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Datasheet for the decision of 22 November 2023

Case Number: T 1676/21 - 3.3.07

Application Number: 12764765.9

Publication Number: 2694072

IPC: A61K31/517, C07D239/70, A61P35/00

Language of the proceedings: EN

Title of invention:
COMBINATION OF AKT INHIBITOR COMPOUND AND ABIRATERONE FOR USE IN THERAPEUTIC TREATMENTS

Patent Proprietor:
Genentech, Inc.

Opponent:
Generics (UK) Ltd

Headword:
Combination of AKT inhibitor compound and abiraterone/ GENENTECH

Relevant legal provisions:
EPC Art. 87(1), 56

Keyword:

Priority - basis in priority document (no)
Main request - Inventive (Yes)

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Beschwerdekammern

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Case Number: T 1676/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 November 2023

Appellant: (Opponent)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 July 2021 concerning maintenance of the European Patent No. 2694072 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	L. Basterreix

Summary of Facts and Submissions

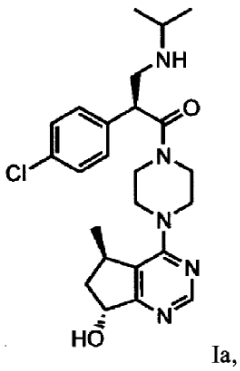
I. European patent No. 2 694 072 was granted on the basis of a set of 11 claims.

II. The patent had been opposed under Article 100 (a) EPC on the grounds that its subject-matter lacked novelty and inventive step.

III. The appeal lies from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on the main request filed on 30 April 2020.

Claim 1 of the main requests read:

"1. A compound of Formula Ia:



Ia,

in combination with abiraterone for use in the therapeutic treatment of a hyperproliferative disorder, wherein the hyperproliferative disorder is prostate cancer."

IV. The documents cited during the opposition proceedings included the following:

P1: US 61/470624 - first priority document
P2: US 61/470803 - second piority document
D1: Brett s. Carver ET AL: "Reciprocal Feedback Regulation of PI3K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer", Cancer cell, vol. 19, no. 5, 2011, pages 575-586,
D2: US 2008/051399 A1
D3: Suppression Versus Induction of Androgen Receptor Functions by the Phosphatidylinositol 3-Kinase/Akt Pathway in Prostate Cancer LNCaP Cells with Different Passage Numbers) also suggests combinations of AKT inhibitors and AR blockers, The Journal of Biological Chemistry, 278, 51,50902-50907, 2003
D4: Progression of prostate cancer by synergy of AKT with genotropic and nongenotropic actions of the androgen receptor, PNAS, 103, 20, 7789-7794, 2006
D5: Targeting the PI3K/AKT Pathway for the Treatment of Prostate Cancer, Clin Cancer Res, 15, 15. 2009
D6: www.clinicaltrial.gov; NCT01485861 available on 2 March 2012
D7: US 2009/013795
D8: Assessment report for zytiga (abiraterone). Procedure No.: EMEA/H/C/002321, European Medicines Agency, Science Medicines Health, 21 July 2011
D9: US 2010/0069357
D10: Copy of declaration of Deepak Sampath

V. According to the decision under appeal, the subject-matter of claim 1 of the main request was entitled to priority from document P2. Consequently, D1 did not represent a valid prior art for assessing inventive step.

With regard to inventive step, D2 was the closest prior art. The main request was inventive over D2.

VI. The opponent (hereinafter the appellant), filed an appeal against said decision.

VII. With a letter dated 22 April 2022, the patent proprietor (hereinafter the respondent), filed auxiliary requests 1-3.

VIII. A communication from the Board, dated 19 July 2023, was sent to the parties. In it, the Board expressed its preliminary opinion that the claimed priority was not valid, and assessed inventive step over D1, D2 and D5. The preliminary opinion of the Board was that the claimed invention was inventive over D2 and D5.

IX. Oral proceedings took place on 22 November 2023 and were conducted by videoconference.

X. The arguments of the appellant may be summarised as follows:

Validity of the priority

The priority claim from P2 was not valid, because the patent claimed a new combination of features and because the claim did not provide evidence that the medical use was effective; P2 did indeed not include any example showing the efficacy of a combination of ipatasertib and abiraterone, let alone for the treatment of prostate cancer.

Main request - Inventive step

D1 was the closest prior art since it was directed to the same purpose as the patent, namely the treatment of prostate cancer. D1 tested a combination of BEZ235 (the PI3K inhibitor dactolisib) and MDV3100 (the androgen receptor (AR) inhibitor enzalutamide), and found a "dramatic" reduction in tumour volume (see page 582). D1 disclosed that the AR inhibitor could also be abiraterone (see page 583). The distinguishing feature starting from D1 was the selection of the agent to disrupt the PI3K/AKT pathway to be the AKT inhibitor ipatasertib. The technical problem could only be defined as the provision of an alternative combination for treating prostate cancer, since the data D10 were not relevant and did not show an effect over the teaching of D1. The claimed solution was obvious in view of D2 which disclosed ipatasertib as a preferred AKT protein kinase inhibitor.

D5 was an alternative closest prior art and disclosed combinations of abiraterone and PI3K/AKT inhibitors as a class. The problem over D5 was the provision of an alternative combination for treating prostate cancer. The solution was again obvious in view of D2.

XI. The arguments of the respondent may be summarised as follows

Validity of the priority

P2 clearly disclosed to a skilled person that ipatasertib is preferred among the compounds of Formula (I) and abiraterone was at most a single selection from a list of chemotherapeutics.

Main request - Inventive step

D1 disclosed combined pharmacologic inhibition of PI3K and AR (androgen-receptor) signalling. However, it did not teach the skilled person to use an AKT inhibitor to target PI3K signalling. Similarly, it did not teach the skilled person to select abiraterone to inhibit AR signalling. D1 did not lead the skilled person to make the selections required to arrive at the claimed combination and did not teach that there could be a synergistic effect for any of these combinations. For this reason at least, the invention was not obvious. Moreover, D1 would in particular not lead the skilled person to expect that an AKT inhibitor would achieve a synergistic effect when combined with abiraterone, as it was the case with claimed combination in view of D10.

D5 did not lead the skilled person to select an AKT inhibitor for use in combination with an endocrine treatment such as anti-androgens and CYP17 inhibitors such as abiraterone. Moreover, D5 did not suggest that any such combination would be synergistic as shown by the data of D10 for the claimed combination.

XII. Requests

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

The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained according to the set of claims filed as auxiliary requests 1-3 with letter of 22 April 2022.

Reasons for the Decision

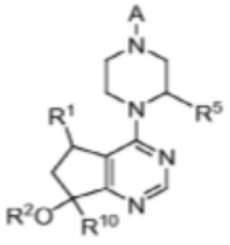
1. Validity of the priority

1.1 Claim 1 of the main request relates to a combination of ipatasertib (compound of formula Ia) with abiraterone for use in the treatment of prostate cancer.

1.2 The present patent claims two different priorities, namely US 61/470624 (P1) and US 61/470803 (P2), both from the same date of 1 April 2011.

1.3 P1 discloses the association of ipatasertib (GDC0068 in P1) with one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gencitabin, SN-38, capcitabine and temozolomide for treating a hyperproliferative disorder. In the absence of any mention of abiraterone in P1, the Board concurs with the opposition division that P1 cannot constitute a valid priority for the present patent. This point was not contested by the respondent.

1.4 P2 discloses in claim 1 and on page 2, second paragraph, the combination of a compound of the general formula (I):



(I).

with one or more agents selected from 5-FU, a platinum agent, irinotcan, docetaxel, doxorubicin, gemticabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, repamycin, lapatinib, PLX-4032, MDV3100, **abiraterone** and GDC-0973 (emphasis added in bold).

The general Formula (I) encompasses ipatasertib. In order to single out this compound it is however necessary to make multiple selections among the different substituents. Abiraterone needs also to be selected from the disclosed list. The claimed combination cannot therefore be derived from this disclosure.

1.4.1 The claims of P2 do not further single out ipatasertib (GDC0068), while claim 43 claims all compounds of formula (I) from examples 1 and 3-13 of P2, thereby excluding ipatasertib which is disclosed in example 2 from the combinations given in the claims.

Dependent claim 36 refers to the method of any of claims 2-6 wherein MDV3100 or abiraterone is administered with a compound of the general formula (I) for the treatment of prostate cancer. Dependent claim 38 discloses the combination of MDV3100 and/or abiraterone together with a compound of general formula (I) for the treatment of prostate cancer. However, these claims are just two of many pairs of dependent claims disclosing possible secondary agents (see claims 10 to 40). There is however no preference for the specific agents of claim 36 above the agents disclosed in the other dependent claims.

It is therefore not possible to derive the claimed combination directly and unambiguously from the claims of P2.

1.4.2 With regard to the description, the only disclosure of ipatasertib as such is to be found in the examples.

Example 2 discloses the preparation of ipatasertib and examples 14 and 15 study the effects of several combinations comprising ipatasertib and a second chemotherapeutic agent.

Example 14 discloses the in vitro potency of the compound of example 2, i.e ipatasertib, with certain chemotherapeutic agents. The experimental data for these combinations with 5-FU, carboplatin, CPT-12, docetaxel, doxorubicin, gemcitabine, SN 38, temodar for certain types of tumours is shown in Figures 16, 17 and 20.

Example 15 studies the in vivo tumor xenography efficacy of the compound of example 2 with docetaxel, cisplation, carboplatin, GDC-0973 and MDV3100, represented also by Figures 1-15.

None of the combination disclosed in examples 14, 15 or in the Figures relate however to a combination with abiraterone, even less for prostate cancer. The further examples 1 and 3-13 disclose alternative compounds to ipatasertib which are also claimed in claim 43 of P2. In view of this disclosure, these compounds must be seen as equal alternatives to ipatasertib.

The main argument of the opposition division in its decision was that the disclosure of ipatasertib in some examples showed that this compound was the preferred

compound which justified its isolation, i.e a selection was not necessary. In the Board's view, these examples do however not demonstrate a general preference for ipatasertib, because they relate to specific combinations with compounds different than abiraterone. Thus, rather than providing a "pointer" to the subject-matter of claim 1, the examples teach that other combinations with ipatasertib are more preferred. The absence of a general preference for ipatasertib in combination with any other secondary compound is also confirmed by the teaching of the description which mentions on page 15, last paragraph, that **"in one aspect of the invention the compound of formula (I) excludes the compound ...Formula (Ia)"**, i.e ipatasertib, which is given in its specific chemical formula on said passage.

Consequently, in the absence of a general preference for using ipatasertib in the combination, at least two selections must be made to arrive at the subject-matter of the claim; the first selection is to define the compound of general formula I to be ipatasertib and the second selection is to define the secondary agent to be abiraterone.

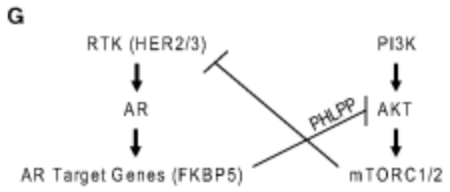
1.5 The claimed priority of P2 is therefore not valid. As a consequence, document D1 is state of the art according to Article 54(2) EPC.

2. Main request -inventive step

2.1 The invention relates to pharmaceutical combinations with activity against prostate cancer, which include ipatasertib (GDC-0068 in the patent), a compound that inhibit AKT kinase activity, and abiraterone, an anti-androgen (AR) compound.

2.2 D1 as closest prior art

2.2.1 D1 notes that prostate cancer is dependent on androgen receptor (AR) and on PI3K activation and discloses that a combined pharmacological inhibition of PI3K/AKT and AR signaled a near-complete prostate cancer regression in a prostate cancer model and human prostate cancer xenografts (see Summary or page 580)). The model of PI3K and AR pathway is illustrated in Figure G on page 582 of D1:



The authors of D1 tested BEZ235 (dactolisib), a dual inhibitor PI3K/mTOR1/2 inhibitor, and RAD001, a mTORC1 inhibitor (see page 576, right hand column, paragraph 2) and also a combination of BEZ235 and MDV3100 (enzalutamide) as AR inhibitor plus castration (see page 582). The combined PI3K and AR pathway inhibition obtained by the combination BEZ235/MDV3100 led to dramatic reductions in tumour volume in Pten mice with established prostate tumors, with a mean tumor volume reduction of 84.25%, with near complete pathological responses and no evidence of residual cell proliferation detectable (see page 582). Combined therapy also induced regression in LNCaP xenografts, whereas average tumor volume in mice treated with either BEZ235 or castration increased; these results show that the combination BEZ235/MDV3100 has a superior effect than the addition of each individual effect,

providing therefore a synergy. D1 mentions finally that addition of BEZ235 to castration plus MDV3100 in PB-MYC mice showed no measurable effects, but that this model makes it difficult to detect any effect of combined PI3K/AR therapy (Figure 5F of page 582).

D1 does no disclose any kind of AKT inhibitor when testing combinations of PI3K plus AR inhibitors but tests individually an AKT (see Figures 2D and 2G), which appears to be AKT VIII (see page 584, "Targeted Pathway Inhibitors").

D1 further concludes to immediate implications for the design of clinical trials evaluating PI3K pathway inhibitors in prostate cancer. The preclinical data of D1 predict that a single agent PI3K pathway inhibitor results in disease stabilization, rather than tumour regression (see page 583, left hand side, 3rd par.). D1 argues then that combined therapy with AR pathway inhibitor is required for maximal efficacy. Patients with castration resistant prostate cancer are likely to require the next generation AR pathway inhibitors such as abiraterone or MDV3100.

Hence, D1 does not disclose the use of ipatasertib as the agent to disrupt the PI3K/AKT pathway and only suggests the use of abiraterone as AR inhibitor.

2.2.2 The opposition division considered the priority to be valid, and therefore inventive step could not be assessed over D1, thereby not defining the problem over this document.

The appellant defines the problem over D1 as the provision of an alternative combination for treating prostate cancer.

The respondent defines the problem as the provision of a combination therapy for prostate cancer that is synergistically active.

2.2.3 The claimed solution for any of these problems is the claimed combination of ipatasertib and abiraterone.

2.2.4 The data of D10 and of the patent were mentioned in support of the existence of a synergistic effect linked with the association of ipatasertib and abiraterone.

D10 is an inventor declaration, which discusses the *in vivo* data in the patent and presents further supporting data regarding the combination ipatasertib/abiraterone. Figures 1A and 2A respectively correspond to Figures 1 and 2 in the patent, while Figures 1B and 2B show the underlying data, i.e. the individual tumour volumes of the LuCAP35V and Du145x1 xenograft subjects; said figures and the corresponding explanations in paragraphs 3 and 4 of D10 show the synergistic effect of the combination. Figures 3A and 3B of D10 show further data in a further prostate cancer xenograft model, denoted "LnCAPx1.2". Paragraph 5 of D10 describes the 99% tumour growth inhibition against the LnCAPx1.2 xenografts that was achieved by the combination therapy of the invention, shown in Figures 3A and 3B, which confirms the data of Figures 1A and 2A.

The appellant did not contest the existence of a synergistic effect. This effect does not imply an actual improvement with respect to the compositions of D1. However, contrary to the appellant’s position the Board finds no reason why the formulation of the objective technical problem could not refer to the

presence of synergism. The combination of the active ingredients defined in claim 1 provides an effect which is more than a simple additive effect. In the Board's view it is appropriate to incorporate in the formulation of the technical problem a reference to this technical effect even if this does not represent an improvement over the state of the art. The formulation of the technical problem as the provision of a mere alternative combination for treating prostate cancer would not fully take into account the technical effects achieved by the combination invention.
Hence, since a synergy was also shown in D1 for the specific combination BEZ235/MV3100, the Board considers that the problem is as defined by the appellant, namely the provision of an alternative synergistic combination for treating prostate cancer.

2.2.5 It remains to determine whether the claimed solution is obvious. D1 and D2 were discussed in this context.

2.2.6 In the present case, the closest prior art D1 discloses the combined pharmacological inhibition of PI3K and AR signalling. This comprises a vast number of possible combinations, which includes whole classes of agents that inhibit different targets. Indeed D1 explains that PI3K pathway inhibitors can target different components of the pathway, in particular PI3K, mTORC1/2, AKT (page 576, left-hand column last paragraph of the introduction). The skilled person would not expect the synergistic effect of a combination to subsist in the vast number of possible prior art combinations. This point is addressed by D1 on page 583 (see right hand column first paragraph), wherein it is said that "because BEZ235 inhibits both PI3K and MTORC1/2, our data do not delineate which target is most critical for the observed effects of combination therapy" and states

further that dual blockade PI3K/mTORC1/2 inhibition (BEZ235) is superior to mTORC1 inhibition (RAD001) when combined with AR blockade and that MEK inhibition (PD0325901) is relatively ineffective. Further pathway activation or inhibition are considered in page 583 of D1. It results from these considerations that D1 still questions all possible combinations. In the absence of any theoric explanation allowing the skilled person to predict which combinations would provide a synergistic effect, the skilled person would not find any guidance in D1 for finding alternative synergistic treatments.

Moreover, D1 does not provide any incitation to use an AKT inhibitor to target PI3K signalling, even less ipatasertib. When testing combined PI3K and AR inhibition in D1, the PI3K inhibitors were indeed BEZ235, a P3K/mTOR inhibitor, and RAD001, a mTORC1 inhibitor (see page 576, right hand column, paragraph 2, for instance). D1 did not use any type of AKT inhibitor when testing combinations of PI3K plus AR inhibitors, but only in monotherapy such as with the AKT inhibitor AKT VIII (cf. Figure 2(D) or page 584). This appears to highlight the fact that D1 does not disclose AKT to be a particularly important element of the PI3K pathway to be targeted. This point is further supported by the Discussion section, which asks whether PI3K or mTORC1/2 inhibition is “most critical” but does not present AKT inhibition as a possible alternative (see page 583).

With regard to AR signalling inhibition, abiraterone has been mentioned as possible combination drug for castration-resistant prostate cancer alongside “next-generation AR pathway inhibitors such as abiraterone or MDV3100” (see page 583).

Consequently, the skilled person, starting from D1, would have to choose to target the AKT component of the PI3K signalling pathway and thereafter choose ipatasertib as the AKT inhibitor, and in a second step choose the AR pathway inhibitor abiraterone to arrive at the present invention. Nothing in D1 leads the skilled person to make the above selections to expect obtaining a synergistic effect on the treatment of prostate cancer.

2.2.7 D2 discloses in example 1 ipatasertib as AKT inhibitor among numerous alternative AKT inhibitors, without any indication that ipatasertib would constitute a preferred choice among the many AKT inhibitors listed in the examples.

D2 discloses in paragraphs [0228]-[0236] the possibility of combination therapy and of a synergistic effect, but does not mention abiraterone, while AR inhibitors are only one among many other alternatives in paragraph [0234], such as anti-estrogens, aromatase inhibitors, lipid kinase inhibitors... Accordingly, there is no teaching in D2 to select ipatasertib or any other AKT inhibitor and combine it with an anti-androgen compound, even less abiraterone, for the treatment of prostate cancer.

Moreover, there is no data or evidence in D2 to suggest that a synergistic effect is achieved by any of the possible combination envisaged.

Consequently, nothing in D2 would lead the skilled person to expect a selection of a particular AKT and to combine it with a particular anti-androgen compound. The combination of the teaching of D2 with D1 does not lead to the claimed solution.

2.2.8 Accordingly, the subject-matter of the main request is inventive over D1.

2.3 D5 as closest prior art

2.3.1 D5 discusses the PI3K/AKT pathway as target for the treatment of prostate cancer (see Figure 1). On the passage bridging pages 4803 and 4804, D5 mentions possible combinations of PI3/AKT inhibitors with anti-androgens and CYP17 inhibitors such as abiraterone, namely that "rational combinations of PI3K/AKT inhibitors with endocrine treatments such as anti-androgens and CYP17 inhibitors such as abiraterone are therefore likely to be investigated in the future, and could restore sensitivity to these agents".

D5 does not disclose a specific combination, even less a combination as claimed.

2.3.2 The opposition division identified the problem as the provision of a synergistic combination, on the basis of D10.

The appellant considers the problem to be the provision of an alternative combination for treating prostate cancer.

2.3.3 In the appellant's view, D10 is not relevant to the objective technical problem starting from D5, since D5 discloses combinations of abiraterone and PI3K/AKT inhibitors as a class. The appellant considers that the patentee’s comparison between the combination and the monotherapies is irrelevant from this starting point.

2.3.4 D10 shows that the claimed combination provides a synergistic action on the treatment of prostate cancer (cf. point 2.2.3 above) in comparison to the monotherapy of ipatasertib and abiraterone.

The Board considers that a comparison with the combination or class of compounds suggested in D5 is not possible, in particular since this document discloses a theoretical teaching and remains very general and unspecific. The skilled person is indeed not taught to select a specific PI3K/AKT inhibitor or even a particular AKT inhibitor in D5. For each identified class of PI3K/AKT inhibitor, i.e. PI3K inhibitors, AKT inhibitors and mTOR inhibitors, D5 cites several possibilities (see page 4803). The second part of the hypothetical combination encompasses anti-androgens and CYP17 inhibitors, with abiraterone being cited, namely also several alternatives. Consequently, a comparison over all the possible combinations disclosed in D5 appears unrealistic. Furthermore, for the reasons provided in point 2.2.4 above it is appropriate in the Board's view to incorporate in the formulation of the technical problem a reference to the synergistic effect.

2.3.5 Since D5 does not provide an explicit combination and any evidence that a possible drug combination envisaged therein might provide a synergistic effect on the treatment of prostate cancer, the problem is as defined by the opposition division in its decision (see 2.3.2 above).

2.3.6 The claimed solution, namely the combination of ipatasertib and abiraterone for the treatment of prostate cancer is not obvious over D5.

D5 does indeed not identify AKT inhibition as a preferred target for prostate cancer treatment and the passage quoting the AKT inhibitors remains very hypothetical with regard to their efficacy and the class of AKT inhibitors possibly efficient and tolerated. In any case, ipatasertib is not mentioned (see page 4803). The skilled person faced with the problem of finding a synergistic composition for the treatment of prostate cancer would not find in D5 any teaching towards the combination of claim 1.

For the reasons given in point 2.2.7 above, the subject-matter of claim 1 is inventive also when considering the teaching of D5 in combination with the teaching of D2.

2.3.7 Consequently, the claimed subject-matter is inventive over D5.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated