 - admitted into the proceedings (no)
Obligation to raise objections - objection dismissed

Decisions cited:
R 0002/14, T 1685/07, T 2102/08

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0562/20 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 19 October 2022

Appellant: (Patent Proprietor)	Cell Signaling Technology, Inc. 3 Trask Lane Danvers, MA 01923 (US)
Representative:	TAORMINO, Joseph STEFFERL, Andreas UNSIN, Claudia YUAN, Lingya Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent)	F. Hoffmann-La Roche AG Grenzacherstr. 124 4070 Basel (CH)
Representative:	WARNER, James MARSHALL, Cameron DEMETRIADES, Emma SALUD, Carlos BERNARD, Guillaume Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 7 January 2020 revoking European patent No. 2450437 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 2 450 437 is based on European patent application No. 12150524.2, filed as a divisional application of the earlier European patent application No. 07775495.0, filed as international patent application published as WO 2008/127248. The patent was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Article 100(b) EPC.

II. The patent proprietor (appellant) lodged an appeal against the decision of an opposition division to revoke the patent. With the statement of grounds of appeal, the appellant filed a main request, auxiliary requests 1 to 5, and new evidence (documents D79 to D95).

III. With its reply to the appeal, the respondent submitted new documents D96 to D101.

IV. By letter dated 29 April 2021, the appellant re-submitted the main request and auxiliary requests 1 to 5 in a corrected form and further submitted new auxiliary requests 6 to 13 and new documents D103 and D104.

V. With letter dated 18 July 2022, submitted after summons for oral proceedings were issued, the appellant filed new documents D105 to D108.

VI. Oral proceedings took place on 19 October 2022. During the oral proceedings, the appellant withdrew all requests on file, except auxiliary request 1, which was re-filed as main request, and auxiliary request 9,

which became auxiliary request 1. It moreover filed a new claim as auxiliary request 2. After the board announced its decision not to admit auxiliary request 2 into the proceedings, the appellant submitted in writing the following objection according to Rule 106 EPC (enclosure 3 to the minutes of the oral proceedings):

"*I hereby submit that at 19:14 I declared to the Board that my right to be heard has been violated because the Board refused to admit Auxiliary Request 2 into the proceedings".*

VII. The sole claim of the **main request** reads as follows:

"1. An ALK inhibitor for use in treating a mammalian NSCLC characterised by the expression of an EML4-ALK fusion polypeptide, wherein said ALK inhibitor inhibits ALK activity by specifically binding to the catalytic site of the enzyme, and/or binding to an ATP-binding cleft, and wherein said ALK inhibitor is a small molecule."

The sole claim of **auxiliary request 1** differs from the claim of the main request as shown:

"1. An ALK inhibitor for use in treating a ~~mammalian~~ human NSCLC characterised by the expression of an EML4-ALK fusion polypeptide, wherein said ALK inhibitor inhibits ALK activity by specifically binding to the catalytic site of the enzyme~~, and/or binding to an ATP-binding cleft,~~ and wherein said ALK inhibitor is a small molecule."

The sole claim of **auxiliary request 2** differs from the claim of the main request as shown:

"1. An ALK inhibitor for use in treating a mammalian NSCLC characterised by the expression of an EML4-ALK fusion polypeptide, wherein said ALK inhibitor inhibits ALK activity by ~~specifically binding to the catalytic site of the enzyme, and/or~~ binding to an ATP-binding cleft, and wherein said ALK inhibitor is a small molecule."

VIII. The following documents are cited in this decision:

D2: Pulford K. *et al.*, J. Cell Physiol. 199, pages 330 to 358 (2004)
D3: Marzec M. *et al.*, Laboratory Investigation, 85, pages 1544 to 1554 (2005)
D89: Duyster J. *et al.*, Oncogene, 20, pages 5623 to 5637, (2001)
D93: Sudbeck E. A. *et al.*, Clinical Cancer Research, 5, pages 1569 to 1582, (1999)
D94: Li R. *et al.*, J. Med. Chem. 49, pages 1006 to 1015, (2006)
D103 Huse M. *et* Kuriyan J.,. Cell, 109, pages 275 to 282 (2002)
D104 Olive D., Expert Review of Proteomics 1:3, pages 327 to 341 (2004)
D105 Database entry for 1IR3 crystal structure
D106 Hubbard S., EMBO J., 16 (18), pages 5573 to 5581 (1997)

IX. The submissions made by the **appellant**, as far as relevant to this decision, were as follows:

Admittance of late-filed documents

Documents D103 and D104 represented common general knowledge. Documents D105 and D106 demonstrated that

the crystal structure of human insulin receptor formed part of the common general knowledge. Documents D103 to D106 were submitted as a precautionary measure and in anticipation of problems that could arise under Articles 83 and 84 EPC.

Main request: Clarity (Article 84 EPC)

The wording "specifically binding to the catalytic site of the enzyme, and/or binding to an ATP-binding cleft" was clear in that the inhibitor might bind to a specific catalytic site of the enzyme and to the ATP-binding cleft, a portion of the catalytic site, or to the catalytic site of the enzyme or alternatively to the ATP-binding cleft.

The term "specifically binding" in the patent was used in direct connection with the phrase "catalytic site of the enzyme and/or the ATP-binding cleft". The claimed ALK inhibitors had to specifically bind to the catalytic site of the enzyme and/or the ATP-binding cleft, and not to other sites on the enzyme.

The "specificity" of ALK inhibitors could be assessed "for example" by examining the ability of such compound to inhibit ALK activity, but not other kinase activity, in a panel of kinases and/or by examining the inhibition of ALK activity in a biological sample comprising lung carcinoma cells (see paragraph [0202], lines 35 to 40 of the patent). For example, some preferred small molecule inhibitors of the ALK activity were WHI-131 and WHI-154 or their analogues, referred to in document D3. They were stated to be useful in the invention. Among other inhibitors, Gleevec® was mentioned to specifically bind and block the ATP-binding site of BCR-ABL fusion kinase (as well as other

kinases). It was therefore specific to a particular site on the ALK kinase, but was not precluded to bind to other kinases (see paragraph [0201], lines 15 to 20 of the patent).

The small molecule ALK inhibitor had to bind to the EML4-ALK fusion polypeptide "wherein said ALK inhibitor inhibits ALK activity". Thus, it had to be capable of binding specifically to the EML4-ALK fusion polypeptide at a well-defined consensus catalytic site/ATP-binding cleft such that the kinase activity of the fusion protein was inhibited to an extent useful for the treatment of mammalian cancers characterized by the expression of EML4-ALK fusion polypeptide as set forth in the claims.

Based on its common general knowledge at the priority date, the skilled person knew, where the limits of the catalytic site as well as the ATP-binding cleft of a kinase like ALK were and that the ATP-binding cleft was an integral part of the catalytic site of a protein kinase, such as ALK, and that the γ-phosphate group of the ATP molecule was transferred by a phosphorylation reaction.

The ALK was a member of the insulin receptor family. The identity of 85% between for example human and murine ALK proteins indicated that they were highly conserved across species. The boundaries of the catalytic site and ATP-binding cleft of ALK kinase could therefore be determined based on the structural informations provided in document D2. In human, the catalytic domain of ALK tyrosine kinase consisted of 254 amino acids, comprising a paired tyrosine residues (residues 1282-1283) being characteristic of the autophosphorylation sites in the major insulin receptor

family (page 331, right-hand column and Figure 1 "Tyrosine kinase domain").

It was known that certain small molecules selectively inhibited tyrosine kinases by competing for ATP binding at their kinase catalytic sites (document D94, page 1006, left-hand column, first sentence of the second paragraph). The method of selecting kinase targeted inhibitors was based on computationally verifiable characteristics (document D94, sentence bridging left-hand column and right-hand column on page 1007). An ALK homology docking model using the insulin receptor kinase domain crystal structure (PDB code: 1IR3) and the c-Abl kinase domain crystal structures bound with either the small molecule inhibitors STI-571 (Gleevec®) or PD173955 was employed to study the interactions between the small molecules and proteins. One of the docking results was illustrated in Figure 1 (page 1009, right-hand column first sentence of the last paragraph).

Document D89 provided a schematic illustration of NPM-ALK fusion protein with a tyrosine kinase domain which was aligned with other tyrosine kinase domains (Figures 1 and 2). The NPM-ALK tyrosine kinase extended from amino acid 178 to 440 and included an ATP-binding site, an active site, in part identical to the ALK kinase present EML4-ALK fusion protein. Three tyrosine residues, Tyr338, Tyr342 and Tyr343 were located within the kinase catalytic domain of NPM -ALK close to the catalytic core (Figure 2) and functionally associated with the ability of NPM-ALK to catalyze phosphorylation.

Auxiliary request 1: Article 123(2) EPC

The binding of the small molecule inhibitors to the catalytic site of the enzyme or to the ATP-binding cleft was not a selection that provided a technical teaching going beyond what was directly and unambiguously disclosed in the patent application. This binding precluded the enzyme from carrying out an aberrant phosphorylation reaction in ALK. All the examples related to "human" NSCLC cell lines, especially H2228 cells, and tumor cells from patients. Neither the treatment of human NSCLC, as introduced in claim 1, nor the selection of a single element from elements linked by the conjunction "and/or" added matter beyond what was already directly and unambiguously disclosed in the examples of the patent application. Thus, from the patent application as a whole, it was clear that the treatment of human cancer was preferred and that the binding of the inhibitor could be limited to one of the target element separated by the "and/or" conjunction (patent application, page 79, second paragraph).

Auxiliary request 2: admittance

Auxiliary request 2 was identical to the main request except that the clause "specifically binding to the catalytic site of the enzyme, and/or" was deleted. Although only submitted at the oral proceedings, admittance was justified by the fact that the appellant had been taken by surprise by the board's conclusion on the objection under Article 123(2) EPC. Thus the filing of auxiliary request 2 was a legitimate reaction to exceptional circumstances, in the sense of Article 13(2) RPBA, since a new procedural situation had been created by the new objection under Article 123(2) EPC. Moreover the conclusion reached under Article 84 EPC could not have been predicted by the appellant either,

since that issue had not been dealt with in the preliminary opinion of the board. Further, the amendment introduced in auxiliary request 2 encompassed the preferred embodiment so that the subject matter could be easily dealt with by both the board and the respondent.

Objection under Rule 106 EPC

The board violated the appellant's right to be heard, to the extent that it denied admittance of auxiliary request 2 into the proceedings, thereby not giving the appellant the possibility to react to the respondent's objection under Article 123(2) EPC, raised for the first time during the oral proceedings. In view of the admittance of the respondent's new objection, the appellant should be given the opportunity to overcome that objection, even at a late stage of the oral proceedings.

X. The submissions made by the **respondent**, as far as relevant to this decision, were as follows:

Admittance of late filed documents

Documents D103 and D104 were review articles that were not referenced in the patent and could not be considered as common general knowledge. No exceptional circumstances were identified that prevented these documents from being submitted earlier. The same also applied to documents D105 and D106, which had been filed even later.

Main request: Clarity (Article 84 EPC)

The expression "specifically binding" compared to "binding" was unclear. There was no consistent and accepted meaning for the expression "specifically binding" neither in the patent and document D3 referenced therein nor in the cited prior art. Neither the patent nor the common general knowledge provided a test for determining whether a compound achieved a "specific binding" or not. The binding specificity was a relative parameter and, without a definition, the claimed specificity could be relative to different sites on ALK, relative to all alternative enzymes or relative to different kinases. Neither the patent nor the cited prior art disclosed a test capable of determining whether an inhibitor was also binding to "other sites" on ALK enzymes.

Moreover, this functional feature could be interpreted in different ways. First, the inhibitor was specific to the claimed sites on ALK but did bind to other kinases as suggested in paragraph [0202] of the patent and shown for WHI-P131 in document D93 (paragraph bridging left-hand and right-hand column, on page 1570 and page 1579, right-hand column, second full paragraph). Secondly, the inhibitor did not bind to "other sites on the enzyme" but was free to bind to other enzymes (statement of grounds of appeal, page 6, second paragraph and patent, paragraph [0201], lines 15 to 19). Thirdly, the inhibitor had to bind and inhibit the enzyme such that the ALK inhibitor was useful "in treating a mammalian cancer" that was characterized by the expression of said EML4-ALK fusion polypeptide as recited in the claims. It was furthermore unclear whether an inhibitor specifically binding to the claimed ALK sites needed to be established when ALK was only fused to ELM4 and not to other fusion partners.

It was also unclear where the ALK inhibitors were required to bind. It was unclear what was the difference between the two binding sites and what was a compound specifically binding to the catalytic site but not binding to the ATP-binding cleft (an option specifically claimed by the term "or"). It was not apparent how a compound could specifically bind to the catalytic site of the enzyme while it was capable of "binding" (but not necessarily specifically) to the ATP-binding cleft. Two different binding standards had to be applied. Finally, there was no selection rule and no explanation how to identify such compounds by routine assays. The catalytic site and ATP-binding cleft and their borders remained unclear structures bound by unknown compounds resulting in an unclear claim 1.

Auxiliary request 1: Article 123(2) EPC

Amended claim 1 constituted a double singling out, in that it restricted the inhibitor to those which were only specifically binding to the catalytic site of the enzyme from all the other options, and in that the inhibitor was only for use in treating human NSCLC (patent application, page 79).

Auxiliary request 2: admittance

The amendments proposed with auxiliary request 2, submitted for the first time on the day of the oral proceedings, to address an issue already raised under Article 123(2) EPC against auxiliary request 1, represented a change of case. It re-extended the therapeutic treatment to mammalian NSCLC, instead of human NSCLC, and replaced the binding site defined in auxiliary request 1 with the previously deleted

alternative binding site. Auxiliary request 2 was not convergent with auxiliary request 1 and at least for this reason should not be admitted into the proceedings under Article 13(2) RPBA 2020.

Objection under Rule 106 EPC

The appellant's objection under Rule 106 EPC was not justified. There was no violation of the appellant's right to be heard in not admitting auxiliary request 2 into the proceedings. The appellant should have filed such amendments at an earlier stage of the proceedings, since the objection under Article 123(2) EPC was not newly raised at the oral proceedings and also since, as argued by the appellant, it encompassed the preferred embodiment.

XI. At the end of the oral proceedings the **parties' requests** were as follows:

The appellant (patent proprietor) requested that:

(a) the decision under appeal be set aside and

(b) the patent be maintained on the basis of the claim of the main request, filed as auxiliary request 1 with letter of 6 October 2022, or, alternatively, that the patent be maintained on the basis of one of the following auxiliary requests:

(c) auxiliary request 1, originally filed as auxiliary request 9 with letter of 29 April 2021,

(d) auxiliary request 2, filed at the appeal oral proceedings.

(e) The appellant moreover requested that documents D79 to D95 and D103 to D108 be admitted into the proceedings.

The respondent (opponent) requested that the appeal be dismissed and the patent be revoked in its entirety. It further requested that none of the main request and auxiliary requests be admitted, that documents D96 to D102 be admitted and that documents D79 to D83, D85 to D95 and D103 to 108 not be admitted into the proceedings under Article 13(2) RPBA and that the appellant's submissions contained in the letters of 18 July and 6 October 2022 not be admitted into the proceedings under Article 13(2) RPBA.

Reasons for the Decision

Admittance of late-filed documents

1. In appeal proceedings a very large number of new documents were submitted by both parties: D79 to D95 by the appellant with the grounds of appeal; D96 to D102 by the respondent with the reply to the grounds of appeal; D103 to D108 by the appellant with later letters. The respondent requested that none of D79 to D83, D85 to D95, D103 and D104 be admitted, while the appellant had no objections to the admittance of documents D96 to D102.

1.1 As regards documents D79 to D102, the board had indicated in its communication pursuant to Article 15(1) RPBA that it was inclined to admit all these documents. At oral proceedings, after the respondent stated that they did not wish to make further submissions concerning admittance of D79 to D95, the board decided to admit all of D79 to D102 into the proceedings. In view of the outcome of the present case, the board sees no need to provide reasons for this part of the decision.

1.2 As regards documents D103 to D108, D103 and D104 were filed after the reply to the statement of grounds of appeal but before the summons to oral proceedings while documents D105 to D108 were submitted after the summons were issued. Accordingly, admittance of documents D103 and D104 is governed by Article 13(1) RPBA and admittance of documents D105 to D108 by Article 13(2) RPBA. At oral proceedings, the appellant stated that it would like to rely on documents D103 to D106. Hence, admittance of documents D107 and D108 was not discussed.

1.3 Article 13(1) RPBA stipulates that any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of the board. Pursuant to Article 13(1) RPBA, the party shall provide reasons for submitting the amendment at this stage of the appeal proceedings and the board shall exercise its discretion in view of, inter alia, the current state of the proceedings, the suitability of the amendment to resolve the issues which were admissibly raised by the other party in appeal proceedings or which were raised by the board, and whether the amendment is detrimental for procedural economy.

1.4 Documents D103 and D104 were filed not to resolve issues newly raised by the other party or the board but rather to address issues under Articles 83 and 84 EPC raised in opposition proceedings. The appellant provided no reason why documents D103 and D104 could only be submitted after the reply to the statement of grounds of appeal. The fact that they allegedly represented common general knowledge (as argued by the appellant but disputed by the respondent) did not

justify that they could be filed at any time in the proceedings (Case law of the Boards of Appeal of the European Patent Office 10th edition 2022, hereinafter "Case Law", Chapter V.A.5.13.1 c)). The board thus decided not to admit D103 and D104 into the appeal proceedings (Article 13(1) RPBA).

1.5 As to documents D105 and D106, submitted after notification of the summons to oral proceedings, Article 13(2) RPBA stipulates that, in principle, such submissions shall not be taken into account unless there are exceptional circumstances which have been justified with cogent reasons by the party concerned. Since the appellant did neither establish why exceptional circumstances, justified by cogent reasons, could support the filing of those documents only at this late stage of the appeal, the board decided not to admit documents D105 and D106 into the appeal proceedings.

Main request

Admittance

2. The main request was filed as auxiliary request 1 with letter of 6 October 2022 and is identical to auxiliary request 2 filed with letter of 29 April 2021, which in turn was the "corrected form" of auxiliary request 2 filed with the statement of grounds of appeal. After hearing the parties at oral proceedings, the board came to the conclusion that the correction introduced into this request on 29 April 2021 fulfilled the requirements of Rule 139 EPC and decided to admit this request into the proceedings. However, in view of the outcome of the present case, there is no need to provide reasons for this part of the decision.

Added subject-matter (Article 123(2) EPC)

3. In its reply to the grounds of appeal, the respondent raised new objections under Article 123(2) EPC against the then main request and stated that the same objections also applied to the then auxiliary requests 1 and 2 (section 3.25 of the letter of reply to the grounds of appeal). At oral proceedings, after hearing the parties on the issue of admittance of these objections, the board decided to admit them into the proceedings, to the extent that they were limited to the amendments introduced in granted claim 1 during oral proceedings in opposition and originated from the description. The merits of these objections were then discussed with the parties and the board came to the conclusion that the main request complied with Article 123(2) EPC. However, in view of the conclusions reached by the board as regards the main request (see below), there is no need to provide reasons as to the admittance and the merits of the objections under Article 123(2) EPC.

Clarity (Article 84 EPC)

4. It is a requirement under Article 84, second sentence, EPC and in accordance with established jurisprudence of the Boards of Appeal, that the claims must be clear in themselves when read by the person skilled in the art, without any reference to the content of the description (see Case Law, II.A.3.1).

5. Claim 1 is a purpose-restricted second medical use claim, wherein the therapeutic compound is an ALK inhibitor. According to the claim, the ALK inhibitor is a small molecule and is further functionally defined by the mechanism of ALK inhibition, namely it inhibits ALK

activity by specifically binding to the catalytic site of the enzyme, and/or binding to an ATP-binding cleft. Moreover, the disease to be treated is human NSCLC (non-small cell lung carcinoma) which is characterised by the expression of an EML4-ALK fusion polypeptide (for the exact wording of the claim, see section VII. above).

6. There is no consistent and accepted meaning for the term "specifically binding" neither in the patent and document D3 referenced therein nor in the cited prior art. Neither the patent nor the prior art provide a procedure for determining whether a compound achieved a "specific binding" or not. Nor is there in the patent any definition of the type of specificity required or how it could be measured. In view of the fact that the claim requires "specifically binding" to the catalytic site but only "binding", without further restrictions, to the ATP-binding cleft, it is considered that there must be a difference between these two types of binding. However neither the patent nor the prior art teach how to distinguish them.

7. Moreover, it is also not clear where the ALK inhibitor should bind (specifically) on the ALK enzyme, because there is no clear definition in the patent or in the prior art of what is the ALK catalytic site. It is unclear where the "catalytic site of the enzyme" and "ATP-binding cleft" are located on the enzyme and what the difference is between the two binding sites. Since the inhibitors should bind to structurally not clearly defined sites of the ALK enzyme, the skilled person is left in doubt regarding whether a compound falls under the scope of protection or not.

Moreover, it is unclear what is a compound that specifically binds at the catalytic site but does not bind the ATP-binding cleft, which is an option explicitly claimed by use of the term "or". It is unclear how to identify a compound specifically binding to the catalytic site of the enzyme but being capable of "binding", even non-specifically, to the ATP-binding cleft as well.

8. Apart from the lack of clarity linked to the different types of binding and to the missing definition of the binding sites, the functional feature is further unclear because it can be interpreted in different ways.

8.1 First, this functional feature may be interpreted such that the inhibitor is specific to catalytic sites (however defined) on ALK but does not bind to other kinases, as suggested in paragraph [0202] of the patent. For example, document D93 (paragraph bridging left-hand and right-hand column on page 1570 and page 1579, right-hand column, second paragraph) showed that the compound WHI-Pl31 (an example of an ALK inhibitor according to the patent: e.g. granted claim 6) inhibited JAK3 but not JAK1 or JAK2 or other protein tyrosine kinases (PTKs).

8.2 Second, this functional feature may be interpreted such that the inhibitors "bind specifically to the catalytic site of the enzyme and/or the ATP binding cleft, and not other sites on the enzyme" (see appellant's statement of grounds of appeal on page 6 second paragraph) but may bind to other enzymes (see appellant's statement of grounds of appeal on page 6 last paragraph, and paragraph [0201], lines 15 to 20 of the patent).

8.3 Third, this functional feature may also be interpreted such that the inhibitor's binding and inhibition of the enzyme must be useful "in treating a mammalian NSCLC characterised by the expression of an EML4-ALK fusion polypeptide" as set forth in the claim (see appellant's submission of 29 April 2021, page 8, section 4.2, first paragraph).

8.4 It is further unclear whether an inhibitor specifically binding to the claimed ALK sites must be assessed when ALK is only fused to ELM4, but not to other fusion partners.

8.5 All these possible interpretations of the functional feature confirm that the skilled person is unable to determine whether a given compound is claimed or not as this would depend on which of the equally possible definitions it would have selected.

9. The appellant argued that it was clear what "specifically binding" meant and that the catalytic domains of protein tyrosine kinases and in particular ALK, being a member of the well characterised insulin receptor family, were known. The skilled person would therefore be able to determine if a compound fulfilled this functional requirement or not. The ATP-binding site was also known and was part of the catalytic site (document D94), so there was no inconsistency that the inhibitor could bind both or could bind the catalytic site but not the ATP-binding site therein. It was moreover clear from paragraphs [0201] and [0202] of the patent that the inhibition was not limited to the EML4-ALK fusion nor to the ALK enzyme and that the compound had to bind specifically enough to prevent a given conformation that would render the enzyme oncogenic.

Small molecule inhibitors of ALK were known e.g from document D3.

9.1 The board disagrees that the skilled person would be in a position to determine whether a compound specifically bound the catalytic site and/or the ATP-binding cleft of ALK. Contrary to appellant's arguments, document D3 does not provide an assay capable of detecting the specific binding of a small molecule at the "catalytic site of the enzyme" or the "ATP binding cleft" of an ALK, let alone of an EML4-ALK fusion polypeptide, because inhibition could be at any site, e.g. "other sites" present in ALK (see paragraph [0202] of the patent). Moreover, as argued by the respondent and apparent from the patent (paragraph [0201]), the two inhibitors disclosed in D3 are not stated to be specific. The appellant argued that the "specificity" of ALK inhibition could be confirmed, for example, by examining the ability of some preferred small molecule inhibitors of the ALK activity, such as WHI-131 and WHI-154 or their analogues, to inhibit ALK activity, but not other kinase activity, in a panel of kinases (see paragraph [0202], lines 35 to 40 of the patent; document D3). However, this definition of "specificity" contrasts with the specificity of Gleevec®, another small molecule inhibitor, which specifically binds to and blocks the ATP-binding site of BCR-ABL fusion kinase (as well as other kinases). It is specific to a particular site on an ALK kinase but can bind to other kinases as well (see paragraph [0201], lines 15 to 20 of the patent).

9.2 As to the definitions of catalytic site and ATP-binding site (or cleft), the board agrees that it is common general knowledge that a catalytic site encompasses the amino acids of the enzyme that are involved and

responsible for catalyzing the enzymatic reaction. The catalytic site is not a catalytic domain but constitutes a portion of the catalytic kinase domain. These different structures explain how an inhibitor may inhibit the ALK activity by specifically binding to the catalytic site of the enzyme "or" by binding to the ATP-binding cleft (see paragraphs [0202] and [0203] of the patent).

9.3 However, even if document D2 discloses that the tyrosine kinase domain of ALK is retained in various ALK fusions (see e.g. Figure 2), the board considers that it does not identify where the borders of the catalytic site or of the ATP-binding cleft are located. Document D2 describes the tyrosine kinase catalytic domain of ALK as consisting of 254 amino acids, while the paired tyrosine residues (residues 1282-1283) are present in the kinase catalytic domain and are characteristic of the major autophosphorylation sites of the insulin receptor family (see page 331, right-hand column and Figure 1 "Tyrosine kinase domain"). However, this document does neither disclose a crystal structure of ALK nor identify a catalytic site and/or an ATP-binding cleft within the ALK tyrosine kinase domain, let alone any borders of these three-dimensional structures. Thus, the board cannot agree with the appellant that the boundaries of the catalytic site and ATP-binding cleft of ALK kinase could be determined based on the structural informations provided in document D2.

9.4 Document D89, on the other hand, identifies important residues for the ALK activity, but does not provide a structural definition of the catalytic site or the ATP-binding cleft. The "active site" is annotated as residue D336 in the tyrosine kinase catalytic domain of

NPM-ALK, and the "ATP-binding site" is annotated as residue K210, thus 126 residues away from the active site (Figure 2). The ATP-binding cleft, which is a portion of the catalytic site, cannot be a single amino acid residue as suggested by the alignment in Figure 2 of document D89. It is also of no assistance to the skilled person to know that the mutation of three tyrosine residues, Tyr338, Tyr342 and Tyr343, led to a severe impairment of NPM-ALK tyrosine kinase activity, which were located within the kinase catalytic domain of NPM-ALK close to the catalytic core (Figure 2) because they might interfere with the ability of NPM-ALK to catalyze phosphorylation, when determining whether or not a small molecule binds to the ATP cleft or to the catalytic site and whether or not it does so in a specific manner.

9.5 As to document D94, even if it mentions that certain small molecules had the capacity to selectively inhibit tyrosine kinases by competing for ATP binding at their kinase catalytic sites (see document D94, page 1006, left-hand column, first sentence of the second paragraph), which is undisputed, it does not disclose whether they were capable of inhibiting the ALK activity by specifically binding to the catalytic site or by binding to the ATP-cleft. The ALK homology docking model, based on the insulin receptor kinase domain crystal structure (PDB code: 1IR3) and the c-Abl kinase domain crystal structures, bound with either the small molecule inhibitors STI-571 (Gleevec®) or PD173955, fails to define whether the small molecules bind to the catalytic site or to the ATP cleft in said kinase domain, since they were not structurally defined in the three-dimensional model provided. Even if, arguendo, they were defined in said homology docking model, document D94 fails to disclose whether the

boundaries of these structures would be identical in the case of ALK.

9.6 The board thus disagrees with the appellant that the skilled person knew, based on its common general knowledge at the priority date, where the limits of the catalytic site as well as the ATP-binding cleft of a kinase such as ALK are located. Consequently, it is not possible to decide whether a compound specifically binds "to the catalytic site of the enzyme and/or" binds "to an ATP-binding cleft" and, as a result, whether a compound is claimed or not.

10. For all these reasons, the main request is not allowable for lack of clarity (Article 84 EPC).

Auxiliary request 1
Admittance (Article 13(1) RPBA)

11. Auxiliary request 1 was filed (as auxiliary request 9) with letter dated 29 April 2021, after the statement of grounds of appeal and the reply thereto. Its admittance is thus governed by Article 13(1) RPBA.

12. After hearing the parties at oral proceedings, the board decided to admit auxiliary request 1 into the appeal proceedings. However, in view of the outcome of the present case, there is no need to give reasons for this part of the decision.

Added subject-matter (Article 123(2) EPC)

13. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the therapeutic indication is "human NSCLC" rather than "mammalian NSCLC" and in that

the feature "and/or binding to an ATP-binding cleft" was deleted.

14. The board reached the conclusion that the claimed subject-matter does not comply with Article 123(2) EPC, because there is no teaching in the application as filed combining treatment of human NSCLC with ALK inhibitors as defined in the claim.

15. The appellant contended that the binding of the small molecule inhibitors to the catalytic site of the enzyme or to the ATP-binding cleft was not a selection that provided a technical teaching going beyond what was directly and unambiguously disclosed in the patent application. The binding of the small molecule inhibitors to the catalytic site of ALK or to the ATP-binding cleft precluded the enzyme from carrying out an aberrant phosphorylation reaction in ALK. All the examples related to "human" NSCLC cell lines, especially H2228 cells, and tumor cells from patients. Thus, from the patent application as a whole, it was clear that the treatment of human cancer was preferred and that the binding of the inhibitor could be limited to one of the target element separated by the "and/or" conjunction, as explicitly stated in the description as filed, on page 79, second paragraph).

15.1 The board disagrees with the appellant's view. The passage on page 79 of the patent application as filed merely provides a general disclosure of ALK small molecule inhibitors, but not in the specific context of treating human NSCLC. As to the examples, while almost all examples may indeed relate to human NSCLC cell lines and NSCLC tumour samples, none of them teaches treatment with small molecules as defined in the claim. Example 5 uses a 3T3 fibroblast cell line transduced

with a retroviral vector to express EML4-ALK or TFG-ALK: the 3T3 fibroblast cell line is not a NSCLC cell. Moreover, like Examples 1 and 2, Example 5 does not teach ALK inhibitors at all. Likewise, Examples 6 and 7 do not refer to small molecule inhibitors targeting an aberrant ALK activity. Example 3 relates to siRNA molecules, which are not small molecule inhibitors as required by claim 1. Example 4 assesses whether two inhibitors, WHI-131 and WHI-154, are capable of inhibiting the growth and viability of fusion-expressing ALK in NSCLC cell line H2228 and in tumour cells.

15.2 Thus, only Example 4 discloses the use of two small molecule inhibitors, WHI-131 and WHI-154 to inhibit the growth of ALK fusion-expressing mammalian solid tumors and of a NSCLC cell line. There is however no direct and unambiguous disclosure in this example that only small inhibitor molecules specifically binding to the catalytic site of the enzyme must be used to treat specifically an EML4-ALK fusion polypeptide expressing human NSCLC cell or tumour. Indeed, the targeted ALK kinase inhibitors in Example 4 indifferently inhibit the growth of NSCLC tumour cells from CS010/011 or CS045 patient expressing EML4-ALK fusion proteins or from patient CS110 expressing TFG-ALK fusion proteins and from NSCLC cells from cell line H2228. Even if example 4 discloses that the NSCLC cells may be treated with a targeted inhibitor of ALK kinase, such as WHI-131 and WHI-154, there is no direct and unambiguous disclosure that the targeted inhibitor of ALK kinase must be a small molecule, let alone a group of small molecule being structurally related or unrelated to WHI-131 and WHI-154, specifically binding to the catalytic site of the enzyme but not other binding sites within the enzyme that prevents the enzyme from

adopting a conformation necessary for its activity. Hence, the combination of features present in amended claim 1 finds no direct and unambiguous disclosure in the patent application, neither in example 4 nor elsewhere.

16. It follows from all these considerations, that the subject-matter of auxiliary request 1 extends beyond the content of the patent application as originally filed and thus contravenes Article 123(2) EPC.

Auxiliary request 2
Admittance (Article 13(2) RPBA)

17. Auxiliary request 2 was filed during the oral proceedings before the board. The request differs from the main request in that the feature "specifically binding to the catalytic site of the enzyme, and/or" was deleted. Hence, claim 1 is limited to inhibitors which bind to an ATP-binding site to which WHI-131 and/or WHI-154 compound also bind.

18. The appellant argued that since the objection under Article 123(2) EPC against auxiliary request 1 was raised for the first time during the oral proceedings, it was legitimate, in accordance with the right to be heard under Article 113 EPC, that the applicant was given an opportunity to react to this newly raised objection by filing a new auxiliary request.

19. The filing of a new auxiliary request amounts to an amendment of the proprietor's appeal case and, if submitted after notification of the summons to oral proceedings, its admittance into the proceedings is subject to Article 13(2) RPBA 2020. According to this provision, which implements the third level of the

convergent approach applicable in appeal proceedings and imposes the most stringent limitations on a party wishing to amend its appeal case at an advanced stage of the proceedings, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

20. If a party submits that either the board or a party to the proceedings raised an objection for the first time, it must explain precisely why this objection is new and does not fall under objections previously raised. In the exercise of its discretion at the third level of the convergent approach, the board may also rely on criteria applicable at the second level of the convergent approach, i.e. as set out in Article 13(1) RPBA (see the explanatory remarks to the amendments to the RPBA 2020 in Supplementary Publication 2, OJ EPO 2020, page 60).

20.1 Admittedly, even if auxiliary request 2 intends to address an issue under Article 123(2) EPC, the board agrees with the respondent that said specific issue was already timely raised against claim 1 of the then auxiliary request 9 in the respondent's letter of 22 February 2022 (item 3.44), which was the respondent's first opportunity to react to the requests newly filed by the appellant with its submission of 29 April 2021, and not for the first time during oral proceedings, as submitted by the appellant: hence, no new objection was taken into account by the board. It rather appears that the appellant could and should have considered that the objections raised by the respondent in the written proceedings under Article 123(2) EPC (as

well as under Article 84 EPC) could be considered convincing by the board and be successful: that the board found that these objections had merit could not be considered an unexpected decision taken during the oral proceedings. Contrary to the appellant's submissions, there was no new procedural situation, nor an unexpected development of the proceedings, which justified the filing of a new claim request at oral proceedings.

20.2 It follows that under these circumstances, the board can neither find any "exceptional circumstance" within the meaning of Article 13(2) RPBA 2020, nor "cogent reasons" as to why the proposed amendment could not have been presented earlier.

20.3 The board considers further that even if the amendments proposed with auxiliary request 2 were to be regarded as a legitimate reaction to a new objection raised for the first time at the oral proceedings, admittance would not be justified by any of the criteria set in Article 13(1) RPBA. Auxiliary request 2 re-extends the therapeutic treatment to mammalian NSCLC, instead of human NSCLC, and replaces the binding site defined in auxiliary request 1 with the previously deleted alternative binding site. Auxiliary request 2 is therefore not convergent with auxiliary request 1 and represents a change of case. Accordingly, it gives rise to new objections and is not *prima facie* allowable.

21. Hence, auxiliary request 2 is not admitted into the proceedings under Article 13(2) RPBA 2020.

Objection under Rule 106 EPC

22. After the board announced during the oral proceedings the intention not to admit into the proceedings auxiliary request 2, in the exercise of its discretion under Article 13(2) RPBA, the appellant raised an objection under Rule 106 EPC and submitted that the appellant's right to be heard according to Article 113(1) EPC had been violated.

23. During the oral proceedings the appellant was heard at length on the question of admittance of auxiliary request 2 into the proceedings and could fully present its arguments without any restriction. The appellant's right to be heard with regard to the question of admittance of the amendment to their appeal case was thus neither restricted nor disregarded. This fact was also not contested by the appellant.

24. Their objection is rather directed against the discretionary decision of the board not to admit into the proceedings the claim amendment as specified in auxiliary request 2. In the appellant's view they should have been given the possibility to react to a changed procedural situation, which had been caused by the respondent's new objection under Article 123(2) EPC. By not admitting the appellant's auxiliary request 2, filed for the first time at the oral proceedings, the board violated their right to be heard under Article 113(1) EPC.

25. The right to be heard according to Article 113(1) EPC is an important procedural right intended to ensure that no party is caught unaware by grounds and evidence in a decision turning down his request on which that party has not had the opportunity to comment (see R 2/14 of 22 April 2016, Reasons 6.). This requirement includes the party's right to have the relevant

submissions and arguments considered and fully taken into account in the written decision in a manner that enables it to understand, on an objective basis, the reasons for the decision.

25.1 The board is however of the view that the appellant cannot derive from the right to be heard according to Article 113(1) EPC, a claim to file auxiliary requests at any given time in the appeal proceedings.

25.2 The parties are in their conduct of the proceedings not entirely free but are subject to certain restrictions, given, in particular, the need in *inter partes* proceedings to act fairly towards the other party and, more generally, the requirements of due process. Parties to *inter partes* proceedings are subject to a particular duty to facilitate due and swift conduct of the proceedings, which includes submitting all relevant facts, evidence, arguments and requests as early and completely as possible (see in particular T 1685/07, Reasons 6.1; T 2102/08, Reasons 4.3.1 and Case Law, V.A.5.2.1). Article 13(2) RPBA, and previously already Article 13 RPBA 2007, sanctions a violation of this procedural obligation, i.e. to make submissions, which are required up to a certain point in the proceedings, but which are omitted.

25.3 Had the appellant in the present case considered it necessary to file amended claims in defence of its legal position, then it would have been the appellant's obligation to file such amendments at the earliest possible time in the appeal proceedings, i.e. in direct response to the respondent's submissions of 22 February 2022. This is particularly valid, since according to the appellant the amendment is straightforward as it encompasses the preferred embodiment of the invention.

The board notes that especially when the amendments are directed to a preferred embodiment, the appellant had reasons to file them at an earlier stage of the proceedings. It should not have waited until the oral proceedings and the board's decision on the objection under Article 123(2) EPC on the first auxiliary request. If it nevertheless does so, then the appellant runs the risk that the amended claims will very likely not be admitted into the appeal proceedings, unless there are exceptional circumstances. This approach is also reflected in the RPBA, as for instance in Article 13(2) RPBA.

25.4 The board further finds that Article 13(2) RPBA does not contradict the parties' right to be heard, enshrined in Article 113(1) EPC, even when a party's amended submission is not taken into account in the appeal proceedings. This provision only regulates the strict requirements for the consideration of amendments filed at a late stage, if the party concerned has failed to take the opportunity to make such amendment at an earlier point in time.

26. For the reasons indicated above (see in particular point 20.1), there was no unexpected procedural development during the oral proceedings, which could have justified admittance of auxiliary request 2.

27. Neither can the board follow the appellant's argument that the discussion and the decisions taken at the oral proceedings could not have been predicted in view of the communication under Article 15(1) RPBA, setting the board's provisional opinion, particularly because that communication did not contain any reference to the objection under Article 84 EPC and did not contain a detailed discussion of the objection under Article

123(2) EPC. In that respect the board would like to underline that an opinion expressed in a communication pursuant to Article 15(1) RPBA is only provisional and non-binding on the board in arriving at its decision. In particular it is not aimed at providing a full discussion of all the issues at stake, its purpose rather being to set out *some of the issues to be discussed* at the oral proceedings (see point 1. of the board's communication under Article 15(1) RPBA). A party cannot therefore rely on the content of a board's preliminary opinion to argue that an objection, which had previously been raised by another party in writing, albeit not dealt with in the board's preliminary opinion, could not be expected at the oral proceedings.

On account of these reasons, the objection under Rule 106 EPC is dismissed.

Order

For these reasons it is decided that:

1. The objection under Rule 106 EPC is dismissed.

2. The appeal is dismissed.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated