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Datasheet for the decision of 28 July 2023

Case Number: T 0814/22 - 3.3.07

Application Number: 18155644.0

Publication Number: 3351246

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Language of the proceedings: EN

Title of invention:
RAPAMYCIN DERIVATIVE FOR THE TREATMENT OF A SOLID TUMOR ASSOCIATED WITH DEREGULATED ANGIOGENESIS

Patent Proprietor:
Novartis Pharma AG

Opponents:
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Zentiva Pharma GmbH
Dr. Reddy's Laboratories Ltd./ Betapharm Arzneimittel GmbH
Generics [UK] Limited
Teva Pharmaceutical Industries Ltd.
ARROW GENERIQUES

Headword:
Everolimus and aromatase inhibitors/NOVARTIS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - obvious modification

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Beschwerdekammern

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Case Number: T 0814/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 July 2023

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 30 March 2022 rejecting the oppositions filed against European patent No. 3351246 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman A. Usuelli
Members: J. Molina de Alba
Y. Podbielski

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision rejecting the nine oppositions filed against European patent No. 3351246.

II. The following documents are referred to in the present decision:

D1 I.C. Smith et al., Current Pharmaceutical Design, 6, 2000, 327-43

D7 WO 97/47317 A1

D9 K. Yu et al., Endocrine-Related Cancer, 8, 2001, 249-58

D9a Letter from Mr Z. Khan dated 6 August 2019

D10 I. Beuvink et al., Proceedings of the American Association for Cancer Research, 42, 2001, Abstract No. 1972

D12 WO 02/066019 A2

D21 N. Tsuchiya et al., Int. J. Clin. Oncol., 5, 2000, 183-7

D24 M. Hidalgo et al., Oncogene, 19, 2000, 6680-6

D26 W. Schuler et al., Transplantation, 64, 1997, 36-42

D34 F.J. Dumont, Current Opinion in Investigational Drugs, 2(9), 2001, 1220-34

D34a Letter from Mr Z. Khan dated 19 September 2019

D37 L.J. Scott et al., Drugs, 58(4), 1999, 675-80

D43 Declaration by Prof. W. Eiermann dated 17 February 2020

D50 E. Crucitta et al., International Journal of Oncology, 17, 2000, 1037-41

D63b H. Hosoi et al., Cancer Research, 59, 1999, 886-94

D68 R. Sedrani et al., Transplantation Proceedings, 30, 1998, 2192-4

D81 G.B. Mills et al., PNAS, 98(18), 2001, 10031-3

D113 A.C. Wolff et al., Journal of Clinical Oncology, 31(2), 2013, 195-202

D114 G.F. Fleming et al., Breast Cancer Res. Treat., 136(2), 2012, 355-63

D120 EP 0562853 A1

D121 S.N. Sehgal et al., The Journal of Antibiotics, XXXVI(4), 1983, 351-4

D123 J. Alexandre et al., Bull. Cancer, 86(10), 1999, 808-11

D124 J.J. Gibbons et al., Proceedings of the American Association for Cancer Research, 40, 1999, Abstract No. 2000

D125 H.H. Neumayer et al., Br. J. Clin. Pharmacol., 48, 1999, 694-703

D170 Declaration by Prof. S.R.D. Johnston dated 20 April 2022

III. The patent in suit stems from European patent application 18155644.0, which was filed as a third-generation divisional of European patent application 02719864.7. The patent had been granted with two claims. Independent claim 1 as granted reads as follows:

"*1. 40-O-(2-hydroxyethyl)-rapamycin for use in combination with an aromatase inhibitor for the treatment of hormone receptor positive breast tumors.*"

The compound 40-O-(2-hydroxyethyl)-rapamycin is also known as everolimus. Other synonyms are RAD001 and SDZ RAD (D34, page 1220, first paragraph).

In the following, hormone receptor positive breast tumours will be referred to as HR+ breast tumours.

IV. In the decision under appeal, the opposition division found, among other things, that:

- the patent did not add subject-matter beyond the content of the application and the earlier applications as filed,
- the claimed subject-matter was sufficiently disclosed in view of the anti-angiogenic and anti-proliferative effect of everolimus in several tumour types shown in the patent and considering the knowledge in the art (D21 and D37) that aromatase inhibitors were suitable for treating HR+ breast tumours,
- D9 belonged to the prior art because claim 1 did not enjoy the earliest priority date, and
- starting from any of the documents cited by the appellants as the closest prior art, including D9, the subject-matter of claim 1 was inventive.

V. Each of opponents 1 to 9 (appellants 1 to 9, respectively) filed an appeal against the decision. In their statements of grounds of appeal, the appellants requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

VI. In its reply to the appeals, the respondent (patent proprietor) requested that the appeals be dismissed. In addition, the respondent maintained the sets of claims

filed during the opposition proceedings as auxiliary requests 1 to 9 and filed document D170.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it further specifies that the HR+ breast tumours are advanced.

Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it further specifies that the treatment is for inhibiting or controlling deregulated angiogenesis.

Claim 1 of auxiliary request 3 differs from claim 1 as granted in that it further specifies that the treatment is for inducing regression of the HR+ breast tumours.

Claim 1 of auxiliary request 4 differs from claim 1 as granted in that it further specifies that everolimus is to be administered orally.

Claim 1 of auxiliary request 5 differs from claim 1 as granted in that it further specifies that the HR+ breast tumours are solid.

Claim 1 of auxiliary request 6 differs from claim 1 of auxiliary request 5 in that it further specifies that the solid HR+ breast tumours are other than lymphatic cancer.

Claim 1 of auxiliary request 7 differs from claim 1 as granted in that it further specifies that the treatment involves no more active ingredients.

Claim 1 of auxiliary request 8 differs from claim 1 of auxiliary request 4 in that it further specifies that everolimus is orally administered in a unit dosage form

comprising from 0.25 to 10 mg everolimus together with one or more pharmaceutically acceptable diluents or carriers.

Claim 1 of auxiliary request 9 is identical to claim 1 as granted.

VII. At the request of appellants 5, 6 and 7, the Board accelerated the appeal proceedings pursuant to Article 10(3) RPBA.

VIII. The Board summoned the parties to oral proceedings and issued a communication under Article 15(1) RPBA which included its preliminary opinion on the case.

IX. Oral proceedings were held before the Board on 27 and 28 July 2023. At the end of the oral proceedings, the Board announced its decision.

X. The appellants' arguments relevant to the present decision can be summarised as follows.

The subject-matter of claim 1 as granted did not involve an inventive step starting from document D9 as the closest prior art.

According to D9, the rapamycin derivative CCI-779 inhibited HR+ breast tumour cell lines both *in vitro* and *in vivo*. The anti-tumour effect of CCI-779 was based on its ability to inhibit the mammalian target of rapamycin (mTOR) protein, which led to the arrest of tumour cell growth. D9 proposed the combination of CCI-779 with an anti-estrogen to enhance the effect against HR+ breast tumours.

The subject-matter of claim 1 differed from the content of D9 in that the mTOR inhibitor was everolimus rather than CCI-779, and in that the mTOR inhibitor was combined with an aromatase inhibitor. The objective technical problem solved by these differences was the provision of an alternative combination for treating HR+ breast tumours.

The solution proposed in claim 1 as granted was obvious in view of document D10 and the common general knowledge.

D10 taught that RAD001, a synonym of everolimus (D34), had anti-tumour activity in a number of human tumour cell lines by mTOR inhibition. Its oral administration to nude mice inhibited the growth of human tumour xenografts. Therefore it was obvious that everolimus, as an mTOR inhibitor with anti-tumour properties, constituted an alternative to CCI-779.

The respondent's interpretation that D10 reported only two *in vitro* tests and that the human tumour xenografts were not solid was flawed. The respondent was also wrong in trying to discredit D10, a publication presented at a conference by respected scientists. Furthermore, contrary to the respondent's contention, the prior art did not teach away from the anti-tumour properties of everolimus. It was clear from D10 that everolimus had an *in vitro* and an *in vivo* anti-tumour effect. This was also apparent from the results on page 16 of D7, which were misinterpreted by the respondent.

With regard to the combination with an aromatase inhibitor, the use of aromatase inhibitors for preventing estrogen biosynthesis in post-menopausal women and thus treating HR+ positive breast tumours was

common general knowledge (see e.g. D37 and D50). Therefore the combination of everolimus with an aromatase inhibitor was obvious.

XI. The respondent's arguments relevant to the present decision can be summarised as follows.

D9 was not the best choice of closest prior art. Although D9 related to the treatment of HR+ breast tumours, it did not disclose the use of either everolimus or an aromatase inhibitor. In addition, the treatment of HR+ breast tumours with CCI-779 was not proven to be effective in D9. The document merely suggested a therapy that in the end did not work. Subsequent studies showed that CCI-779 neither was suitable for treating HR+ breast tumours (D113) nor improved the effect of an aromatase inhibitor (D114).

The two differences between the subject-matter of claim 1 as granted and D9 resulted in an effective method for treating HR+ breast tumours. Therefore the objective technical problem was the provision of an effective alternative combination therapy to treat HR+ breast tumours.

D10 did not render the solution proposed in claim 1 obvious because it did not provide the skilled person with any expectation that everolimus would exhibit an *in vivo* anti-tumour effect, let alone one against HR+ breast tumours. The skilled person would not have identified the compound RAD001 in D10 as being everolimus, since the content of D34 was not common general knowledge. Furthermore, D10 did not disclose any test on HR+ breast tumour cell lines. It merely reported on two *in vitro* studies, one of which demonstrated that RAD001 had no anti-tumour effect even

if it could inhibit mTOR. With regard to the *in vivo* studies, D10 did not specify the tumour type tested in mice. The tests could have been carried out on lymphoma or leukaemia and the results would not be applicable to solid tumours. In addition, the low number of times that D10 had been cited in the scientific literature indicated that its teaching was not significant.

Actually, the prior art taught against replacing CCI-779 with everolimus. Everolimus and CCI-779 were rapamycin derivatives of different natures that had been developed for different purposes. They had different routes of administration (D24 and D26) and very different half-lives (D24 and D125). CCI-779 was an ester prodrug developed to retain the anti-tumour activity of rapamycin (D24). Everolimus was an ether derivative developed as an immunosuppressant (D26 and D68). Therefore the skilled person would not expect everolimus to have anti-tumour activity, as corroborated in D7. The fact that CCI-779 and everolimus inhibited mTOR *in vitro* did not mean that they would exhibit the same effects *in vivo*. It was known that mTOR inhibition did not necessarily translate into an anti-tumour and/or immunosuppressive effect. For instance, CCI-779 did not have a significant immunosuppresive effect (D124), while everolimus and 29-demethoxyrapamycin were immunosuppressants but did not show any anti-tumour effect (D7, D120 and D121). It was even known that the anti-tumour effect of rapamycin and CCI-779 could be mediated by a mechanism other than mTOR inhibition (D63b and D81). In any case, the inhibition of mTOR was not a relevant aspect for the skilled person, represented by a medical oncologist. The view that the skilled person would have had no reasonable expectation

that everolimus would exhibit anti-tumour properties was shared by an expert oncologist in D170.

Lastly, the skilled person had no reason to replace the anti-estrogen of D9 with an aromatase inhibitor, let alone in addition to exchange CCI-779 with everolimus. There was no suggestion in the prior art to do so, and anti-estrogens and aromatase inhibitors could not be regarded as equivalents.

XII. The parties' final requests relevant to the present decision were as follows.

- All the appellants requested that the decision under appeal be set aside and that the patent be revoked.

  Appellant 7 also requested that the case not be remitted to the opposition division under any circumstances.

- The respondent requested that the appeals be dismissed and the patent be maintained as granted (main request) or, as an auxiliary measure, that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 9 filed during the opposition proceedings and a description to be adapted thereto.

Reasons for the Decision

1. Priority (Article 87 EPC)- claim 1 as granted

In its preliminary opinion, the Board noted that the respondent had not contested the opposition division's conclusion that claim 1 as granted did not enjoy the priority right of the earlier priority application GB 0104072, filed on 19 February 2001. The Board agreed with the opposition division that GB 0104072 disclosed neither the combination of everolimus with aromatase inhibitors nor the treatment of HR+ breast tumours.

At the oral proceedings before the Board, the respondent conceded that the opposition division's finding was correct. It was undisputed that, as a consequence, documents D9, D10 and D34 belonged to the prior art under Article 54(2) EPC. These documents had been published after the invalid priority date of 19 February 2001 but before the priority date of 17 October 2001. D9a and D34a confirmed that D9 and D34 had been published in September 2001.

As a consequence, D9, D10 and D34 can be used in assessing inventive step.

2. Inventive step (Article 56 EPC) - claim 1 as granted

2.1 Claim 1 as granted is directed to the use of everolimus in combination with an aromatase inhibitor for the treatment of HR+ breast tumours. Document D9 is one of

the starting points cited by the appellants for assessing inventive step.

2.2 D9 (title and abstract) discloses preclinical tests of a compound designated as CCI-779 for the treatment of breast cancer. In its introduction, D9 explains that CCI-779 is an ester of the natural product rapamycin that was developed for intravenous administration in cancer chemotherapy. Rapamycin is a macrolide antibiotic with anti-fungal, immunosuppressive and anti-tumour properties that inhibits the mTOR protein. This protein regulates cell cycle progression by its mediation in protein translation through two direct targets: p70S6 kinase and 4E-BP1/PHAS-1. The inhibition of mTOR precludes protein translation and leads to cell growth arrest. D9 explains that rapamycin binds first to the cytoplasmic immunophilin FKBP-12, and that the complex formed then inhibits mTOR.

As several of the cell cycle targets that are regulated by mTOR appeared to be dysregulated in human breast cancer, the aim of the research reported in D9 was to study the effect of the mTOR inhibitor CCI-779 in models of human breast cancer (page 250, second paragraph). Preliminary *in vitro* tests on eight breast cancer cell lines showed that CCI-779 inhibited mTOR in all the cases. Six of the cell lines, including three that were estrogen-receptor positive (i.e. HR+), were sensitive to CCI-779 and their growth was inhibited at nanomolar concentrations (abstract and Table 1 on page 251). The other two cell lines were resistant. Based on these preliminary results, *in vivo* tests were carried out in nude mice with one sensitive and one resistant cell line (page 255, left-hand column, penultimate paragraph). The tumours of the sensitive line were inhibited by CCI-779 with tumour regression at the

higher dose. The tumour of the resistant line was not inhibited, but the difference in tumour responsiveness was not due to a failure of CCI-779 to inhibit mTOR function (page 255, right-hand column, first paragraph, last two sentences).

Considering the complementary modes of action of anti-estrogens and mTOR inhibitors, it was concluded that there was a strong rationale for combining CCI-779 with anti-estrogen therapy. D9 also referred to results, to be reported elsewhere, of *in vitro* and *in vivo* tests with such combinations in an HR+ breast cancer cell line: the compounds acted synergistically *in vitro* and CCI-779 potentiated the effect of the anti-estrogen *in vivo* (page 256, left-hand column, penultimate paragraph, last two sentences).

2.3 It was undisputed that the subject-matter of claim 1 differs from the teaching of D9 in two respects: the rapamycin derivative is everolimus instead of CCI-779, and it is combined with an aromatase inhibitor instead of an anti-estrogen.

2.4 The appellants formulated the objective technical problem solved by the subject-matter of claim 1 as being the provision of an alternative composition for the treatment of HR+ breast tumours. The respondent considered that the problem was the provision of an effective alternative combination therapy to treat HR+ breast tumours.

In the Board's view, both formulations are acceptable since they relate essentially to the same objective technical problem.

2.5 To assess whether the solution proposed in claim 1 was obvious, it needs to be established whether the skilled person would have carried out the two modifications required in D9 to arrive at the subject-matter of claim 1 in an obvious manner. In the following, the Board will explain that this was indeed the case. The skilled person would have regarded the combination of everolimus with an aromatase inhibitor as an obvious alternative to the combination of CCI-779 with an anti-estrogen for treating HR+ breast tumours.

Everolimus as an alternative to CCI-779

2.5.1 On the equivalence between CCI-779 and everolimus, the appellants referred to document D10, an abstract presented at a conference of the American Association for Cancer Research entitled "Antitumor Activity of RAD001, an Orally Active Rapamycin Derivative".

D10 reports on the *in vitro* and *in vivo* anti-tumour effect of an orally bioavailable rapamycin derivative designated as RAD001. According to D10, RAD001 demonstrated *in vitro* anti-proliferative activity against a number of human tumour cell lines. As for CCI-779 in D9, D10 identified sensitive and resistant cell lines, but in all cases RAD001 inhibited mTOR with a prolonged effect that resulted in sustained down-regulation of p70S6 kinase and 4E-BP1. As to the *in vivo* effect, D10 reported that RAD001 inhibited the growth of human tumour xenografts in nude mice by oral administration. Furthermore, the compound was well tolerated.

Considering that both CCI-779 and RAD001 were able to inhibit the growth of human tumours *in vivo* and that they did it through the same mechanism, as shown *in*

vitro, the skilled person would have reasonable expectations that RAD001 would inhibit HR+ breast tumours *in vivo*, as CCI-779 did. Furthermore, the teaching in D10 that RAD001 exerted its anti-tumour effect by oral administration, that it was well tolerated and that it had shown a sustained mTOR inhibiting effect *in vitro*, provided the skilled person with motivation to replace CCI-779 with RAD001.

The respondent argued that the skilled person would not know that RAD001 was everolimus because D10 only mentioned that RAD001 was a hydroxyethyl ether derivative of rapamycin and everolimus was not known in the field of anti-tumour agents. This argument cannot succeed. D34, which reviews the information available on the rapamycin derivative everolimus up until 2001 and thus represents common general knowledge, discloses that RAD001 is one of the synonyms of everolimus.

Therefore the skilled person was aware that RAD001 was everolimus and that it was an obvious alternative to CCI-779 for treating HR+ breast tumours.

2.5.2 Against this conclusion the respondent submitted several arguments:

- D9 did not disclose the treatment of HR+ breast tumours, it merely proposed a treatment that did not materialise into an effective therapy. Post-published documents D113 and D114 showed that CCI-779 neither effectively treated HR+ breast tumours nor improved the effect of an aromatase inhibitor.

  This argument fails because knowledge made publicly available after the effective filing date of the

application on which the patent is based cannot influence the skilled person's mindset.

- D10 did not teach that everolimus generally inhibited solid tumours *in vivo*. It merely taught that *in vitro* everolimus could successfully inhibit one cell line and that another cell line was not inhibited. With regard to the inhibition of tumours *in vivo*, the sentence in D10 on human tumour xenografts could refer to a single tumour type and did not indicate that the treated tumour was solid. Therefore the skilled person would not conclude from D10 that everolimus was effective against solid tumours *in vivo*. Moreover, D10 was not an important disclosure: it was only an abstract in a conference and had hardly been cited in the subsequent scientific literature.

  The Board disagrees. It is clear from D10 that RAD001 had shown anti-proliferative activity against a number of human tumour cell lines, not only two cell lines. D10 states that "*some tumor cell lines are very sensitive to RAD001 treatment*" and "*others are intrinsically more resistant*" (emphasis added by the Board). The two cell lines explicitly mentioned in D10 (A549 and HCT-116) were examples of one sensitive and one resistant cell line that were selected for further research. It was found that mTOR was down-regulated even in resistant cells. With regard to the growth inhibition of human tumour xenografts in mice, the Board agrees with the appellants that the skilled person would have considered that they were most likely solid tumours. First, because solid tumours are by far the most prevalent tumour types. Second, because the cell lines specifically disclosed (A549

and HCT-116) were known to form solid tumours, namely lung and colon carcinomas.

With regard to the scientific relevance of D10, the Board sees no reason to call into question the credibility of an abstract presented in a reputed conference. The fact that D10 had not been cited many times in the scientific literature after the effective filing date of the patent does not play any role in the skilled person's mindset.

- The prior art taught away from replacing CCI-779 with everolimus. Rapamycin was known to be anti-tumour and immunosuppressive. CCI-779 and everolimus were rapamycin derivatives that had been developed for improving rapamycin bioavailability with different purposes. CCI-779 had been developed as an anti-tumour agent for intravenous administration, while everolimus had been developed as an immunosuppressant for oral administration. Even if the anti-tumour and immunosuppressive effect of rapamycin derivatives were mediated by mTOR inhibition, mTOR inhibition would not necessarily translate into an *in vivo* anti-tumour and/or immunosuppressive effect. In fact, D7 proved that everolimus had no anti-tumour properties. Furthermore, mTOR inhibition was not a relevant aspect for the skilled person, who was represented by a medical oncologist and not by an expert in molecular biology. Therefore the skilled person had no reasonable expectation that everolimus would exhibit the anti-tumour effect of CCI-779. This was confirmed by an expert oncologist in D170.

These arguments are not convincing. D9 and D10 explicitly disclose that the inhibition of mTOR by

CCI-779 and RAD001 translates into the inhibition of human tumour xenograft growth *in vivo*. The skilled person was presented with experimental evidence that everolimus had anti-tumour activity *in vivo*. Against this teaching, the respondent and the expert in D170 (point 16) argued that D7 demonstrated that everolimus had no *in vivo* anti-tumour effect. This argument must fail, since it is based on a misinterpretation of the results in D7. As noted by the appellants, D7 (page 16) explains immediately after the title "Results" that tumour size values were determined after four weeks. However, the values of the control group corresponded to the tumour size after three weeks; the animals had to be killed because the tumour became excessively large. The respondent's argument is based on a direct comparison of the volume size of the control after three weeks (4020 mm^3) with the size of the tumour treated with everolimus (Compound B) after four weeks (3685 mm^3), taking into account the standard variations of 579 mm^3 and 263 mm^3 respectively. Such a direct comparison is clearly wrong, as it fails to take account of the different times when the measurements were taken for the control sample and for everolimus.

Aromatase inhibitors as an alternative to anti-estrogens

2.5.3 It was undisputed that, at the effective filing date of the application on which the patent is based, it was common general knowledge that the growth of HR+ breast tumours was promoted by estrogens. Therefore the treatment of HR+ breast tumours was based on preventing or reducing the effect of estrogens on tumour cells. This could be achieved by two strategies (see, for

instance, D1, page 334, paragraph bridging the two columns): i) blocking the estrogen receptors on tumour cells with an anti-estrogen, or ii) reducing the level of estrogens by inhibiting estrogen biosynthesis with an aromatase inhibitor. These two strategies were also acknowledged in D12 (page 6, last two paragraphs), the publication of the earliest application on which the patent is based.

Document D50 (abstract and conclusion) is a review article that reflects common general knowledge. It was cited by appellant 5 in its discussion of the technical background of the invention (statement of grounds of appeal, paragraph 64) and by Prof. Eiermann in declaration D43 (paragraph [7]). D50 demonstrates that the use of aromatase inhibitors in first-line and second-line treatment of advanced HR+ breast cancer in post-menopausal women was well established as a treatment of choice. This is also confirmed by the common general knowledge disclosed in D37, a review on the aromatase inhibitor exemestane cited by several appellants. D37 (page 680) discloses that exemestane was approved in the UK and pre-registered in Europe and the US for the treatment of advanced breast cancer in post-menopausal women.

2.5.4 The respondent argued that anti-estrogens and aromatase inhibitors are different families of compounds with different modes of action. Therefore the skilled person would not have considered them as being equivalent.

This argument is not convincing. It is true that anti-estrogens can be used in a broader range of patients because, unlike aromatase inhibitors, their use is not limited by the production of estrogens in the ovaries. However, based on their ability to reduce the effect of

estrogens on HR+ breast tumour cells, anti-estrogens and aromatase inhibitors were well established as the methods of choice for treating HR+ breast tumours in post-menopausal women.

Combination of everolimus with aromatase inhibitors

2.5.5 It has been explained above (point 2.5.1) that the combination of D9 with D10 teaches that CCI-779 and everolimus are promising agents for the treatment of HR+ breast tumours, either alone or in combination with anti-estrogen therapy. It has also been explained (point 2.5.3) that anti-estrogens and aromatase inhibitors were well-established alternatives for treating HR+ breast tumours in post-menopausal women.

As noted by the expert in breast cancer treatment Prof. Eiermann (D43, paragraphs [16] and [17]), it is a standard clinical approach in developing new anti-tumour therapies to combine a known anti-tumour agent with another known or promising anti-tumour agent. No ethical concerns arise if one of the anti-tumour agents has proven efficacy since patients would be protected by the therapeutic effect of the agent known to be effective.

Therefore it was an obvious strategy to the skilled person to combine everolimus as a promising agent against HR+ breast tumours with one of the established therapies for treating HR+ breast tumours, in particular with an anti-estrogen or an aromatase inhibitor. Therefore, in the light of the common general knowledge, the combination of documents D9 and D10 would have led the skilled person to combine everolimus with an aromatase inhibitor as an obvious strategy for treating HR+ breast tumours.

2.6 The Board therefore concludes that the subject-matter of claim 1 as granted does not involve an inventive step, contrary to Article 56 EPC.

3. Inventive step (Article 56 EPC) - auxiliary requests

In the written appeal proceedings, appellant 5 (statement of grounds of appeal, pages 84 to 93, and letter dated 3 March 2023, pages 32 to 39) and appellant 7 (statement of grounds of appeal, pages 48 to 51) explicitly objected to the auxiliary requests for lack of inventive step. The objections were either very succinct or merely referred to the arguments presented for claim 1 as granted. The reasons for inventive step given by the respondent (reply to the statements of grounds of appeal, points 16.3 to 16.19) in relation to the auxiliary requests were also very succinct.

At the oral proceedings before the Board, the appellants presented some inventive-step arguments against the auxiliary requests that had not been explicitly developed in the written proceedings against these requests. Nevertheless, the Board disagrees with the respondent that these arguments constitute an amendment to the appellants' case. The arguments involve exclusively elements that had been discussed in the written proceedings in the context of inventive step or sufficiency of disclosure for claim 1 as granted and which clearly apply to the auxiliary requests. Therefore, rather than an amendment, the arguments reflect a natural development of the case and, consequently, are not to be disregarded under Article 13(2) RPBA.

3.1 Auxiliary request 1

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it further specifies that the HR+ breast tumours are advanced. According to the respondent (reply to the statements of grounds of appeal, paragraph bridging pages 52 and 53), Examples A.2 and B.6 of the patent showed that everolimus had anti-angiogenic activity. This effect was particularly important and effective for the treatment of advanced tumours.

Appellant 7 (statement of grounds of appeal, page 45, point 4.2.5) argued in relation to the patent as granted that the combination of everolimus with an aromatase inhibitor was obvious in view of the common general knowledge reflected in D37. Appellant 5 (statement of grounds of appeal, paragraphs 60 and 64) referred to the common general knowledge in D37 and D50 in its discussion of the technical background of the invention relevant to inventive step. These documents show that aromatase inhibitors were a standard treatment for advanced HR+ breast tumours.

Therefore in the written proceedings the appellants had pointed to the common general knowledge in D37 and D50 that aromatase inhibitors were effective against advanced HR+ breast tumours. In view of this common general knowledge, the combination of everolimus with aromatase inhibitors was an obvious solution to the objective technical problem of providing an effective combination therapy for treating advanced HR+ breast tumours.

3.2 Auxiliary request 2

Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it further specifies that the treatment of HR+ breast tumours is for inhibiting or controlling deregulated angiogenesis. The respondent (reply to the statements of grounds of appeal, page 53, points 16.7 and 16.8) argued in the written proceedings that Examples A.2 and B.6 of the patent show that everolimus has anti-angiogenic properties. At the oral proceedings before the Board, it added that HR+ breast tumours are particularly susceptible to undergoing angiogenesis and that the latter is essential for tumour growth. Therefore the anti-angiogenic effect of everolimus made it particularly suitable for treating advanced HR+ breast tumours.

As noted for auxiliary request 1, aromatase inhibitors were known for treating advanced HR+ breast tumours. Therefore, in line with the respondent's submissions, it was known, at least implicitly, that aromatase inhibitors prevent angiogenesis. Consequently, the reasons why the subject-matter of auxiliary request 1 was obvious also apply to the subject-matter of auxiliary request 2.

3.3 Auxiliary request 3

Claim 1 of auxiliary request 3 differs from claim 1 as granted in that it further specifies that the treatment is for inducing regression of the HR+ breast tumours. The respondent (reply to the statements of grounds of appeal, page 53, point 16.10) noted that Example B.1 of the patent showed that everolimus induces tumour regression, but did not provide particular arguments as

to why the amendment in auxiliary request 3 would render the claimed subject-matter inventive.

It was common general knowledge (D37, page 676, right-hand column, penultimate paragraph, and D50, page 1038, second full paragraph) that aromatase inhibitors induce HR+ breast tumour regression. Therefore the subject-matter of auxiliary request 3 was also obvious.

3.4 Auxiliary request 4

Claim 1 of auxiliary request 4 differs from claim 1 as granted in that it further specifies that everolimus is to be administered orally. The respondent (reply to the statements of grounds of appeal, page 53, point 16.12) argued that this amendment distanced the subject-matter of claim 1 further from the closest prior art since CCI-779 was administered intravenously.

This argument fails since, as noted by appellant 5 (statement of grounds of appeal, page 88, point 441) and appellant 7 (statement of grounds of appeal, page 50, paragraph 326), D10 explicitly teaches that everolimus is administered orally. Therefore the subject-matter of auxiliary request 4 was also obvious for the reasons presented for the main request.

3.5 Auxiliary requests 5 and 6

Claim 1 of auxiliary request 5 differs from claim 1 as granted in that it further specifies that the HR+ breast tumours are solid. Claim 1 of auxiliary request 6 further specifies that the solid HR+ breast tumours are other than lymphatic cancer.

The Board agrees with the respondent (reply to the statements of grounds of appeal, page 54, point 16.14) that HR+ breast tumours are solid. Therefore auxiliary requests 5 and 6 do not distinguish the claimed subject-matter further from the closest prior art than the main request. The reasons for considering the subject-matter of claim 1 as granted obvious apply equally to the subject-matter of auxiliary requests 5 and 6.

3.6 A*uxiliary request* 7

Claim 1 of auxiliary request 7 differs from claim 1 as granted in that it further specifies that the treatment involves no more active ingredients. This limitation does not change the issue of inventive step as discussed for the main request, because the prior-art disclosure does not require any further active ingredient either (statement of grounds of appeal of appellant 5, paragraph bridging pages 90 and 91, and statement of grounds of appeal of appellant 7, page 51, point 332). Therefore the subject-matter of auxiliary request 7 was obvious, too.

3.7 Auxiliary request 8

Claim 1 of auxiliary request 8 further specifies that everolimus is orally administered in a unit dosage form comprising from 0.25 to 10 mg everolimus together with one or more pharmaceutically acceptable diluents or carriers. According to the respondent (reply to the statements of grounds of appeal, page 54, point 16.18), the dose defined in auxiliary request 8 was surprisingly low and could not be expected to be successful.

As argued by appellant 7 (statement of grounds of appeal, page 51, paragraph 336 and 337), claim 1 does not define a particular total daily dose. It refers to a unit dosage form but does not specify how many units are to be administered daily. Therefore the amendment of auxiliary request 8 cannot confer an inventive step on the claimed subject-matter.

3.8 Auxiliary request 9

Claim 1 of auxiliary request 9 is identical to claim 1 as granted. Therefore its subject-matter was also obvious.

3.9 The Board then concludes that, contrary to Article 56 EPC, the subject-matter claimed by the auxiliary requests does not involve an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated