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Datasheet for the decision of 10 July 2025

Case Number: T 1934/23 - 3.3.07

Application Number: 16837150.8

Publication Number: 3338779

IPC: A61K31/47, A61K31/675, A61K31/7048, A61P35/00

Language of the proceedings: EN

Title of invention:
LENVATINIB IN COMBINATION WITH ETOPOSIDE AND IFOSFAMIDE FOR USE IN TREATING A TUMOR

Patent Proprietor:
Eisai R&D Management Co., Ltd.

Opponent:
STADA Arzneimittel AG

Headword:
Lenvatinib in combination with etoposide and ifosfamide/EISAI

Relevant legal provisions:
RPBA 2020 Art. 12(6) sentence 1, 13(2)
EPC Art. 56

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Keyword:

Fresh ground of opposition - admitted (no)
Amendment after notification communication Article 15(1) RPBA - exceptional circumstances (no)
Inventive step - reasonable expectation of success (yes)

Decisions cited:

G 0010/91, G 0007/95, G 0002/21, T 1340/15, T 1437/21, T 0239/16, T 0237/15, T 1123/16, T 0096/20

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Case Number: T 1934/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 July 2025

Appellant: (Opponent)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	Eisai R&D Management Co., Ltd. 4-6-10 Koishikawa Bunkyo-ku Tokyo 112-8088 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 29 September 2023 concerning maintenance of the European Patent No. 3338779 in amended form.**

Composition of the Board:

Chairwoman	Y. Podbielski
Members:	J. Lécaillon
	J. Molina de Alba

Summary of Facts and Submissions

I. European patent 3 338 779 (hereinafter "the patent") was granted on the basis of 4 claims. The independent claim of the patent as granted read as follows:

"1. Lenvatinib or a pharmacologically acceptable salt thereof for use in treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step and it was not sufficiently disclosed.

III. The opposition division took the decision that, on the basis of the amended main request filed on 19 August 2022, the patent met the requirements of the EPC.

IV. The decision of the opposition division, posted on 29 September 2023, cited *inter alia* the following documents:

D1: Botter *et al.*, Current Opinion in Pharmacology, 16, 2014, pages 15-23
D6: The ESMO/European Sarcoma Network Working Group, Annals of Oncology, 25 (supplement 3), 2014, pages iii113-iii123
D7: EMA, Assessment report Lenvima, Procedure No. EMEA/H/C/003727/0000, 26 March 2015
D9: Gaspar *et al.*, Lancet Oncology, 2021, 22, pages 1312-1321

D14: Supplementary appendix to Gaspar *et al.*, Lancet Oncology, 2021, 22, pages 1312-1321
D17: Bruheim *et al.*, International Journal of Cancer, 129, 2011, pages 742-750
D18: Fleuren *et al.*, Biochimica et Biophysica Acta 1845, 2014, pages 266-276

V. The opposition division decided in particular as follows:

(a) The claimed subject-matter was sufficiently disclosed.

(b) The new ground of opposition under Article 100(a) EPC in combination with Article 54 EPC was not admitted into the proceedings.

(c) The claimed subject-matter involved an inventive step starting from either D6 or D7 as closest prior art. In particular, starting from D7, the distinguishing feature resided in that D7 did not disclose the efficacy of the triple combination in the treatment of osteosarcoma. The data in examples 1 to 3 of the patent and in D9/D14 substantiated said efficacy and even demonstrated an improvement over known treatments of osteosarcoma. The objective technical problem was therefore formulated as the provision of an effective treatment for osteosarcoma in humans, which was more effective than known treatments of osteosarcoma. The cited prior art did not provide any reasonable expectation of success of solving said problem with the combination of lenvatinib, ifosfamide and epotoside. The skilled person would have been aware from D6 or Dl8 that the treatment of osteosarcoma was difficult and unpredictable.

The skilled person would hence not have expected an improved efficacy from the announcement of clinical trials in D7.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the amended main request filed during the opposition proceedings on 19 August 2022. This request contained two claims and independent claim 1 read as follows:

"1. Lenvatinib or a pharmacologically acceptable salt thereof for use in treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide, and wherein the tumor is osteosarcoma."

VIII. Oral proceedings were held before the Board on 10 July 2025.

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

They further requested that the decision of the opposition division not to admit the ground of opposition under Article l00(a) EPC in combination with Article 54 EPC be overruled.

X. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained on the basis of the amended main request filed during the opposition proceedings on 19 August 2022.

They further requested that the appellant's objection of lack of novelty not be admitted into the appeal proceedings in accordance with Article 12(6) RPBA.

XI. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The fresh ground of opposition under Article 100(a) EPC in combination with Article 54 EPC raised during the oral proceedings before the opposition division was to be admitted. The reasoning of the opposition division in support of the non-admittance of this fresh ground reached beyond *prima facie* relevance. Furthermore, D7 *prima facie* anticipated the claimed subject-matter.

(b) The main request did not meet the requirement of Article 56 EPC.

D7 represented the closest prior art. This EMA assessment report of lenvatinib disclosed the announcement of a clinical trial evaluating lenvatinib in pediatric patients with relapsed or refractory osteosarcoma and an extension phase thereof to evaluate lenvatinib in combination with ifosfamide and etoposide (see page 116 under "paediatric population"). This trial corresponded to the "Study 207" reported on page 156 of D7.

Although D7 did not provide any experimental results, the claimed subject-matter did not provide a new element or technical contribution over D7 because the data in the patent did not provide more evidence of an effective treatment in humans than D7. Since there was no distinguishing feature, the

claimed subject-matter could not involve an inventive step over D7.

However, in case the efficacy of the treatment was seen as a distinguishing feature, the objective technical problem would reside in the provision of an effective treatment of osteosarcoma.

The announcement of the clinical trial and its extension phase in D7 necessarily presupposed that a successful pre-clinical study with the administered combination had been performed. Furthermore, ifosfamide and etoposide were already known as being effective in said treatment (see D1, page 17). Moreover, there was no indication in the prior art, including in D18, that no treatment of osteosarcoma would be achieved with the triple combination. The skilled person would therefore have had a reasonable expectation of success when carrying out the clinical trial announced in D7. Any improvement of the efficacy by the addition of a third agent also described to be effective in the treatment of osteosarcoma in addition to ifosfamid and etoposide would be a mere bonus effect. Finally D17 (see page 749 right column, 2nd paragraph) already suggested that lenvatinib could sensitise the tumor to other chemotherapeutic agents, so that improved efficacy could be obtained.

XII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The decision of the opposition division not to admit the fresh ground of opposition under Article 100(a) EPC in combination with Article 54 EPC should not be overturned. The opposition division

exercised its decision by applying the correct criteria of lack of *prima facie* relevance in a reasonable manner.

(b) The main request fulfilled the requirement of Article 56 EPC.

D6 represented a better choice as starting point than D7. It disclosed the anti-tumor activity of ifosfamide and etoposide (see page iii115, right column, third full paragraph) and stated that the treatment of recurrent osteosarcoma "often includes ifosfamide ± etoposide ± carboplatin" (page iii116, left column, lines 7 to 12 from the bottom). D6 hence described effective treatments. On the contrary, in the absence of a detailed protocol and experimental data, D7 disclosed nothing more than the aim of the announced clinical trial.

However, starting from D7, the distinguishing feature resided in the efficacy of the treatment and the objective technical problem was to be formulated as the provision of an effective treatment of osteosarcoma. The data provided in D9 and D14 substantiated that this problem was solved by the claimed combination.

As indicated in T 1437/21, the mere announcement of a clinical trial did not imply that positive results were necessarily expected. Furthermore, D18 (see page 273, left column last paragraph, 2nd and 3rd sentences) described primary and acquired resistance to multiple tyrosine kinase inhibitors (such as lenvatinib) and would therefore have taught the skilled person away from using such an inhibitor. Finally, D9 and D14 substantiated that

the claimed triple combination was particularly favourable in terms of efficacy since the progression-free survival of patients was higher than when treated with lenvatinib alone or other known combinations of chemotherapeutic agents (see D9, page 1319, paragraph bridging both columns). The skilled person would not have had any expectation of success of reaching such a level of efficacy.

Reasons for the Decision

Main request - filed on 19 August 2022

1. Admittance of a fresh ground of opposition

1.1 The ground of opposition under Article 100(a) EPC in combination with Article 54 EPC was not raised in the notice of opposition but only during the oral proceedings before the opposition division. The opposition division did not admit this fresh ground for lack of *prima facie* relevance of the objection raised.

1.2 The appellant requested to overturn this decision and to admit the fresh ground of opposition into the appeal proceedings. The appellant argued that the reasoning of the opposition division would reach beyond *prima facie* relevance.

Furthermore, according to the appellant, novelty had to be assessed in comparison with the patent. Since the patent did not provide evidence of the effective treatment of osteosarcoma in humans, the absence of such results in D7 was not sufficient to deny *prima facie* relevance of D7. The appellant concluded that the claimed invention did not provide any new element vis-

a-vis D7. Therefore, according to the appellant, the opposition division had applied its discretion in an unreasonable manner.

1.3 The Board observes that according to G 10/91 a fresh ground of opposition may exceptionally be admissible "in cases where, prima facie, there are clear reasons to believe that such grounds are relevant and would in whole or in part prejudice the maintenance of the European patent" (see reasons 16.).

In the present case, the opposition division had therefore to determine whether there were *prima facie* clear reasons to consider the issue of novelty over D7. In the present case, the lack of a clear direct link between the two passages of D7 cited by the appellant (passage on page 116 and study 207 on page 156) and hence the lack of unambiguous disclosure of an ongoing clinical trial with the claimed triple composition, and the absence of results on the effectiveness of the treatment for both studies appear to constitute valid reasons for the opposition division to consider the objection raised not relevant in the sense that it would not prejudice the maintenance of the European patent in line with G 10/91.

1.4 Concerning the appellant's argument on an evaluation going beyond *prima facie* relevance, the Board agrees with the observation made in T 1340/15 in the context of admittance of a fresh ground under Article 100(c) EPC, that the "*prima facie*" test for admitting the fresh ground was not to be interpreted as narrowly as meaning that a definitive conclusion on the relevance could be reached "at first glance" (see reasons 1.4).

In a similar manner, while the present reasoning of the opposition division may require a study of the disclosure of D7 going beyond a first glance, it still remains an assessment of whether there were *prima facie* clear reasons to consider the issue of novelty over D7. This is in contrast to a complete assessment on the issue of whether the claimed subject-matter is novel in view of D7.

1.5 Moreover, the argument of the appellant that the claimed invention would not provide a new element vis-a-vis D7 is not convincing.

Assessment of novelty requires to evaluate the subject-matter claimed *versus* the subject-matter disclosed in the prior art. The present claims are purpose limited product claims, which implies that the product defined therein (here triple combination of active agents) necessarily achieves the claimed therapeutic effect since the latter is a functional feature of the claims. The issue of actual substantiation of the achievement of the claimed therapeutic effect with the claimed combination is an issue of sufficiency of disclosure, not of novelty. It follows that the alleged issue of lack of experimental results in the patent raised by the appellant is irrelevant for the assessment of the novelty of the claimed subject-matter. It remains that an effective treatment of osteosarcoma with the claimed triple combination is *prima facie* not unambiguously disclosed in D7.

1.6 Accordingly, the Board sees no reason to overrule the decision of the opposition division not to admit the fresh ground of ground of opposition under Article 100(a) EPC in combination with Article 54 EPC (Article 12(6), 1st sentence, RPBA).

1.7 The Board nevertheless observes that the arguments in relation with the identification of any distinguishing feature over D7 will be taken into account in the first step of the problem-solution approach when examining the issue of inventive step starting from D7 (see G 7/95, headnote and reasons 7 and 7.2).

2. Inventive step

2.1 Closest prior art

2.1.1 The parties disagreed on the choice of the closest prior art. The appellant considered that D7 represented an appropriate choice while the respondent considered that D6 constituted a better starting point.

2.1.2 In accordance with established case law of the Boards of Appeal, when two or more pieces of prior art are feasible starting points for the assessment of inventive step, a conclusion that the subject-matter claimed is inventive can only be reached after assessing this requirement starting from all the possible pieces of closest prior art. Conversely, if the invention is obvious to the skilled person in respect of at least one of these routes, then an inventive step is lacking (see Case Law of the Boards of Appeal, 11th Edition, 2025, I.D.3.3).

2.1.3 The main request relates to lenvatinib administered in combination with ifosfamide and etoposide for use in the treatment of osteosarcoma.

2.1.4 D7 is the EMA assessment report of lenvatinib. An extension phase of a clinical trial evaluating the combination of lenvatinib, ifosfamide and etoposide in

paediatric patients with relapsed or refractory osteosarcoma is announced on page 116 under "paediatric population". However no results are provided.

2.1.5 The Board considers that D7 represents a promising starting point. For inventive step to be acknowledged, the claimed subject-matter must therefore be non-obvious over D7 as the starting point.

Problem solution approach starting from D7

2.2 Distinguishing feature

2.2.1 The respondent argued that the distinguishing feature over D7 was the efficacy of the treatment. The appellant disagreed and considered that the claimed subject-matter did not provide a new element or technical contribution over D7 because the data in the patent did not provide more indication with regard to an effective treatment in humans than D7.

2.2.2 As already detailed above (see 1.5), the distinguishing feature is evaluated with respect to the claimed subject-matter, which in the present case is defined in terms of a purpose-limited product.

However, D7 does not directly and unambiguously disclose a successful treatment of osteosarcoma with the claimed combination. The reasons are the following:

- The passage on page 116 of D7 cited by the appellant only mentions that a clinical trial of the triple combination of lenvatinib, ifosfamide and etoposide in pediatric patients with osteosarcoma will be done as an extension phase of a clinical study on lenvatinib.

- The further passage cited by the appellant (see D7, page 156) mentions a clinical study ("Study 207") in paediatric patients with an extension phase in patients with osteosarcoma to evaluate lenvatinib in combination with "two other chemotherapy agents". These agents are however not specified. Even assuming that, as argued by the appellant, this study corresponded to the one mentioned on page 116, the passage on page 156 on Study 207 does not provide any indication regarding the effectiveness of the triple combination.

- Contrary to the appellant's view, the question of whether a successful treatment could be plausible based on the double combination of ifosfamide and etoposide known as a gold standard in the treatment of osteosarcoma (see D1, page 17 under "chemotherapeutic drugs and combinations thereof") is not the appropriate standard to be applied when determining the distinguishing features.

2.2.3 As a consequence, the distinguishing feature over D7 resides in the efficacy of the treatment.

2.3 Objective technical problem

2.3.1 Based on this distinguishing feature, both parties formulated the objective technical problem starting from D7 as the provision of an effective treatment of osteosarcoma.

2.3.2 It was undisputed during the oral proceedings that this problem was solved by the claimed combination as confirmed by the data provided in D9 (see

"interpretation" in the abstract) and D14 (supplemental Figure 5 on page 11).

In this context, the Board observes that treatment of osteosarcoma with the claimed triple combination was described in the original application (see claims and *e.g.* paragraph [0014]) and *in vivo* data in animal mouse model indicated such successful treatment (see examples 1 to 3). In line with the impugned decision (see paragraph 4.3), the data provided in the post-published documents D9 and D14 can therefore by taken into account in accordance with G 2/21.

During the oral proceedings, in the context of the discussion on inventive step starting from D6, the appellant contested for the first time in the appeal proceedings that such post-published evidence could be taken into consideration. This argument, in so far as it applies to the present reasoning, is not admitted into the appeal proceedings because there were no exceptional circumstances justifying its submission at such a late-stage of the proceedings (Article 13(2) RPBA).

2.4 Obviousness

2.4.1 The key issue in evaluating inventiveness of the claimed subject-matter in the present case resides in determining whether the skilled person based on its common general knowledge and the prior art would have had a reasonable expectation of success in treating osteosarcoma with the triple combination of ifosfamide, etoposide and lenvatinib as in the clinical trial announced in D7.

2.4.2 The Board observes that, at the effective date of the patent, the use of cytotoxic drugs and combinations thereof, including ifosfamide and etoposide, was commonly recognised as the gold standard of osteosarcoma treatment (see D1, page 17, under "chemotherapeutic drugs and combinations thereof", as evidence of common general knowledge). This was also acknowledged in the application as originally filed and in the patent (see both in paragraph [0007]).

Moreover, lenvatinib was known as an antiangiogenic agent useful in the treatment of osteosarcoma and a potential effect in sensitising tumours to other chemotherapeutic agents was described (see D17, abstract, Table 1, and page 749 right column, 2nd paragraph).

Finally, as argued by the appellant, the approval of the announced clinical trial with the triple combination in osteosarcoma patients presupposes that successful pre-clinical studies were performed, which implies that no incompatibility between the three agents in terms of effectiveness and safety had been observed.

It follows that the skilled person would have expected the triple combination to be effective in the treatment of osteosarcoma.

2.4.3 The respondent argued that D18 taught the skilled person away from using an inhibitor of multiple tyrosine kinases (such as lenvatinib) due to the risk of primary and acquired resistance to these inhibitors (see page 273, left column last paragraph, 2nd and 3rd sentences).

This argument is however not convincing since this indication was not specific for lenvatinib and, as underlined by the appellant, the conclusion of D18 is that combinations of several mono- or multi-targeted receptor tyrosine kinase inhibitors should be a more effective approach (see page 273, sentence bridging both columns). Even if it could be concluded from D18, as done by the respondent, that pre-clinical studies on receptor tyrosine kinase inhibitors do not always provide an expectation of clinical success, the present situation relates to a combination with chemotherapeutic agents known to be clinically effective and not lenvatinib alone. In this specific case, successful pre-clinical studies would have provided the skilled person with a reasonable expectation that lenvatinib would not compromise the known clinical efficacy and safety of ifosfamide and itoposide for treating osteosarcoma.

2.4.4 During the oral proceedings, the respondent insisted that D9 and D14 substantiated that the triple combination was particularly favourable in terms of efficacy since the progression-free survival was better than with lenvatinib alone or with other known combinations of chemotherapeutic agents (see D9, page 1319, paragraph bridging both columns).

The Board considers however that the level of effectiveness achieved is not decisive in the present case. For the reasons detailed above (see 2.4.2), the skilled person would already have had a reasonable expectation of solving the problem posed and obtaining a safe and effective treatment of osteosarcoma with the claimed combination based on the approval of the clinical trial announced in D7 together with the common general knowledge on the combination of ifosfamide and

etoposide and the properties of lenvatinib mentioned in D17, in particular the suggested sensitisation of tumors to other chemotherapeutic agents. The claimed subject-matter therefore lacks an inventive step, irrespective of the level of activity obtained.

2.4.5 Finally, the respondent considered that, as stated in T 1437/21, the mere description of a clinical trial did not necessarily provide a reasonable expectation of success.

The Board first observes that, in the case underlying decision T 1437/21, the claimed subject-matter related to the treatment of a sub-population of patients while the clinical trial described in the prior art did not distinguish between the various sub-populations. This case therefore differs from the present one, so that the conclusion reached in T 1437/21 does not necessarily apply in the present case.

Moreover, the Board notes that the present conclusion is in line with several other decisions which considered that, under specific circumstances, the existence of a clinical trial protocol establishes a reasonable expectation of success even without results demonstrating the efficacy of the invention, unless dissuaded from this by the prior art (see *e.g.* T 239/16, T 237/15, T 1123/16, T 96/20). The Board has explained above (see paragraph 2.4.2) that those are also the circumstances of the present case.

2.5 As a result, the subject-matter of claim 1 of the main request does not involve an inventive step starting from D7. The requirement of Article 56 EPC is therefore not met.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairwoman:

B. Atienza Vivancos Y. Podbielski

Decision electronically authenticated