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Datasheet for the decision of 13 April 2026

Case Number: T 0592/24 - 3.3.07

Application Number: 14752433.4

Publication Number: 3033086

IPC: A61K31/519, A61K31/551, A61K45/06, A61P35/00

Language of the proceedings: EN

Title of invention:
COMBINATION THERAPY FOR THE TREATMENT OF CANCER

Patent Proprietor:
Novartis AG

Opponents:
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
Stada-Arzneimittel Aktiengesellschaft
Generics [UK] Limited
Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB
Bachelin, Martin

Headword:
Cancer combination therapy/NOVARTIS

Relevant legal provisions:
EPC Art. 123(2), 83, 56
RPBA 2020 Art. 12(4), 13(1), 13(2)

Keyword:
Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes) - unexpected improvement shown - closest prior art - try-and-see situation (no)
Amendment to case - amendment admitted (no)
Amendment to appeal case - amendments admitted (no)

Decisions cited:
T 0419/16, T 0512/02, T 0484/09, T 0686/91, G 0002/21, T 0840/22, T 1989/19, T 1994/22, T 0314/20, T 0887/21, T 0405/14, T 0722/24

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Case Number: T 0592/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 April 2026

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Respondent: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted/ electronically transmitted on 27 March 2024 concerning maintenance of the European Patent No. 3033086 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

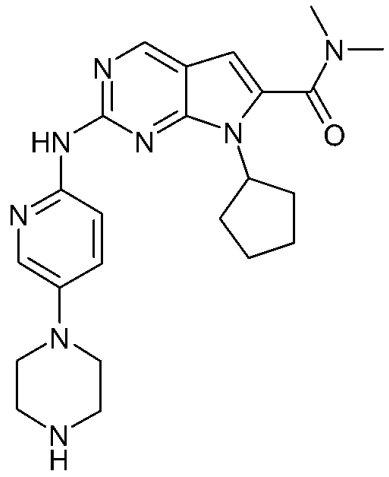
Summary of Facts and Submissions

I. European patent 3033086 ("the patent") was granted with fifteen claims.

Claim 1 as granted defines:

"A pharmaceutical combination comprising

(a) Compound A1, described by Formula A1 below:



(A1),

or a pharmaceutically acceptable salt thereof,

and

(b) letrozole, or a pharmaceutically acceptable salt thereof."

Claim 3 as granted defines the combination for use in treating hormone sensitive and/or hormone-receptor positive cancer, with dependent claims 4-9 further specifying the treatment, including the treatment of breast cancer which is an estrogen receptor positive cancer as defined in claim 8 as granted.

Claim 10 as granted defines the combination for use in treating HR^+, $HER2^-$ breast cancer.

Claim 14 as granted defines Compound A1, or a pharmaceutically acceptable salt thereof, for use in treating hormone sensitive and/or hormone-receptor positive breast cancer by simultaneous, separate or sequential administration with letrozole.

Compound A1 is herein referred to by the subsequently assigned International Non-proprietary Name (INN) "ribociclib".

II. Five oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

The opposition division decided that the patent as amended in accordance with the main request filed on 5 January 2024 met the requirements of the EPC.

The claims of this main request correspond to the claims as granted, wherein dependent claim 8 as granted is reformulated to relate to an estrogen receptor positive cancer or progesterone receptor positive cancer, granted claim 10 is reformulated to define the combination for use in therapy, granted claims 11-13 and 15 are deleted and granted claim 14 is renumbered as claim 11.

In its decision the opposition division cited *inter alia* the following documents:

D3: Nature Biotechnology (2013), 31(3), 187
D4: WO 2013/006532 A1
D6: Oncology Times (2013) Supplement to February 10, 24-25
D10: Nature Reviews Clinical Oncology (2013), doi: 10.1038/nrclinonc.2013.29
D12: Cancer Discovery (2013), 3(1), 27-34
D13: ASCO 2013 EDUCATIONAL BOOK, (2013), 49th Annual Meeting, volume 33, e37-e42
D14: Transforming Healthcare through Innovative and Impactful Research, posted online by Slamon, 15 May 2013
D15: Breast Cancer Research (2009), 11:R77
D16: Breast Cancer Research (2009), 11:112
D17: npj Breast Cancer (2019), 27, 1-8
D18: Breast Cancer Research (2011), 13:215
D20: Nature Biotechnology (2009), 27(7), 659–666, with online supplement
D25: BioDrugs (2019), 33, 125–135
D28: Cancer Discovery (2011), 1(4), 287–288
D29: US 8 415 355 B2
D30: EMA summary of Kisqali (ribociclib) (2020)
D33: Journal of the National Cancer Institute (2012), 104, 476–487
D34: Journal of Clinical Oncology (2010), 28, 2010 ASCO annual meeting, Abstract 3060
D35: Nature Reviews Clinical Oncology (2013), 10, 494–506
D36: Cancer Discovery (2011), 1(4), 338–351
D41: Endocrine-Related Cancer (2013), 20(4), R183–201
D42: Annals of Oncology (2012), 23 (Suppl. 2), ii43–ii45, Abstract 100-O
D42b: Proc SABCS 2012, abstract S1-6
D43: Nature (2012), 11, 892-894
D45: Deutsche Apotheker Zeitung (2017), 40, 36

D46: WO 2010/020675 A1
D47: Breast Cancer Research and Treatment (2019), https://doi.org/10.1007/s10549-019-05133-y
D49: EMA Public Assessment Report for Kisqali (2017)
D51: WO 2011/101417 A1
D52: Declaration by Dr Caponigro of 31 January 2023
D53: New England Journal of Medicine (2022), 386(10), 942-950
D54: Journal of Clinical Oncology (2022), 40(7) Suppl., LBA1003
D55: EBCC13 presentation, 18 November 2022, "Matching adjusted indirect comparison of PFS & OS comparing ribociclib + letrozole vs palbociclib + letrozole as first-line treatment of HR+/HER2-ABC: Analysis based on updated PFS & final OS results of MONALEESA-2 & PALOMA-2"
D56: European Journal of Cancer (2022), 175 (Suppl. 1), S2-S3, Abstract 3
D59: Clinical Cancer Research (2002), 8, 665-669
D60: Breast Cancer Research and Treatment (2002), 105, 7-17
D62: Novartis press release (October 2023),"Novartis Kisqali® NATALEE analysis reinforces consistent reduction in risk of recurrence across key subgroups of patients with early breast cancer"
D64: FiercePharma, December 2020, https://www.fiercepharma.com/marketing/sabcs-novartis-touts-kisqali-s-5-year-breast-cancer-survival-advantage-over-pfizer-s

The opposition division arrived at the following conclusions:

(a) The main request complied with Article 123(3) and Rule 80 EPC.

(b) The application as originally filed specifically defined in claim 27 the combination of ribociclib with letrozole and disclosed on page 26 and in original claim 1 that pharmaceutically acceptable salts of these agents were intended to be included. Claim 1 of the main request therefore found an adequate basis in the application as originally filed.

The combination defined in claim 1 was disclosed as a preferred embodiment. Its utility in the treatment of specific forms of cancer as defined in claims 3 and 5-8 was adequately based on the disclosure of these specific forms of cancer on page 28 of the original description.

In accordance with the considerations in T 419/16, the first medical use as introduced in claim 10 did not result in added-matter. Such use was in any case implicit in the disclosure of a pharmaceutical combination of two therapeutically active agents.

Claim 11 was also adequately based on the disclosed preference for the relevant combination of agents and its utility described on page 28 of the application as originally filed.

The main request therefore complied with Article 123(2) EPC.

(c) In view of the known anticancer activity of the individual compounds of the defined combination, the patent plausibly disclosed the suitability of the combination for the therapeutic use as defined in the claims. The opponents had not provided any evidence to the contrary.

The main request therefore complied with Article 83 EPC.

(d) The subject-matter of the main request enjoyed the claimed priority. The claimed subject-matter was new over the cited prior art.

(e) Documents D3, D6, D12, D14, D33-D35, D41 and D42/D42b described the combination of letrozole with palbociclib instead of ribociclib, as defined in claim 1 of the main request. The results from *in vitro* experiments in the patent showed an improved synergistic effect for the claimed combination with ribociclib compared to the known combination with palbociclib. The evidence from the post-published documents D55, D56 and D64 could be relied on and clearly indicated an advantage for ribociclib over palbociclib when combined with letrozole in the treatment of cancer. Starting from the known combination of letrozole with palbociclib, the objective technical problem was the provision of an improved combination for the treatment of hormone-sensitive or hormone-receptor positive breast cancer. The prior art did not allow any conclusion as to whether ribociclib would perform as well as palbociclib, let alone better.

Document D4 described the combination of ribociclib with a PI3K inhibitor. The difference between the claimed combination and the combination of document D4 involved the addition of letrozole. The experimental results in the patent demonstrated that the addition of letrozole to the combination of ribociclib and a PI3K inhibitor as known from document D4 led to improved antitumour effects.

Starting from the combination of ribociclib with a PI3K inhibitor as described in document D4, the objective technical problem was the provision of an improved combination for treating hormone-receptor-positive breast cancer. None of documents D28, D36 and D41 suggested the improvement resulting from the addition of letrozole. Moreover, no prior art suggested a triple combination.

The subject-matter of the main request therefore also involved an inventive step.

III. The opponents (O1, O2, O3, O4 and O5) filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with the main request meets the requirements of the EPC.

IV. The following additional documents were filed during the appeal proceedings:

A66: ASCO Journal of Clinical Oncology (2024), 42:994-1000
by O4 with its statement of grounds of appeal

A67: ClinicalTrials.gov ID: NCT01872260
A68: Future Oncol. (2023), 19(10), 727-736
A69: Scientific Reports (2024), 14:3129
A70: Bioorg. Med. Chem. Lett. 23 (2013) 3741–3748
by O1 with its statement of grounds of appeal

A71: Endocrine-Related Cancer (2011) 18, C19-C24
by O2 with its statement of grounds of appeal

A72: Cell Cycle (2012), 11(14), 2756-2761
by O5 with its statement of grounds of appeal

A73: Expert declaration of Dr Neil Umbreit of 30 January 2025
A74: The New England Journal of Medicine (2024), 390:1080-91
A75: Annals of Oncology (2024), p1-9
A76: Novartis press release: FDA approval of ribociclib for EBC
A77: Novartis press release: European Commission approval of ribociclib for EBC
A78: "Effekten av ribociclib, palbociklib og abemaciklib på overlevelse av metastatisk HR-positiv HER2-negativ brystkreft: Real-world analyse fra Norge"; The Cancer Registry of Norway; 19 June 2024
A78A: English translation A78: "The effect of ribociclib, palbociclib, and abemaciclib on survival of metastatic HR-positive HER2-negative breast cancer: a real-world analysis from Norway"
A79: Norwegian Oncology Recommendations; 17 December 2024
A79A: English translation A79
by the patent proprietor with the reply to the appeals

A80: NCCN Guidelines for Patients 2024
by O5 with the letter of 12 May 2025

A81: NCCN Guidelines 2025
by the patent proprietor with the letter of 14 August 2025

A82: The Oncologist (2022), 27 (Supplement 1), S11-S12
A83: ESMO Open (2025),10(11), 1-9
A84: Annals of Oncology (2026), 37(2), 271-277
by the patent proprietor with the letter of 13 March 2026.

V. Oral proceedings were held on 13 April 2026.

VI. The arguments of the opponents relevant to the present decision are summarized as follows:

(a) Admittance of documents

Document A66 could not have been filed earlier, because this document had only been published in January 2024. Document A66 supported the argument that, contrary to the finding in the decision under appeal, document D55 does not convincingly demonstrate superior overall survival for the claimed combination, because document D55 compares the results of trials with different follow-up periods.

The filing of document A67 was responsive to the finding in the decision under appeal that the prior art provided no suggestion towards triple combinations. This finding represented a change with respect to the opposition division's preliminary opinion. Document A67 demonstrated at least that relevant double and triple combinations were already under investigation in the prior art. Document A70 demonstrated that the compound "BYL719" as mentioned in document A67 was the known PI3K inhibitor referred to as "Compound B2" in document D4.

Documents A68 and A69 were responsive to the finding in the decision under appeal that documents D55 and D56 demonstrate superior overall survival for the claimed composition over the prior art composition. The recently published documents A68 and A69 contradicted the suggestion in documents

D55 and D56 that the claimed combination allows for superior overall survival.

Document A71 demonstrated that CDK4/6 inhibition was known to block cell cycle progression in endocrine resistant cell lines and thereby supported the argument that the skilled person in search for an alternative synergistic combination with letrozole would test further known CDK4/6 inhibitors.

Document A72 was filed in response to the finding in the decision under appeal that no evidence on file indicated that the claimed combination would not be effective for medical use indications encompassed by claim 3. Document A72 presented evidence of HR^+ cancers which are not responsive to CDK4/6 inhibition.

Document A80 was filed in response to the patent proprietor's reference to document D62 suggesting an exclusive special status ("Category 1") for the claimed combination in the NCCN Guidelines for Breast Cancer. Document A80 (see page 48) demonstrated that more recent NCCN Guidelines do not confirm such exclusive special status.

Documents A73-A79A and A82-A84 should not be admitted. The filing of the declaration in document A73 was not justified, because the objections against the comparison of synergy data in the patent had been raised during the first instance proceedings. Documents A74-A79A lacked *prima facie* relevance. No exceptional circumstances justified the late filing of documents A82-A84.

(b) Basis for the amendments

The combination defined in claim 1 constituted an impermissible intermediate generalisation with respect to original claim 27, in particular because it additionally encompassed salts of letrozole.

The therapeutic indications defined in claims 3 to 11 amounted to an impermissible generalisation in comparison with original claims 35 and 36, which were limited to HR+/HER2- breast cancer.

Claims 3 and 5 resulted from an impermissible combination of selections, namely the selection of specific active agents together with the selection of specific cancer types.

The application as filed referred to the treatment of cancer which is a solid tumour, but did not disclose the treatment of solid HR+ cancers as defined in claim

While the application as filed mentioned the treatment of hormone-sensitive HR+/HER2- breast, endometrial, ovarian or cervical cancer, it did not disclose hormone-sensitive and/or hormone-receptor-positive cancer as more broadly defined in claims 6 and 7.

The definition of the combination for a first medical use in claim 10 represented an impermissible generalisation beyond the specific therapeutic applications disclosed in the application as filed.

(c) Sufficiency

The patent disclosed experimental evidence only for efficacy of the defined combination in HR+/HER2- breast cancer, whereas the claims covered the treatment of hormone-sensitive and/or hormone-receptor-positive cancer more generally, including the cancers defined in claims 3, 5 and 6. Hormone-receptor-positive cancers were heterogeneous, as demonstrated by documents D20 and D35, and it was therefore not credible that such cancers will generally respond to the claimed combination. Tumour cells lacking functional retinoblastoma protein were resistant to CDK4/6 inhibition, as shown in documents D15, D16 and D28. Documents D18, D30, D49 and D60 further supported the view that not all hormone-receptor-positive cancers respond to the claimed combination including the CDK4/6 inhibitor ribociclib and letrozole. The patent therefore failed to credibly disclose that the claimed combination would be effective over the whole scope of the claims and confronted the skilled person with an undue burden when attempting to carry out the invention across the claimed indications.

(d) Inventive step - starting from the known combination of palbociclib and letrozole

Documents D3, D6, D12, D14, D33–D35, D41 and D42/D42b reported the greatly enhanced clinical effectiveness resulting from the combination of the CDK4/6 inhibitor palbociclib (PD-0332991) with the aromatase inhibitor letrozole in the treatment of breast cancer. The difference between the claimed

subject-matter and this prior art concerned the replacement of palbociclib by ribociclib.

The *in vitro* results presented in Figures 1, 4 and 8 of the patent did not demonstrate any real advantage of the claimed combination of ribociclib with letrozole over the known combination of palbociclib with letrozole. The reported synergy scores of 4.12 and 3.9 for the claimed combination were close to the score of 3.7 reported for the known combination and showed substantial variability. The observed numerical differences did not establish a statistically significant improvement. In accordance with the established jurisprudence, reliable and statistically meaningful evidence of an improvement was required, but was not provided.

The *in vitro* synergy data relied on experiments using different concentration ranges for ribociclib and palbociclib, although it was known from the prior art that the occurrence and extent of synergy depended on the selected dose ranges. The use of different concentration ranges therefore undermined the comparability of the reported synergy values and the credibility of any alleged improvement as a result of the use of ribociclib instead of palbociclib.

The *in vitro* experiments only concerned a particular $HR^+/HER2^-$ breast cancer cell type and were therefore not suitable to demonstrate any effect over the whole scope of the claims. Moreover, as shown in Figures 4 and 10 of the patent, the synergy score of 3.3 for the triple combination comprising ribociclib (A1), letrozole

(B1) and everolimus (C3) was lower than the synergy score of 4.5 for the corresponding triple combination comprising palbociclib (A3). These results demonstrated that an improvement over the prior art was not achieved across the whole scope of the claims, which included triple combinations.

The maximum inhibition of cell proliferation reported in the patent for the known combination of palbociclib with letrozole compared favourably with the inhibition levels reported for the claimed combination of ribociclib with letrozole, such that the reported *in vitro* data did not demonstrate any actually improved effect of the claimed combination over the combination of the prior art. As in the cases of T 512/02 and T 484/09, the reported synergy values reflected merely effects relative to the individual agents and did not demonstrate an overall improvement in the inhibition of cell proliferation over the known combination.

The *in vitro* synergy data disclosed in the patent did not demonstrate any improvement over the enhanced *in vivo* efficacy already known for the prior-art combination of palbociclib with letrozole. The reported *in vitro* effects did not establish that the claimed combination exceeded the clinically established benefit of the known combination and therefore did not demonstrate an inventive improvement.

In view of the considerations in G 2/21, the post-published documents D55, D56 and D64 could not be relied upon to establish any advantage of the claimed combination. The application as filed lacked any reference to an effect in overall

survival, which was according to document D64 in any case not related to the disclosed synergy of ribociclib with letrozole, but to the selectivity of ribociclib for CDK4 over CDK6. The considerations in T 887/21 applied. Moreover, the application as filed also encompassed compositions comprising palbociclib and letrozole within the originally claimed subject-matter. Any alleged improvement of ribociclib over palbociclib was therefore not derivable from the application as filed and could not be established merely based on post-published evidence. The situation corresponded to that underlying T 1994/22 and T 314/20, in which post-published data were not accepted in comparable circumstances, whereas the considerations applied in T 840/22 and T 1989/19 were not applicable.

In any event, documents D55 and D56 relied on indirect comparisons between different clinical trials with different follow-up periods, patient populations and dosing regimens, which did not allow a reliable conclusion to be drawn as to any superiority of the claimed combination over the prior-art combination. Document D64 likewise did not provide any direct comparison between the claimed combination of letrozole with ribociclib and the known combination with palbociclib.

The objective technical problem associated with replacing palbociclib by ribociclib in claim 1 could therefore only be seen in the provision of an alternative effective combination of a CDK4/6 inhibitor with letrozole.

The synergistic, enhanced effect reported in the prior art for the palbociclib/letrozole combination

was attributed to CDK4/6 inhibition of palbociclib. Ribociclib was known from the prior art, including documents D4, D29, D46 and D51, to act as an effective CDK4/6 inhibitor. In view of this known activity, the skilled person would have expected ribociclib to provide a similar enhancement when combined with letrozole, and the replacement of palbociclib by ribociclib therefore represented an obvious solution to the problem of providing an alternative effective combination.

It was furthermore obvious for the skilled person to routinely test combinations of letrozole with other known CDK4/6 inhibitors as a matter of "try-and-see", given the known benefit of combining CDK4/6 inhibition with endocrine therapy, the limited number of available CDK4/6 inhibitors at the relevant date, and the high activity of ribociclib reported in the prior art, for example in document D46.

(e) Inventive step - starting from the known combination of ribociclib with a PI3K inhibitor

Document D4 disclosed a synergistic combination comprising ribociclib and a PI3K inhibitor for the treatment of breast cancer.

The claimed combination of ribociclib and letrozole, as a double combination, differed from the combination disclosed in document D4 only by the replacement of the PI3K inhibitor with letrozole. In line with the considerations in T 405/14 and in view of the similar therapeutic purpose pursued, the teaching of document D4 could not be disqualified as a suitable starting point.

No improvement over the synergistic combination disclosed in document D4 was demonstrated for the claimed double combination. Ribociclib was explicitly described in document D4 as a CDK4/6 inhibitor. From the prior art, including documents D3, D6, D16 and D43, it was known that CDK4/6 inhibitors act synergistically with letrozole in the treatment of hormone-receptor-positive breast cancer. This prior knowledge suggested replacing the PI3K inhibitor in the synergistic combination of document D4 with letrozole as a straightforward alternative. The claimed double combination of ribociclib with letrozole therefore represented an obvious alternative synergistic combination.

Triple combinations comprising ribociclib, a PI3K inhibitor and letrozole, as also covered by the claims, differed from the combination disclosed in document D4 by the additional presence of letrozole. At best, only a marginal increase in *in vitro* activity for the triple combination was shown in Figure 4 of the patent. Given the well-established aromatase-inhibiting activity of letrozole, as described for example in document D60, any additional effect observed upon adding letrozole in the patent's experiments was predictable. The MCF7 cells used in these experiments were, according to paragraph [0099] of the patent, transfected with an aromatase expression vector and were therefore expected to respond to letrozole. Such additional activity was all the more to be expected in light of the known enhancement of letrozole's activity in the presence of a CDK4/6 inhibitor, as described for example in documents D6, D16 and D42b. Moreover, the possibility of combining endocrine therapy with

inhibitors targeting the CDK4/6 and PI3K pathways had already been suggested in documents D10, D12 and D13. In addition, documents D28, D41 and D36 directly pointed towards therapeutic strategies involving triple combinations comprising a CDK4/6 inhibitor, a PI3K-pathway inhibitor and an aromatase inhibitor. The claimed triple combination therefore merely followed the direction already indicated in the prior art and was not supported by any demonstrated surprising or unexpected technical effect. In view of the clear pointers in the prior art towards combining endocrine therapy with inhibitors acting on the CDK4/6 and PI3K pathways, the situation corresponded to a "try-and-see" approach.

VII. The arguments of the patent proprietor relevant to the present decision are summarised as follows:

(a) Admittance of documents

Document A73 was an expert-declaration filed in reaction to the opponents' criticism that, in view of the different concentration ranges tested, the experimental results reported in the patent did not show an improvement in synergy resulting from replacement of palbociclib by ribociclib.

Documents A74-A79A were filed as further evidence that the claimed combination allows for a favourable outcome in the treatment of patients with early breast cancer (A74-A77) and patients with metastatic breast cancer (A78-A79A). These documents were only recently published.

Document A81 was filed in response to the filing of document A80. Document A81 confirmed the special status ("Category 1") for the claimed combination also in the more recent NCCN Guidelines for Breast Cancer as previously reported in document D62.

Document A82 was filed in response to an observation in the Board's communication pursuant Article 15(1) RPBA regarding the $HER2^-$ status of the HER2-enriched patients mentioned in document D64.

Documents A83 and A84 were only recently published and served merely to support the effects previously relied upon during the first-instance proceedings against the opponents' arguments in their appeals.

Documents A67-A72 and A80 should not be admitted. The late filing of these documents was not justified and these documents lacked relevance.

(b) Basis for the amendments

Claim 1 of the application as originally filed defined a combination of a CDK inhibitor or a pharmaceutically acceptable salt thereof with an anti-hormonal agent or a pharmaceutically acceptable salt thereof. The application as filed specifically disclosed letrozole as the anti-hormonal agent. Moreover, the application as filed explicitly disclosed that ribociclib and letrozole could be included in the defined combinations as free bases or as pharmaceutically acceptable salts. Claim 1 of the main request therefore complied with Article 123(2) EPC.

The application as filed identified the disclosed combinations as particularly useful in the treatment of hormone-sensitive and/or hormone-receptor-positive cancers. According to disclosed embodiments, the cancer could be a solid tumour and could be selected from breast, endometrial, ovarian or cervical cancer. The subject-matter of claims 3, 5 to 8 and 11 of the main request was therefore directly and unambiguously derivable from the application as filed.

The definition of the combination for a first medical use in claim 10 derived from the originally disclosed specific indications for the defined pharmaceutical combination.

The objection of added subject-matter had not been raised against dependent claims 4 and 9 during the opposition proceedings. The admittance of this objection into the appeal proceedings was not justified. The objection was in any case unfounded in view of the content of the original claims.

(c) Sufficiency

The patent demonstrated that the claimed combination of ribociclib with letrozole exhibits synergistic activity in reducing the proliferation of HR^+/HER^- human breast carcinoma cells and inhibits tumour growth in a human breast tumour xenograft model.

These experimental results credibly established the suitability of the claimed combination for the treatment of hormone-sensitive and/or hormone-receptor-positive cancer as defined in the claims.

None of the documents relied upon in support of the objection demonstrated that the skilled person would be unable to carry out the invention, nor that any allegedly non-responsive tumour sub-populations would give rise to an undue burden when carrying out the claimed invention.

In the absence of substantiated evidence to the contrary, the disclosure in the patent was sufficient to meet the requirements of Article 83 EPC.

(d) Inventive step - starting from the known combination of palbociclib and letrozole

The combination of palbociclib and letrozole was known in the prior art for the treatment of hormone-receptor-positive breast cancer. Starting from this known combination, the claimed subject-matter differed by replacing palbociclib with ribociclib.

The experimental results disclosed in the patent showed that ribociclib in combination with letrozole achieved a greater degree of synergy than the palbociclib/letrozole combination. This enhanced synergy was consistently demonstrated through higher synergy scores, favourable Loewe excess values, and advantageous isobolograms obtained from *in vitro* experiments performed in triplicate in accordance with document D20. The opponents submitted no evidence to the contrary. The comparison remained valid despite the use of different concentration ranges, because the evaluation of synergy was based on equivalent

effect levels of ribociclib and palbociclib when used as individual agents.

The circumstance that Figures 4 and 10 of the patent reported for one particular triple combination comprising ribociclib (A1), letrozole (B1) and a PI3K inhibitor (C3) a lower synergy score than for the corresponding triple combination comprising palbociclib (A3) was of no consequence for the issue of inventive step, because that triple combination comprising palbociclib was not part of the prior art.

The increased synergy constituted, in line with the considerations in T 686/91, a technically relevant effect in its own right, especially in view of the clinically meaningful advantages associated with higher synergy, such as achieving the same therapeutic effect at lower dose levels and thereby widening the therapeutic window. The suggestion that the demonstrated increase in synergy might nevertheless fail to reflect an overall technical improvement was speculative.

The technical relevance of the improved synergy in the *in vitro* experiments was supported by the results of *in vivo* xenograft experiments reported in Figures 20-22 of the patent.

Post-published clinical evidence further demonstrated that the claimed combination provided for a meaningful clinical improvement. This clinical improvement was encompassed by the technical teaching and embodied by the originally disclosed invention. The considerations in T 840/22 applied. Documents D55 and D56 reported improved

overall survival for ribociclib and letrozole compared with palbociclib and letrozole based on a matching-adjusted indirect comparison of the MONALEESA-2 and PALOMA-2 trial data. Document D64 provided additional clinical support for a superior outcome of ribociclib-enhanced endocrine therapy that typically involved its combination with letrozole.

The objective technical problem starting from the palbociclib/letrozole combination was the provision of an improved combination therapy for the treatment of hormone-sensitive or hormone-receptor-positive breast cancer.

The prior art did not suggest replacing palbociclib with ribociclib in combination with letrozole as a solution to this problem. In the absence of any direct suggestion in the prior art, a try-and-see approach did not apply.

(e) Inventive step - starting from the known combination of ribociclib with a PI3K inhibitor

Document D4 disclosed a synergistic combination comprising ribociclib and a PI3K inhibitor for the treatment of breast cancer.

The double combination of ribociclib with letrozole as defined by the claims required replacing the PI3K inhibitor of document D4 with an agent from a difference class, namely the aromatase inhibitor letrozole. Having regard to the known combination of palbociclib with letrozole, document D4 could not be considered to represent the closest prior art. In any case, the synergistic effect disclosed

in document D4 related specifically to the interaction between ribociclib and a PI3K inhibitor. Any disclosure in the prior art of synergy between the CDK4/6 inhibitor palbociclib and letrozole did not suggest that synergy would be retained following the replacement of the PI3K inhibitor required in the combination with ribociclib of document D4 by letrozole. The double combination of ribociclib with letrozole was therefore not obvious as a solution to the problem of providing a further synergistic combination starting from the combination described in document D4.

The disclosure of document D4 differed from the triple combination comprising ribociclib, a PI3K inhibitor and letrozole covered by the claims in that it did not define the presence of letrozole. The patent demonstrated, on the basis of the results reported in Figure 4, that the addition of letrozole resulted in an increased antiproliferative effect compared with the corresponding double combination as disclosed in document D4. The MCF7 cells used in the experiments, which were transfected with an aromatase expression vector, were appropriate for assessing the interaction between ribociclib, the PI3K inhibitor and letrozole in the treatment of $HR^+/HER2^-$ breast cancer. This was further confirmed by the results of *in vivo* xenograft experiments in figures 20-22 of the patent. Neither the well-established aromatase-inhibiting activity of letrozole as such, as described in document D60, nor the enhanced efficacy of letrozole in combination with a CDK4/6 inhibitor, as described in documents D6, D16 and D42b, suggested that,

where cell proliferation is already synergistically inhibited by a CDK4/6 inhibitor in combination with a PI3K inhibitor, the addition of letrozole would result in a further suppression of cell proliferation. Documents D10, D12 and D13 were review-type publications providing background information on endocrine resistance and signalling pathways, including references to double combinations, but without disclosing or suggesting any triple combination comprising a CDK4/6 inhibitor, a PI3K inhibitor and an aromatase inhibitor. Documents D28, D41 and D36 likewise discussed therapeutic strategies involving endocrine therapy and pathway inhibitors without suggesting triple combinations. In the absence of any direct suggestion in the prior art, a try-and-see approach did not apply. The triple combination of ribociclib with letrozole, including a PI3K inhibitor, was therefore not obvious as a solution to the problem of providing a combination with enhanced antiproliferative activity over the combination of document D4.

VIII. The appellants-opponents requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Insofar as relevant to the decision, they further requested that documents A73 to A79A and A82 to A84 not be admitted.

IX. The respondent-patent proprietor requested that the appeals be dismissed.

Insofar as relevant to the decision, the patent proprietor further requested that documents A67 to A72 and A80 not be admitted.

Reasons for the Decision

1. Admittance of documents filed during the appeal proceedings

1.1 Document A66

Document A66 was filed for the first time with the statement of grounds of appeal and therefore constitutes an amendment to opponent 4's appeal case within the meaning of Article 12(4) RPBA.

Following the withdrawal of the patent proprietor’s objection against the admittance of document A66 during the oral proceedings, the Board decided to admit document A66 into the appeal proceedings under Article 12(4) RPBA.

1.2 Documents A67 and A70

Documents A67 and A70 were filed for the first time with the statement of grounds of appeal and therefore constitute an amendment to the opponent 1's appeal case within the meaning of Article 12(4) RPBA. O1 argued that the filing of document A67 was responsive to the finding in the decision under appeal that, starting from document D4, the prior art provided no suggestion towards triple combinations.

According to the decision under appeal, when starting from document D4, the objective technical problem underlying the claimed subject matter concerning a triple combination including ribociclib and letrozole, was the provision of an improved combination. Document A67 does not disclose any experimental results relating to the triple combination underlying the claimed subject matter. Moreover, whilst document A67 refers to the agent LEE011 as part of a triple combination, the identity of this agent was not known from that document. Document A67 therefore does not address the issue which led to the decision under appeal.

Document A70 describes the nature of another agent of the combination referred to in document A67, namely BYL719. However, document A70 could only be of potential relevance in combination with document A67. Since document A67 does not address the issue which led to the decision under appeal, the same applies to document A70.

In the absence of convincing reasons justifying their late filing, the Board, exercising its discretion under Article 12(4) RPBA, decided not to admit documents A67 and A70 into the appeal proceedings.

1.3 Documents A68, A69, A71 and A72

Documents A68, A69, A71 and A72 were filed by the opponents for the first time with the statement of grounds of appeal and therefore constitute amendments to the opponents' appeal cases within the meaning of Article 12(4) RPBA.

In the communication pursuant to Article 15(1) RPBA (sections 1.2-1.4), the Board indicated that the

justification for the late filing of these documents appeared unconvincing, also taking account of their relevance as contested by the patent proprietor.

Since no further arguments were submitted by the relevant parties in response to that communication, the Board, exercising its discretion under Article 12(4) RPBA, decided not to admit documents A68, A69, A71 and A72 into the appeal proceedings.

1.4 Documents A80 and A81

Document A80 was filed by O5 after the filing of the statement of grounds of appeal and therefore constitutes an amendment to O5's appeal case within the meaning of Article 13(1) RPBA. Document A81 was filed by the patent proprietor in response to document A80 and likewise constitutes an amendment to the patent proprietor's appeal case within the meaning of Article 13(1) RPBA.

Document A80 was filed to substantiate the argument that, in more recent guidelines, contrary to document D62, combination treatment with ribociclib is no longer the only "Category 1" treatment and that combination treatment with palbociclib is equally recommended. However, document A80 does not mention a "Category 1" recommendation for palbociclib and therefore does not support the argument for which it was filed.

Document A81 was filed solely in response to document A80 and does not give rise to an independent assessment.

Accordingly, the Board, exercising its discretion under Article 13(1) RPBA, decided not to admit documents A80 and A81 into the appeal proceedings

1.5 Documents A73–A79A

Documents A73–A79A were filed by the patent proprietor for the first time with the reply to the appeals and therefore constitute an amendment to the patent proprietor's appeal case within the meaning of Article 12(4) RPBA.

Documents A82-A84 were filed by the patent proprietor for the first time with its submission filed after the Board's communication pursuant to Article 15(1) RPBA and therefore constitute an amendment to the patent proprietor's appeal case within the meaning of Article 13(2) RPBA.

In its communication pursuant to Article 15(1) RPBA (section 1.5), the Board questioned the justification for the filing of documents A73-A79A. In view of the outcome of the appeal proceedings, no further reasoning is required as to the admittance of documents A73–A79A and A82-A84, and the Board, exercising its discretion under Articles 12(4) and 13(2) RPBA, decided not to admit these documents into the appeal proceedings.

As noted by the Board during the oral proceedings, the decision not to admit document A73 as new evidence does not preclude the evaluation of the patent proprietor's technical arguments in the appeal proceedings.

2. Main request - Basis for the amendments

2.1 Claim 1

According to the opponents, the combination defined in claim 1 constitutes an impermissible intermediate generalisation with respect to original claim 27, in particular because it additionally encompasses salts of letrozole.

Original claim 27 relates to a pharmaceutical combination comprising Compound A1 (ribociclib) or a pharmaceutically acceptable salt thereof and letrozole, without expressly referring to salts of letrozole.

Original claim 1 discloses a pharmaceutical combination comprising a CDK inhibitor and an anti-hormonal agent, each as free base or a pharmaceutically acceptable salt thereof. In this context, original dependent claim 5 specifies Compound A1 (ribociclib) as the CDK inhibitor, while original dependent claim 11 specifies letrozole as the anti-hormonal agent. In addition, the application as filed contains an explicit and general disclosure that the compounds of the disclosed pharmaceutical combination, including CDK inhibitors such as ribociclib and anti-hormonal agents such as letrozole, may be incorporated in either free form or in the form of any salt thereof (page 26, lines 9–10).

The skilled person therefore directly and unambiguously derives from the application as filed that the originally disclosed combination of ribociclib and letrozole encompasses the salt forms of both agents.

Accordingly, claim 1 of the main request does not extend beyond the content of the application as filed

and complies with the requirements of Article 123(2) EPC.

2.2 Claims 3-11

With respect to claims 3 to 11 of the main request, the Board explained in its communication pursuant to Article 15(1) RPBA (section 3.2) that the application as filed (in particular page 28) discloses the therapeutic use of the originally disclosed combination in the treatment of hormone-sensitive and/or hormone-receptor positive cancers as a particularly preferred embodiment and identifies specific types of cancer falling within that disclosure.

On this basis, the Board expressed in the communication (section 3.2, page 16, second paragraph and page 17 second paragraph) its preliminary assessment that the subject-matter of claims 3, 5–7 and 11 is directly and unambiguously derivable from the application as filed.

Furthermore, as set out in the communication (section 3.2, page 17, first paragraph), the subject-matter of claim 10, which relates to the pharmaceutical combination for a first medical use, was considered to be implicitly disclosed in the application as filed, having regard to the explicit disclosure of a pharmaceutical combination of therapeutically active agents and its stated therapeutic utility.

As regards the objections raised against claims 4 and 9, the Board noted in the communication (section 3.2, page 16, last paragraph) that the features defined in claims 4 and 9 are based on original claims 3 and 26 of the application as filed.

The opponents did not submit any further arguments in response to the Board's preliminary assessment of their objections of added subject-matter against claims 3 to 11.

In the absence of any further submissions from the opponents, the Board sees no reason to deviate from its preliminary opinion. The Board therefore confirms its assessment that claims 3 to 11 of the main request do not extend beyond the content of the application as filed and meet the requirements of Article 123(2) EPC.

3. Main request - Sufficiency

As indicated in its communication pursuant to Article 15(1) RPBA (see point 4), the Board considers that the experimental results presented in the patent credibly demonstrate the suitability of the claimed combination for the treatment of cancer as defined in claims 3, 5 and 6. In particular, Figures 1 and 20–22 of the patent show synergistic inhibition of tumour cell proliferation in HR+/HER2– human breast carcinoma cells and prevention of tumour growth in an in vivo breast tumour xenograft model.

The documents relied upon by the opponents do not cast doubt on this conclusion.

Document D20 addresses variability of responses in different cell lines but does not concern the claimed combination. Document D35 highlights the heterogeneity of luminal breast cancer but does not suggest a lack of efficacy of the claimed combination within the defined indications.

Documents D15, D16 and D28 describe resistance of tumour cells lacking functional retinoblastoma protein to CDK4/6 inhibitors. However, it was not demonstrated that the existence of such tumour cells would prevent the skilled person from carrying out the treatment of hormone-sensitive or hormone-receptor-positive cancer as defined in the claims without undue burden.

Document D18 shows that hormone-receptor-positive cancers include progesterone-receptor-positive tumours, while document D60 explains that letrozole acts as an aromatase inhibitor blocking estrogen synthesis. This does not contradict the claimed therapeutic effect, taking account of document D13, which explains that the progesterone receptor is an estrogen-regulated gene product. Notably, document D59 confirms that letrozole is approved for the treatment of hormone-receptor-dependent breast cancer in general.

The limited scope of the authorised indications for ribociclib, as reflected in documents D30 and D49, does not constitute evidence that the claimed combination is ineffective outside those authorised indications and does not in any way affect the technical teaching of the patent.

In the absence of any substantiated evidence demonstrating that the skilled person would be unable to carry out the claimed invention across the scope of the claims, and in the absence of any further arguments from the opponents in response to the Board’s preliminary assessment, the Board concludes that the requirements of Article 83 EPC are met.

4. Main request - Inventive step - starting from the known combination of palbociclib and letrozole

4.1 It was not in dispute that the combination of the CDK4/6 inhibitor palbociclib with the aromatase inhibitor letrozole as described in any of documents D3, D6, D12, D14, D33–D35, D41 and D42/D42b represents a suitable starting point in the prior art.

The subject-matter of claim 1 differs from this starting point in the prior art in that palbociclib is replaced by ribociclib.

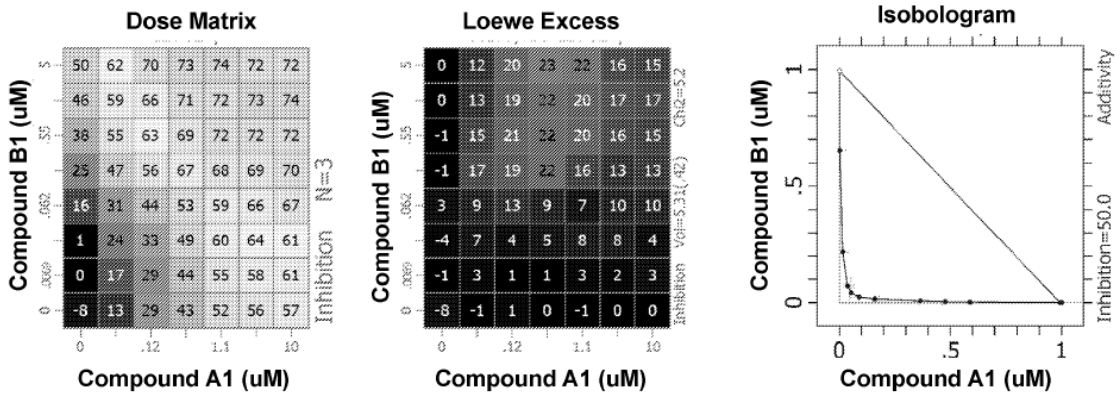
4.2 The objective technical problem

4.2.1 The patent (paragraph [0078]) and the original application on which it is based describe the combination of the invention as particularly useful for the treatment of hormone sensitive and/or hormone receptor positive cancers, in particular breast cancer.

The patent and the original application on which it is based describe in Example 1 (see paragraphs [0097]-[0108]) *in vitro* experiments for assessing and quantifying the synergy in anti-proliferative activity of the combination of ribociclib (A1) with letrozole (B1), with or without the additional presence of a PI3K inhibitor (C1 or C2). Example 2 of the patent (see paragraphs [0109]-[0121]) and the original application present similar experiments involving combinations comprising palbociclib (A3) instead of ribociclib. The described experiments involve MCF7 human breast carcinoma cells transfected with an aromatase expression vector ("MCF7/Aro") and use identical concentration ranges of letrozole together with essentially equipotent concentration ranges of

ribociclib or palbociclib (when used as individual agents). According to the patent (paragraphs [0100], [0105], [0112], [0117]) and the original application, the assays of the experiments are carried out in triplicates to create a dose matrix and the synergistic interaction is evaluated in terms of synergy scores, Loewe excess and Isobolograms with reference to the methods in document D20 ("Lehar et al, 2009"). The relevant results of the experiments of Examples 1 and 2 are presented in Figures 1, 4, 8 and 10, which are reproduced below:

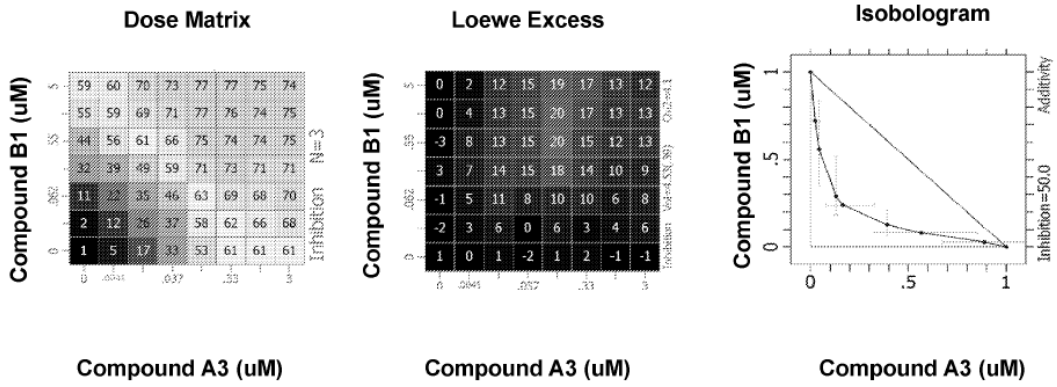
Compound A1 + Compound B1



Synergy Score: 4.12

Figure 1

Compound A3 /Compound B1



Synergy Score: 3.7

Figure 8

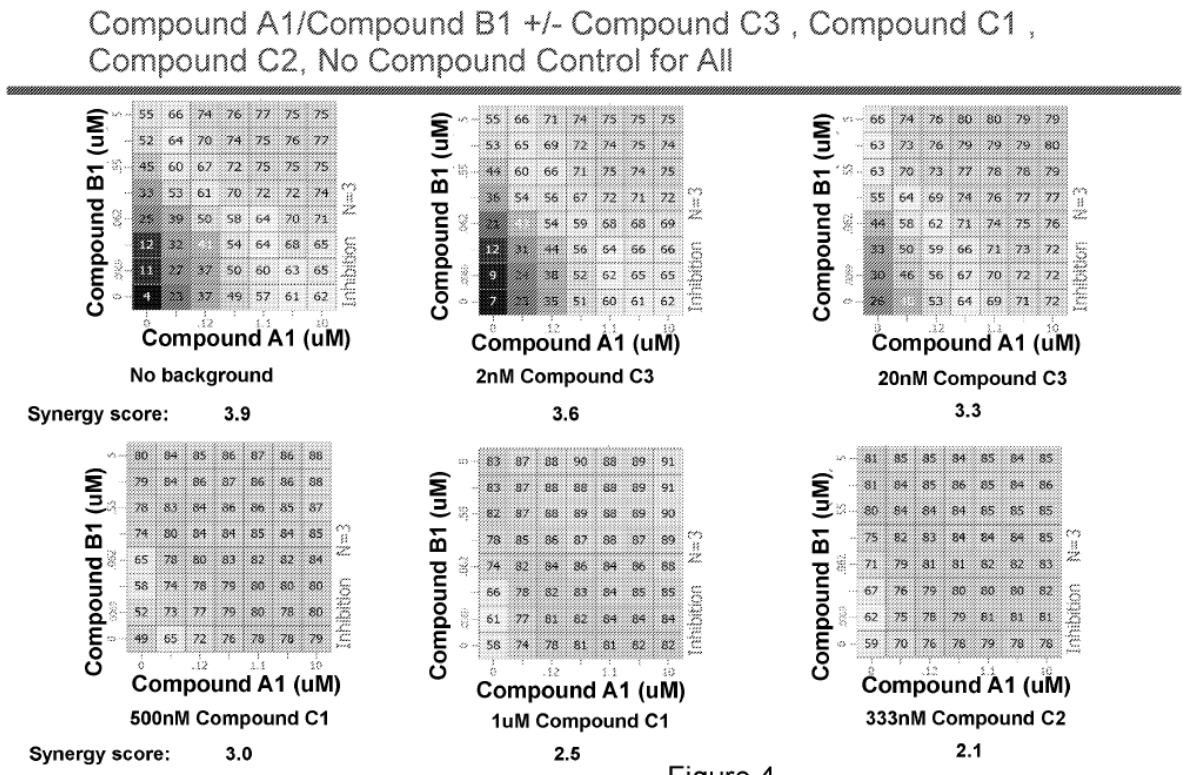


Figure 4

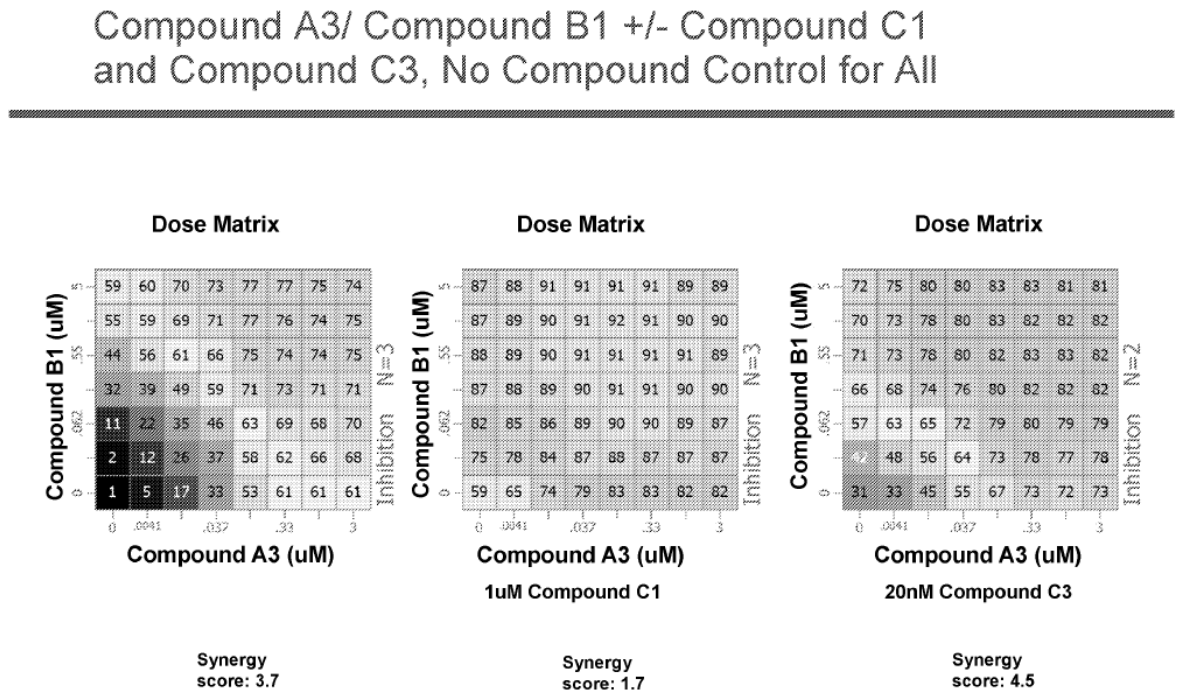


Figure 10

In Example 7, the patent (see paragraphs [0155]-[0177]) and the original application describe experiments for determining the *in vivo* antitumor efficacy of ribociclib (A1), letrozole (B1) and a PI3K inhibitor (C1 or C2), alone or in combination, in a HBCx-34 human breast cancer xenograft mice model. The results of the experiments of Example 7 are presented in Figures 20-22. Figure 20, reproduced below, includes the results of Figures 21 and 22.

Triplet combination in ER+ PIK3CAWT BC PDx model

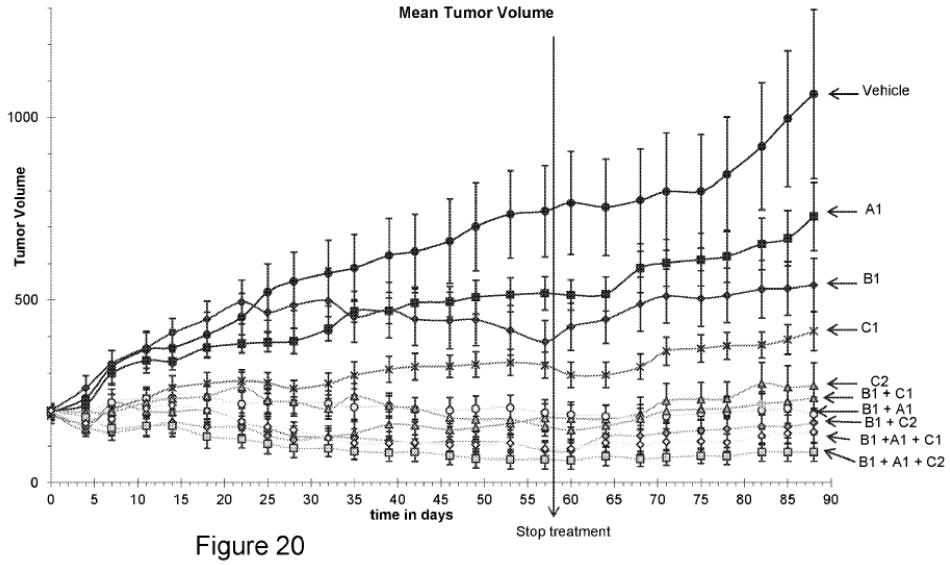


Figure 20

The patent and the original application further describe in Examples 3 and 4 the set up of clinical studies involving the combination of ribociclib and letrozole for the treatment of $HR^+/HER2^-$ breast cancer, either in patients with advanced or metastatic disease or in patients at early stage of the disease.

Document D55 is a post-published (2022) presentation of a matching adjusted indirect comparison (MAIC) of progression free survival (PFS) and overall survival

(OS) of patients with $HR^+/HER2^-$ advanced breast cancer based on the results of the MONALEESA-2 ("ML2", ribociclib+letrozole) and PALOMA-2 ("PAL-2", palbociclib+letrozole) clinical trials. Document D56 is a post-published (2022) abstract describing the same comparison as document D55. It is concluded in documents D55 and D56 that the combination of ribociclib with letrozole was associated with significantly greater overall survival than the combination of palbociclib with letrozole (D55, page 10; D56, "Conclusions").

4.2.2 The Board considers that the results of the *in vitro* experiments reported in Figures 1 and 8 of the patent convincingly demonstrate an increased level of synergy for the claimed combination of ribociclib with letrozole compared with the known combination of palbociclib with letrozole. This is evident from the higher synergy score (4.12 as opposed to 3.7) and from the more pronounced curvature of the isobologram.

4.2.3 The Board observes in this context that the assays of the in vitro experiments were carried out in triplicate and that the resulting data were evaluated in accordance with established methods as described in document D20. Notably, the synergy scores of 4.12 and 3.9 reported in Figures 1 and 4 for ribociclib/ letrozole both substantially exceed the score of 3.7 reported in Figure 8 for palbociclib/letrozole. The declaration in document D52 further confirms that the results for inhibition by letrozole alone showed a high degree of consistency. Under these circumstances, the opponents' argument that the results reported in the patent lack statistical significance, based on the different synergy scores reported in Figures 1 and 4 for the same ribociclib/letrozole combination and on

the variation in the entries in the left column of the dose matrices of Figures 1, 4 and 8 for inhibition by letrozole alone, remains unsubstantiated in the Board's view.

4.2.4 The Board further observes that the dose matrices in Figures 1, 4 and 8 involve different, but approximately equipotent dose ranges for ribociclib and palbociclib, based on the efficacy of the individual agents. This was not contested by the opponents, who instead argued that by using different dose ranges the results did not show an enhanced effect resulting from the replacement of palbociclib by ribociclib, let alone any effect over the whole scope of the claims, which was not limited to specific concentrations. However, as illustrated by the isobolograms in Figures 1 and 8 of the patent, the level of synergy is measured in terms of enhanced effects of the combination of the agents relative to their calculated mere additive effects and is therefore normalized to the potency of the individual agents. For a comparison of the level of synergy resulting from agents with different potencies, such as ribociclib and palbociclib, the dose ranges of these individual agents are therefore appropriately adapted to equipotent doses, precisely as in the dose matrices in Figures 1, 4 and 8. Notably, the curvatures in the isobolograms of Figures 1 and 8 indicate in this context favourable synergy for ribociclib relative to palbociclib over the entire concentration range for the combinations of ribociclib with letrozole achieving 50% inhibition, which justifies the conclusion that the enhanced synergy indeed results from the choice of ribociclib instead of palbociclib.

4.2.5 The opponents' argument that the *in vitro* experiments only involved a particular $HR^+/HER2^-$ breast cancer cell

type and were therefore not suitable to demonstrate any effect over the whole scope of the claims remained without substantiation. In any case, an inventive merit of a combination as defined in the claims is not affected by the suggested possibility that the improved synergy against $HR^+/HER2^-$ breast cancer may not be extrapolated to other cancer types.

4.2.6 As observed by the opponents, Figure 4 of the patent reports for the combination of ribociclib (A1) and letrozole (B1) in the presence of everolimus (C3), as comprised by the claims, a synergy score of 3.3, which is lower than the synergy score of 4.5 reported in Figure 10 for the corresponding combination of palbociclib (A3) with letrozole in the presence of everolimus. However, this lower synergy score for the combination of ribociclib with letrozole in the presence of everolimus is not inconsistent with the conclusion that the results reported in Figures 1 and 8 of the patent demonstrate the enhanced synergy of the claimed combination over the prior art, since the triple combination with palbociclib achieving a synergy score of 4.5 did not form part of the prior art.

4.2.7 The opponents' objection that the reported synergy values merely reflect an effect relative to the individual agents and do not demonstrate an improvement in efficacy over the known combination is also not persuasive. Unlike the situations underlying decisions T 512/02 and T 484/09, the patent includes direct comparative data for the claimed ribociclib/letrozole combination and the palbociclib/letrozole combination of the prior art, generated using the same assay system and therefore allowing a direct assessment of the relative degree of synergy between the two combinations. The demonstrated synergy concerns the

interaction between the components rather than absolute inhibition values at a particular concentration.

This increase in synergy resulting from the replacement of palbociclib by ribociclib constitutes a technically relevant effect. The greater synergy observed with the claimed combination comprising ribociclib and letrozole is associated with the pharmacologically meaningful advantage of achieving a given anti-proliferative effect at a greater reduction of the doses of the combined agents than in the case of the known combination comprising palbociclib.

4.2.8 The opponents' argument that the enhanced *in vitro* synergy of the claimed combination does not substantiate any clinical advantage over the enhanced *in vivo* efficacy of the combination of palbociclib with letrozole described in the prior art remained in this context without substantiation.

In line with the established jurisprudence, as for instance formulated in T 686/91 (reasons 4), the enhanced synergy is an advantage that needs to be taken into account for the formulation of the objective technical problem and may not be disregarded as unrealistic and artificial.

4.2.9 In addition, the post-published evidence in documents D55 and D56 demonstrates that the clinical treatment with the combination of ribociclib with letrozole is associated with significantly greater overall survival of patients with $HR^+/HER2^-$ advanced breast cancer compared to treatment with the known combination of palbociclib with letrozole.

The opponents disputed that, in the absence of a head-to-head comparison, documents D55 and D56 could demonstrate any improvement in overall survival for the claimed combination of ribociclib with letrozole compared with the prior-art combination of palbociclib with letrozole. They relied on documents D25, D45 and D47 to contest the existence of any significant advantage, referred to document A66 regarding the relevance of differences in follow-up periods and indicated the different doses of ribociclib and palbociclib used in the trials.

These arguments are not convincing.

The conclusions in documents D55 and D56 are based on a matching-adjusted indirect comparison of overall survival between the MONALEESA-2 trial, investigating ribociclib in combination with letrozole, and the PALOMA-2 trial, investigating palbociclib in combination with letrozole. Document D55 refers in this context to results as available in 2022 from the MONALEESA-2 trial as, *inter alia*, reported in document D53 and from the PALOMA-2 trial as, *inter alia*, reported in document D54 (D55, references on page 3). As explained in D55, this analytical approach statistically controls for cross-trial differences in baseline patient characteristics and allows comparative conclusions to be drawn in the absence of head-to-head studies (D55, page 3, “Introduction”, and page 10, “Conclusions”).

Documents D25, D45 and D47 concern earlier analyses of overall-survival data from the MONALEESA-2 and PALOMA-2 trials and indicate that, at the time of those publications, the available data were not yet mature (see D25, page 129, right column; D45, page 3,

“Verlängertes Gesamtüberleben?”; D47, page 7, left column). These documents do not address the matching-adjusted indirect comparison reported in documents D55 and D56 on the basis of later data sets and therefore do not contradict the conclusions reported therein.

The reliance on document A66 to argue that differences in follow-up duration influenced the overall-survival outcomes likewise does not undermine the conclusions of documents D55 and D56. The improvement in overall survival reported therein is assessed relative to monotherapy with letrozole within each of the respective trials forming the basis of the comparison. The analysis therefore concerns the effect attributable to the CDK4/6 inhibitor added to letrozole within each study. Notably, document A66 indicates that the effect on overall survival remained insignificant for the palbociclib-letrozole combination over time (A66, page 996, Figure 1), whereas the corresponding effect increased with time for the ribociclib-letrozole combination (D53, page 945, Figure 1). Differences in follow-up duration between the MONALEESA-2 and PALOMA-2 trials do therefore not call into question the conclusion that treatment with ribociclib in combination with letrozole is associated with a greater overall-survival benefit than treatment with palbociclib in combination with letrozole, as reported in D55 and D56.

As indicated, for instance, in document D17, ribociclib and palbociclib have distinct pharmacological and toxicity profiles (D17, page 5, Table 2). The use of different dosing regimens for ribociclib and palbociclib in the trials merely reflects these distinct profiles and does not detract from the

relevance of the comparative survival outcomes reported in documents D55 and D56.

Accordingly, documents D55 and D56 support the conclusion that treatment with the claimed combination of ribociclib and letrozole is associated with improved overall survival compared with treatment with the prior-art combination of palbociclib and letrozole.

4.2.10 The opponents also argued with reference to document D64 that any improved clinical outcome associated with ribociclib did not result from the claimed combination with letrozole, but merely reflected a property of the known agent ribociclib itself, in particular its higher selectivity for CDK4 compared with CDK6 (D64, page 3, section "CDK4 versus CDK6"). In their view, the improvement in overall survival reported in documents D55 and D56 could therefore not be attributed to the combination as claimed.

This argument is also not convincing.

Documents D55 and D56 assess overall survival in patients treated with ribociclib in combination with letrozole and compare these results with those obtained with palbociclib in combination with letrozole. The comparison underlying documents D55 and D56 therefore concerns combination therapies in both cases. Any difference in overall survival identified reflects the clinical performance of the respective combinations.

The relevant passage in document D64 merely suggests an explanation for differences observed with ribociclib in a clinical context involving endocrine therapy and does not call into question the relevance of the comparative

clinical evidence in documents D55 and D56 for the claimed combination of ribociclib with letrozole.

4.2.11 The opponents submitted, with reference to G 2/21, that the skilled person could not derive from the application as filed any clinical improvement of the claimed combination over the prior-art combination, let alone the specific improvement in overall survival reported in documents D55, D56 and D64. This applied all the more since the original disclosure expressly encompassed, in original claim 7, the prior-art combination of palbociclib with letrozole.

According to the order of G 2/21, the patent proprietor may rely upon a technical effect for inventive step, if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

The decisions in T 1994/22, T 314/20, T 840/22 and T 1989/19 consistently apply the order of G 2/21.

In T 1994/22, the patent proprietor could not rely on post-published evidence of improved photostability of a particular claimed polymorph (II) over another polymorph (III), which was disclosed on equal terms in the application as filed, because it could not be derived from the application as filed that photostability represented a relevant property, let alone that the claimed polymorph exhibited any improved photostability over the other disclosed polymorphs, because the compared polymorphs were presented in the application as filed in equal terms (T 1994/22, reasons 1.3).

In T 314/20, the Board found as a matter of fact that the application as filed disclosed several combinations at an equal level of preference and taught that these combinations achieved the same technical effect. Against that factual background, post-published data asserting a superior effect for one specific combination were held to contradict the original technical teaching and therefore not to be encompassed by, nor embodied in, the originally disclosed invention (T 314/20, reasons 6.20–6.25 and 6.13.11).

In T 1989/19, the Board accepted post-published evidence for an improvement of a technical effect over the closest prior art, since the technical effect itself was already derivable from the application as filed. Reliance on post-published evidence to substantiate an improvement was considered permissible under G 2/21 (T 1989/19, reasons 3.3.15–3.3.16).

The same principle was applied in T 840/22, which confirmed that post-published data may substantiate an improvement of an encompassed technical effect even if the superiority of one originally disclosed embodiment was recognised only later (T 840/22, reasons 15.2).

Notably, decision T 887/21 related to a different situation, in which the post-published evidence concerned an asserted technical effect that could not even be derived, as such, from the application as originally filed, and therefore could not be relied on in support of an inventive step (T 887/21, reasons 2.15.4).

According to the cited jurisprudence, post-published evidence may thus be relied upon in support of an

improved effect over the prior art where the underlying technical effect is derivable from the application as filed and the improvement is consistent with the original technical teaching.

In the present case, the patent and the original application on which it is based explicitly teach the utility of the combination of the invention in the treatment of hormone sensitive and/or hormone receptor positive cancers, report the particular efficacy of the claimed combination of ribociclib with letrozole as demonstrated in *in vitro* and *in vivo* experiments representative of $HR^+/HER2^-$ breast cancer, and present the outlines for the clinical studies involving the use of this combination in the treatment of patients with $HR^+/HER2^-$ breast cancer in advanced or early stages of the disease. When carrying out the subject-matter as originally disclosed, the skilled person, having the common general knowledge in mind, would certainly take into account any improvement in overall survival of patients suffering from $HR^+/HER2^-$ breast cancer resulting from treatment with the claimed combination. Moreover, the effect of improved overall survival may well be considered consistent with the original technical teaching, especially given the originally disclosed enhanced synergy of the claimed combination. The fact that clinical evidence demonstrating an improvement achieved by the claimed combination over another combination also disclosed in the original application only emerged years after the filing date of the patent is inherent to the technical field concerned and does not affect the technical teaching of the patent and the application as filed, nor the invention disclosed therein. In any event, the Board holds that reliance on post-published evidence to demonstrate an improved technical effect of the claimed subject-matter

over a further embodiment originally claimed does not normally change the nature of the invention, as long as the technical effect is derivable from the application as filed and the improvement is not in contradiction with the original disclosure.

In line with the cited jurisprudence, the Board therefore considers that the effect of the improved overall survival may be derived from the application as originally filed as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

In accordance with the order in G 2/21, this effect and the post-published evidence in document D55 and D56 in support of it may therefore be relied on by the patent proprietor for the formulation of the objective technical problem.

4.2.12 In view of the experimental results reported in the patent as well as the post-published evidence the objective technical problem may therefore be formulated as the provision of an improved combination for the treatment of hormone-sensitive or hormone-receptor-positive cancer.

4.3 Assessment of the solution

4.3.1 The prior art provides no suggestion that the combination of ribociclib with letrozole would provide an improved combination for the treatment of hormone-sensitive or hormone-receptor positive cancer. Document D4 describes ribociclib as a CDK4/6 inhibitor used in combination with a PI3K inhibitor, but does not contain any indication that ribociclib would perform better than palbociclib when combined with letrozole. More

generally, none of the cited prior-art documents points to an improvement associated with the use of ribociclib in place of palbociclib in combination therapy with letrozole.

4.3.2 The opponents argued that the claimed solution was nevertheless obvious on the basis of a "try-and-see" approach, according to which the skilled person would have replaced palbociclib by another known CDK4/6 inhibitor, such as ribociclib, and assessed the outcome experimentally.

This argument is not convincing.

According to established jurisprudence, a "try-and-see" approach may lead to a finding of obviousness only in exceptional situations, namely where, in view of the teaching of the prior art, the skilled person would already have clearly envisaged a particular modification or a defined group of alternatives and where routine testing would be expected to confirm that the envisaged modification solves the posed technical problem without any particular technical difficulty (Case Law of the Boards of Appeal of the European Patent Office, 11th edition, 2025, I.D.7.4).

In the present case, the prior art contains no suggestion that replacing palbociclib by ribociclib, chosen from a multitude of available CDK4/6 inhibitors (see for instance document D46), in combination with letrozole would lead to an improvement. Document D4 refers to the preparative methods of document D46 for the synthesis of ribociclib (D4, page 10) and only describes the combination of the CDK4/6 inhibitor with a PI3K inhibitor. The skilled person therefore had no reason to select ribociclib or to expect that its

combination with letrozole would solve the identified technical problem.

4.3.3 In the absence of any suggestion in the prior art towards the claimed improvement and without a reasonable expectation of success, the skilled person would not have arrived at the claimed solution in an obvious manner.

The claimed subject-matter therefore involves an inventive step starting from the known combination of palbociclib and letrozole (Article 56 EPC).

5. Main request - Inventive step - starting from the known combination of ribociclib and a PI3K inhibitor

5.1 Double combination of ribociclib with letrozole

5.1.1 Document D4 describes a combination comprising ribociclib and a PI3K inhibitor which is presented as synergistic. For the assessment of the claimed double combination of ribociclib with letrozole, this disclosure does not represent the closest prior art.

Starting from document D4, it requires the replacement of a PI3K inhibitor by an agent from a different class, namely the aromatase inhibitor letrozole, to arrive at the claimed double combination. By contrast, starting from the known palbociclib/letrozole combination requires only exchanging one CDK4/6 inhibitor for another. Whilst both the prior art relating to the palbociclib/letrozole combination and document D4 pursue a similar therapeutic purpose as the claimed combination, the functional distinction relating to the replacement of a PI3K inhibitor with an aromatase inhibitor renders the teaching of document D4

definitively more remote from the claimed invention than the replacement of one CDK4/6 inhibitor for another.

5.1.2 The Board notes that the problem-solution approach implies that if an inventive step is convincingly denied in view of a realistic starting point in the prior art, an argument that the claimed subject-matter nevertheless involves an inventive step in view of a supposedly closer prior art is generally unconvincing, since in such a case the supposedly closest prior art appears to be less promising. However, if an inventive step can be acknowledged starting from a particular prior art that is convincingly identified as the most promising starting point and therefore indeed constitutes the closest prior art, the Board need not address an attempt to deny an inventive step starting from a less promising starting point (see Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.3.1 to I.D.3.4; see also T 405/14, reasons 18 and T 722/24, reasons 5.1.2).

The concept of the closest prior art in the problem solution approach not only obviates the need to address repetitive and redundant lines of argument, it also allows for the due appreciation of specific effects in relation to the prior art that may be associated with the distinguishing features (compare Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.3.8.5).

Certainly, there may be situations in which it is not possible to determine whether a particular document is closer to the subject-matter of the invention than any other documents, thereby making it impossible to identify the "closest prior art". Only in such cases is

it necessary to assess inventive step starting from any suitable prior art document before concluding that the claimed subject-matter is inventive.

In view of the Board's findings under sections 4.3 and 5.1.1 a comprehensive evaluation of inventive step of the claimed double combination starting from document D4 is therefore considered unnecessary.

Nevertheless, in view of the parties submissions on this matter during the appeal proceedings, the Board presents the following assessment.

5.1.3 The claimed subject-matter differs from the combination disclosed in document D4 in that the PI3K inhibitor is replaced by letrozole. The opponents submitted that no improvement over the synergistic combination of ribociclib with a PI3K inhibitor disclosed in document D4 had been demonstrated, such that the objective technical problem was merely the provision of an alternative synergistic combination. They further argued that, in view of the known synergistic combination of palbociclib with letrozole, it was obvious that another CDK4/6 inhibitor, such as ribociclib, would also show synergy when combined with letrozole, so that the claimed combination represented an obvious solution.

This line of argument is not convincing. The synergistic interaction disclosed in document D4 is specifically associated with the combination of ribociclib and a PI3K inhibitor. The skilled person would not combine this teaching with the known synergy of a different CDK4/6 inhibitor, namely palbociclib, with the aromatase inhibitor letrozole in order to derive the claimed combination. The prior art therefore

provides no suggestion that the PI3K inhibitor in the combination of document D4 could be replaced by letrozole while retaining synergistic activity. In the absence of such guidance, the claimed subject-matter cannot be regarded as an obvious solution to the problem of providing an alternative synergistic combination to the combination of document D4.

5.2 Triple combination comprising ribociclib and letrozole

5.2.1 The objective technical problem

A triple combination comprising ribociclib and letrozole encompassed by claim 1 differs from the combination of ribociclib with a PI3K inhibitor disclosed in document D4 by the additional presence of letrozole. The experimental results presented in Figure 4 of the patent demonstrate an increased antiproliferative activity of the triple combination when letrozole (B1) is added to the double combination of ribociclib (A1) and a PI3K inhibitor (C1) corresponding to the double combination of document D4. The objective technical problem may therefore be formulated as the provision of a combination with enhanced antiproliferative activity over the combination disclosed in document D4.

The opponents suggested that, at best, the addition of letrozole led only to a marginal increase in activity and could therefore not support a qualified formulation of the objective technical problem. However, the relevant comparison is between the synergistic double combination disclosed in document D4 and the claimed triple combination. Where, as shown in the patent, the addition of letrozole results in a consistent increase in antiproliferative activity relative to that already

synergistic combination of document D4, this increase constitutes a technical effect which cannot be disregarded in the formulation of a qualified objective technical problem. The fact that the starting combination already exhibits synergistic activity underlines the relevance of the further increase in activity.

5.2.2 Assessment of the solution

The prior art provides no suggestion that the further addition of letrozole to the combination of document D4 would result in a combination with enhanced antiproliferative activity.

The opponents contended that any additional activity upon adding letrozole was to be expected, and therefore obvious, because the assay employed aromatase-overexpressing, letrozole-responsive cells. However, the chosen MCF7/Aro cell system constitutes an appropriate model for testing the effectiveness of combinations for the treatment of hormone-sensitive cancer, which is confirmed by the results of *in vivo* xenograft experiments in Figures 20-22 of the patent. Nevertheless, the letrozole responsiveness of the cell system does not imply that proliferation already synergistically suppressed by the ribociclib/ PI3K-inhibitor combination of document D4 remained susceptible to further suppression by letrozole, and therefore does not provide any pointer towards a further enhancement. The well-established aromatase-inhibiting activity of letrozole as such, as described in document D60 (page 11-12, under “Conclusions”), did therefore not suggest that the addition of letrozole would further suppress cell proliferation where proliferation was already synergistically inhibited by

a CDK4/6 inhibitor in combination with a PI3K inhibitor as disclosed in document D4. Nor did the enhanced efficacy of letrozole in combination with the CDK4/6 inhibitor PD-033991 (palbociclib), as reported for example in documents D6 (page 2, left column), D16 (page 2, left column) and D42b (page 11, under "Investigator Commentary") suggest that adding letrozole to the ribociclib/PI3K-inhibitor combination of document D4 would result in a further suppression of cell proliferation.

Documents D10, D12 and D13 relied upon by the opponents are review-type publications discussing mechanisms of endocrine resistance and signalling pathways in hormone-receptor-positive breast cancer. These documents discuss *inter alia* the interaction between agents targeting the PI3K pathway and endocrine therapy and the enhanced clinical efficacy observed with the combination of letrozole with the CDK4/6 inhibitor PD-0332991 (palbociclib) (D10, page 2, paragraph bridging the columns and page 9, right column; D12, page 28, paragraph bridging the columns and page 30, right column; D13, page e39, left column and page e40, left column lines 1-6 and right column, under "Conclusion"). None of these documents discloses or suggests a triple combination comprising a CDK4/6 inhibitor, a PI3K inhibitor and an aromatase inhibitor, let alone that adding letrozole to the ribociclib/ PI3K-inhibitor combination of document D4 would lead to a further enhanced antiproliferative effect.

The opponents further specifically maintained that documents D28, D36 and D41 would have suggested adding letrozole to the combination of ribociclib and a PI3K inhibitor disclosed in document D4 and that at least a

try-and-see approach applied. This argument is also not convincing.

Document D28 reports that interference with estrogen-receptor signalling, for example by the estrogen-receptor destabiliser fulvestrant, and inhibition of CDK4/6 are associated with effects on hormone-stimulated tumour cell proliferation, whereas inhibition of the PI3K pathway is associated with effects on tumour cell survival (D28, Figure 1). The combinations discussed in document D28 are based on this distinction and only concern double combinations. However, document D28 neither discloses nor suggests any triple combination, let alone that adding the aromatase inhibitor letrozole to a combination of the CDK4/6 inhibitor ribociclib and a PI3K inhibitor would provide any additional benefit.

Document D36 conveys a similar teaching. It describes inhibition of estrogen-receptor- and CDK4/6-dependent tumour cell proliferation and inhibition of PI3K-dependent tumour cell survival as affecting distinct pathways and discusses combinations of these approaches (D36, abstract under “Significance”; page 2, right column; page 8 under “Combined targeting”). Figure 5 of document D36 illustrates that combining inhibition of estrogen-receptor signalling by fulvestrant with PI3K inhibition by BKM120 enhances antitumour effects compared with either approach alone. The scheme in Figure 5F confirms in this context that fulvestrant and the CDK4/6 inhibitor PD-0332991 (palbociclib) act on the same axis. However, this disclosure remains limited to double combinations. Document D36 therefore neither discloses nor suggests a triple combination comprising a CDK4/6 inhibitor, an aromatase inhibitor and a PI3K inhibitor, let alone

that adding the aromatase inhibitor letrozole to a combination of the CDK4/6 inhibitor ribociclib and a PI3K inhibitor would provide any additional benefit.

Document D41 reviews the development of aromatase inhibitors, including letrozole among other third-generation drugs (D41, Table 1). In the context of resistance to aromatase inhibitors, document D41 discusses several combination strategies under investigation, including combinations of aromatase inhibitors with CDK4/6 inhibitors and combinations of aromatase inhibitors with PI3K inhibitors (D41, Figure 2). All these strategies concern double combinations. Document D41 further concludes that, in view of the increasing number of signal inhibitors, the challenge lies in selecting which drugs to combine, how to combine them and how such combinations will be tolerated with respect to side effects (D41, page R194, right column). Document D41 therefore neither discloses nor suggests a triple combination comprising a CDK4/6 inhibitor, an aromatase inhibitor and a PI3K inhibitor, let alone that adding the aromatase inhibitor letrozole to a combination of the CDK4/6 inhibitor ribociclib and a PI3K inhibitor would provide any additional benefit.

Accordingly, none of documents D60, D6, D16, D42b, D10, D12, D13, D28, D36 or D41 provides any pointer that adding letrozole to the combination disclosed in document D4 would solve the objective technical problem with a reasonable expectation of success. The opponents' try-and-see approach is instead based on hindsight and, for the same reasons as set out in section 4.3.2, cannot support a finding of obviousness.

The triple combination of ribociclib and letrozole including a PI3K inhibitor was therefore not obvious starting from document D4.

5.3 Accordingly, the claimed subject-matter also involves an inventive step starting from document D4.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated