Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 3 June 2025

Case Number: T 0136/24 - 3.3.04

Application Number: 10782039.1

Publication Number: 2493466

IPC: A61K31/164, A61K31/56, A61K45/06, A61P35/00

Language of the proceedings: EN

Title of invention:
Novel antitumoral use of cabazitaxel

Patent Proprietor:
SANOFI

Opponents:
Glenmark Pharmaceuticals Europe Ltd
Accord Healthcare Ltd
Zentiva k.s.
Fresenius Kabi Deutschland GmbH
Dr. Reddy's Laboratories Ltd./ Betapharm Arzneimittel GmbH
Generics (U.K.) Limited
Vossius & Partner Patentanwälte Rechtsanwälte mbB
STADA Arzneimittel AG
Maiwald GmbH
Accord Healthcare S.L.U.

Headword:
Cabazitaxel / SANOFI

Relevant legal provisions:
EPC Art. 87, 100(a), 54(2), 54(5), 56, 100(b), 100(c), 113(1)
EPC R. 103(1)(a)
RPBA 2020 Art. 12(4), 13(2)

Keyword:
Grounds for opposition - do not prejudice maintenance of the patent

Decisions cited:
T 0158/96, T 1009/97, T 1491/14, T 0072/18, T 2344/19, T 2506/12, T 0239/16, T 1806/18, T 2963/19, T 3165/19, T 0096/20, T 1045/21, T 1437/21, T 1941/21

Catchword:
On the issue of reasonable expectation of success in view of (announcements of) clinical studies in the prior art, see Reasons 7.14 to 7.14.10

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0136/24 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 3 June 2025

Appellant: (Opponent 1)	Glenmark Pharmaceuticals Europe Ltd Building 2 Croxley Park Watford WD18 8YA (GB)
Representative:	Brand Murray Fuller LLP 50 Eastcastle Street London W1W 8EA (GB)
Appellant: (Opponent 2)	Accord Healthcare Ltd Sage House 319 Pinner Road North Harrow Middlesex HA1 4HF (GB)
Representative:	Aera A/S Niels Hemmingsens Gade 10, 5th Floor 1153 Copenhagen K (DK)
Appellant: (Opponent 5)	Zentiva k.s. U kabelovny 130 10237 Praha 10 (CZ)
Representative:	Greiner, Elisabeth df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Appellant: (Opponent 7)	Fresenius Kabi Deutschland GmbH Else-Kröner-Str. 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department

Else-Kröner-Straße 1
61352 Bad Homburg (DE)

Appellant: (Opponent 8)
Dr. Reddy's Laboratories Ltd./ Betapharm Arzneimittel GmbH
8-2-337 Road No. 3 /Kobelweg 95
Banjara Hills
Hyderabad
500034 Telangana IN / 86156 Augsburg DE (IN)

Representative:
Maiwald GmbH
Elisenstraße 3
80335 München (DE)

Appellant: (Opponent 9)
Generics (U.K.) Limited
Building 4, Trident Place
Mosquito Way
Hatfield Herts AL10 9UL (GB)

Representative:
Elkington and Fife LLP
Prospect House
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

Appellant: (Opponent 10)
Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München (DE)

Representative:
Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstraße 3
81675 München (DE)

Appellant: (Opponent 11)
STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel (DE)

Representative:
Hamm&Wittkopp Patentanwälte PartmbB
Jungfernstieg 38
20354 Hamburg (DE)

Appellant: (Opponent 12)
Maiwald GmbH
Postfach 33 05 23
80065 München (DE)

Representative:
Maiwald GmbH
Elisenhof
Elisenstraße 3
80335 München (DE)

Respondent: (Patent Proprietor)
SANOFI
46 avenue de la Grande Armée
75017 Paris (FR)

Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Party as of right: (Opponent 13)	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona s/n Edifici Est, 6th floor 08039 Barcelona (ES)
Representative:	Aera A/S Niels Hemmingsens Gade 10, 5th Floor 1153 Copenhagen K (DK)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 January 2024 rejecting the opposition filed against European patent No. 2 493 466 pursuant to Article 101(2) EPC.**

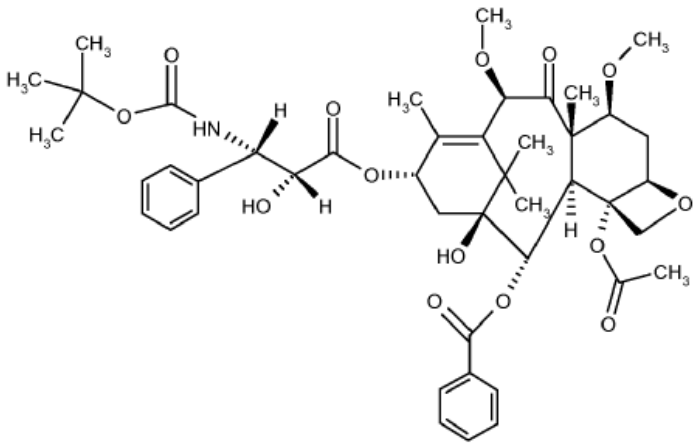
Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 2 493 466 (patent in suit) was granted with a set of nine claims. Claim 1, which is the only independent claim, and dependent claim 8 read as follows:

"1. Compound of formula



which may be in base form or in the form of a hydrate or a solvate,
in combination with prednisone or prednisolone,
for use in treating prostate cancer,
in patients with castration resistant metastatic prostate cancer who have been previously treated with docetaxel based regimen and have prostate cancer that progressed during or after said treatment.

[...]

8. Compound for use according to any one of claims 1 to 7, in combination with prednisone."

II. The compound according to claim 1 is also known as cabazitaxel, XRP6258 and RPR-116258A. XRP6258 was known to be cabazitaxel and to have the structure formula

shown in claim 1 at the first priority date (see **D2**: title; **D9**: page 930, Table 1, Index 62). Both cabazitaxel and docetaxel are taxane anticancer agents.

III. In the written opposition and opposition appeal proceedings, the therapeutic indication of metastatic castration-resistant prostate cancer (or castration resistant metastatic prostate cancer, as it is termed in claim 1) was referred to in abbreviated form as mCRPC. This abbreviation, as well as CRPC for castration-resistant prostate cancer, is also used below.

IV. The patent in suit was opposed by 12 opponents under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

V. Opponents 3 and 4 later withdrew their oppositions.

VI. In the proceedings before the opposition division, the patent proprietor requested as its main request that the oppositions be rejected and that the patent be maintained as granted.

VII. The documents cited in the proceedings before the opposition division included the following:

P1: US 61/256,160 (first priority application)

D1: ClinicalTrials.gov, Extract relating to study no. NCT00417079, the TROPIC study (last updated 14 November 2008)

D2: NHSC, "Cabazitaxel (XRP-6258) for hormone refractory, metastatic prostate cancer - second line after docetaxel" (April 2009)

D3: The Prostate cancer Blog, blog post by Dr Barry Mirtsching (12 October 2007)

D4: Clin Cancer Res 15(2), 723-730 (15 January 2009)

D6: ClinicalTrials.gov, Extract relating to study no. NCT00417079, last updated 14 November 2008

D7: Current Opinion in Supportive and Palliative Care 2, 161-166 (2008)

D9: ChemMedChem 2, 920-942 (2007)

D10: Sanofi-Aventis Press Release (21 December 2009)

D11: Les Echos, "Un projet de médicament stoppé in extremis" (22 December 2009)

D13: Annals of Oncology 19, 1547-1552 (2008)

D14: "TAXOTERE (docetaxel) Injection Concentrate", Highlights of Prescribing Information (2007)

D15: The Lancet 376, 1147-1154 (2 October 2010)

D18: EMA Guidelines on the Evaluation of Anticancer Medicinal Products in Man (June 2006)

D20: Sanofi-Aventis Annual Review (17 April 2009)

D21: EMA/CHMP/66633/2011 Assessment Report for Jevtana (cabazitaxel), procedure no.: EMEA/H/C/002018, footnote on 2-66: EMA/CHMP/782336/2010

D26: Pathologie Biologie 54, 72-84 (2006)

D37: The Canadian Journal of Urology 15(1), 3942-3949 (2008)

D39: Urology 67, 1235-1240 (2006)

D46: "JEVTANA (cabazitaxel) Injection", Highlights of Prescribing Information (revised June 2010)

D58: Declaration by T.M. Beer (23 April 2022)

D72: J Clin Oncol 26, 1148-1159 (2008)

D92: Clinical Trial Agreement relative to XRP6258, protocol no. EFC6193 (25 January 2007)

D93: "JEVTANA® (cabazitaxel) injection", Highlights of Prescribing Information (revised September 2017)

D105: Expert Rev. Anticancer Ther. 5(1), 53-62 (2005)

VIII. The decision under appeal is the opposition division's decision rejecting the oppositions, announced on 15 December 2023 and posted on 25 January 2024.

IX. The decision under appeal includes, *inter alia*, the following findings.

Claim construction

(a) Claim 1 as granted was limited to follow-on treatment of patients with mCRPC who had undergone a previous treatment with a docetaxel-based regimen for the same therapeutic indication, rather than "any" indication as suggested by the opponents.

(b) Dependent claim 8 was restricted to combination treatment with prednisone (i.e. one of the two alternative combination partners specified in independent claim 1). It did not claim a triple combination of cabazitaxel, prednisone and prednisolone as suggested by the opponents.

Added subject-matter (Article 100(c) EPC)

(c) Claim 1 was based on claim 1 and claim 12 of the application as filed and the corresponding disclosure on page 1, lines 3 to 7 and page 3, lines 11 to 12. The feature "previously treated with docetaxel based regimen" in claim 1 as granted found support on page 7, lines 11 to 19, of the application as filed.

(d) The subject-matter of claim 8 found a basis in claim 12 of the application as filed.

Sufficiency of disclosure (Article 100(b) EPC)

(e) The opponents had submitted that, in view of the disclosure in the application as filed, there was doubt that a therapeutic benefit in treating prostate cancer could be achieved across the scope claimed. The objections focused on (i) patient subsets without evidence of a therapeutic effect, (ii) subsets affected by adverse events or contraindications and (iii) dosage ranges without a therapeutic effect or with unacceptable adverse effects. The opposition division concluded that the opponents had failed to provide adequate substantiation for serious doubt as to the achievement of a therapeutic benefit. The subject-matter of the claims as granted met the requirement of sufficiency of disclosure.

Right to priority (Article 87 EPC)

(f) Contrary to the opponents' objection, the feature of claim 1 specifying prostate cancer that progressed during or after treatment with a docetaxel-based regimen was not the result of an undue intermediate generalisation and did not extend the claimed subject-matter beyond the content of **P1** as filed.

(g) As a consequence, documents **D10**, **D11**, **D15** and **D46**, all published after the effective date of the opposed patent, did not belong to the state of the art pursuant to Article 54(2) EPC.

Novelty (Articles 100(a), 52(1) and 54 EPC)

(h) The claimed subject-matter was novel over the written disclosure of **D1**, **D2** and **D6**, all of which disclosed the phase III study protocol for cabazitaxel (the TROPIC study) without revealing

any data resulting from this study. Furthermore, the public prior use that had been alleged on the basis of **D1**, **D2** and **D6** was not adequately substantiated.

(i) The blog post in **D3** that commented on current clinical studies for prostate cancer did not anticipate the claimed subject-matter, either.

(j) Since the priority claim based on **P1** had been found valid, the publications **D10**, **D15** and **D46**, which had been cited by the opponents as anticipating the claimed subject-matter, did not form part of the opposable state of the art.

Inventive step (Articles 100(a), 52(1) and 56 EPC)

(k) In a first approach, inventive step of claim 1 as granted was assessed starting from the disclosure of the protocol of the phase III TROPIC study in **D1** and **D2**. This disclosure was also considered representative of documents **D3**, **D7** and **D37**, all of which referred to an ongoing study while not disclosing more detail than **D1** and **D2**. The objective technical problem was the provision of an effective treatment of mCRPC patients with tumour progression during or after docetaxel therapy that resulted in an improved therapeutic outcome relative to therapy with mitoxantrone and PRED *[sic]*.

(l) In a second approach, inventive step was assessed starting from the disclosure of **D4** on phase I study results. The objective technical problem was the same as in the first approach.

(m) In a third approach, inventive step was assessed starting from the disclosure of established second-line treatment options as disclosed in **D7** and **D39**,

namely docetaxel re-treatment (for a selected subgroup of patients who responded to first-line docetaxel) and mitoxantrone palliative therapy. The objective technical problem was the provision of an effective treatment for the entire group of mCRPC patients with tumour progression during or after docetaxel therapy that resulted in an improved therapeutic outcome relative to therapy with mitoxantrone and PRED *[sic]*.

(n) In each of these settings, the opposition division came to the conclusion that the claimed follow-on therapy with cabazitaxel was not rendered obvious by the prior art. Thus, the claimed subject-matter involved an inventive step within the meaning of Article 56 EPC.

X. Opponents 1, 2 and 5 to 12 all filed appeals against this decision. Opponent 6 subsequently withdrew its opposition and appeal (see the Minutes of the oral proceedings before the board, page 3). The remaining appellants are opponents 1, 2, 5 and 7 to 12.

XI. A further party filed a notice of intervention to join the oppositions against the patent in suit (Article 105(1)a) EPC, see point 1. below). The intervener was designated as opponent 13. For ease of reading, the appellants and the intervener are in the following referred to as the opponents.

XII. The patent proprietor (respondent) submitted replies to the appeals and to the notice of intervention. With its reply to the appeals, it also filed 25 sets of claims as auxiliary requests 1 to 25.

XIII. The following documents were submitted in the course of the appeal proceedings.

D108: H. Barraclough and W. Davis, "Fundamental statistics" (February 2023)

D109: L. Albarqouni, Tutorial about Hazard Ratios (posted online in April 2016)

D110: Form 20-F filed by Sanofi-Aventis with the United States Securities and Exchange Commission concerning the fiscal year 2008

D111: National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology, Prostate Cancer, v.-2.2009

D111a: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Prostate Cancer, v.-3.2010

D112: Tribunal Judiciaire de Paris, 3ème chambre, 2ème section, Jugement N°RG 21/06416-N°Portalis 352J-W-B7F-CUMKO, in Accord v Sanofi (6 September 2024)

D112a: Machine translation of D112 into English

D113: European Urology Supplements 8, 738-746 (2009)

D114: Extracts from Sanofi's Form 20-F, fiscal year 2006

D108 and **D109** were filed by opponent 5 with its grounds of appeal.

D110 was filed by opponent 13 with its notice of intervention.

D111 and **D111a** were filed by the patent proprietor with its reply to the appeals.

D112 and **D112a** were filed by opponent 9 with its letter dated 10 October 2024.

D113 and **D114** were filed by the patent proprietor with its reply to the notice of intervention.

XIV. Oral proceedings before the board took place on 2 to 3 June 2025. At the close of the oral proceedings, the board announced its decision dismissing the appeals.

XV. The board's decision is, accordingly, based on the patent proprietor's main request, which is directed to the maintenance of the patent in suit as granted.

XVI. The opponents' pertinent arguments may be summarised as follows.

Claim construction

According to opponent 12, the definition of the patient group in claim 1 as granted did not require that the prior treatment with a docetaxel-based regimen was for prostate cancer (specifically mCRPC). The prior treatment could as well be for any other type of cancer that was a known therapeutic indication of docetaxel.

According to opponent 1, the wording of dependent claim 8 as granted covered a triple combination of cabazitaxel, prednisone and prednisolone.

Added subject-matter (Article 100(c) EPC)

The objections of added subject-matter pursued by opponents 1, 11 and 12 concerned claims 1 and 8.

As to claim 1, the opponents argued that previous treatment with docetaxel was disclosed in the application as filed only in association with a cumulative dose of at least 225 mg/m^2 of docetaxel, a limitation that was absent from claim 1 as granted. Contrary to the patent proprietor's approach, it was not permissible to combine the embodiment defined by claims 1, 3 and 5 as filed with a technical feature taken from a separate embodiment disclosed in the description.

Furthermore, the term "docetaxel treatment" used on page 7 of the application as filed could only mean docetaxel monotherapy, which was not identical to the meaning of the term "docetaxel based regimen" employed in claim 1 as granted.

In addition, at the oral proceedings before the board, opponent 8 argued that the term "metastatic" used in claim 1 as granted but absent from claims 1, 3 and 5 as filed required an additional selection from the disclosure of the application as filed.

The objection against claim 8 was based on the understanding that the scope of claim 8 as granted encompassed a triple combination of cabazitaxel, prednisone and prednisolone. Such a triple combination was not disclosed in the application as filed.

Sufficiency of disclosure (Article 100(b) EPC)

Opponent 1, opponent 5 and opponent 10 pursued objections of insufficiency of disclosure, mainly along the lines of what had been discussed in the proceedings before the opposition division. Thus, according to the opponents, there was doubt, in view of the information provided in the patent itself, that the envisaged treatment with cabazitaxel provided therapeutic efficacy and safety across the scope claimed, i.e. including for certain patient subsets and dosage regimens encompassed by claim 1. Moreover, in the absence of a clear definition of disease progression, it was uncertain which patients were included in the patient group defined in claim 1. Opponent 5 also submitted that if the patent proprietor or the board were to adopt the position that claim 1 required both active agents (cabazitaxel and prednisone or prednisolone) to exert a therapeutic effect, as such or

in combination, it should be taken into consideration that the patent provided no evidence in this regard.

Right to priority (Article 87 EPC)

The feature specifying progression of disease during or after docetaxel-based treatment was disclosed in **P1** explicitly only in a specific context and in combination with further restrictions that were not reflected in claim 1 as granted, *inter alia*, that the previously administered cumulative dose of docetaxel, administered as Taxotere, was at least 225 mg/m^2, that the patients' life expectancy should be at least two months and that they should have undergone hormone therapy (see **P1**: page 5, line 34 to page 6, line 21).

Opponent 2 pointed out that the disclosure on page 5 of **P1**, relied on by the patent proprietor in support of claim 1 as granted, did not refer to metastatic cancer.

Opponent 5 contended that the phrase "patients who are not catered for by a taxane-based treatment" was too vague to support the more specific feature in claim 1 as granted of disease progression during or after docetaxel-based treatment.

According to opponent 8, the combination of technical features in claim 1 as granted was also not enabled in **P1**.

Novelty (Articles 100(a), 52(1) and 54 EPC)

The subject-matter of claim 1 as granted lacked novelty over the disclosure of documents **D1**, **D2**, **D3**, **D4**, **D6** and **D26**. Since the claimed subject-matter was not entitled to priority from **P1**, it also lacked novelty over the disclosure of **D10** (in combination with **D1**).

The claimed subject-matter was anticipated not only by the written disclosure of these prior-art documents

but also by a public prior use in a phase III clinical study as evidenced by **D1, D2** and **D6.**

Opponent 5 furthermore mentioned **D15** and **D46** as novelty-destroying (see point 33 of the statement setting out the grounds of appeal).

Inventive step (Articles 100(a), 52(1) and 56 EPC)

Documents **D1, D2, D3, D4, D6, D7, D37, D39** and **D110** were suggested as possible starting points for the assessment of inventive step; **D10** and **D11** were suggested should the board find that the claimed subject-matter was not entitled to priority.

The various approaches to be considered for the assessment of inventive step started from (i) the announcement of the TROPIC study and its set-up, (ii) the results reported for the phase I evaluation of cabazitaxel in mCRPC, and (iii) previously known therapeutic standards for the treatment of docetaxel-resistant mCRPC.

Irrespective of the chosen starting point in the prior art, the conclusion in each case must be that the person skilled in the art would have had a reasonable expectation of success in relation to the therapeutic use defined in claim 1 as granted.

Appeal fee reimbursement (Rule 103(1)(a) EPC)

Appellant-opponent 2 submitted that the opposition division's decision did not address several of its arguments, especially those based on **T 1806/18, D18** and **D21** and mentioned in sections 3.3, 4.2, 4.3 and 4.4 of its statement setting out the grounds of appeal. Reimbursement of the opponent's appeal fee under Rule 103(1)(a) EPC was therefore requested.

XVII. The patent proprietor's pertinent arguments may be summarised as follows.

Claim construction

From the phrasing of claim 1 and the technical context provided in the patent in suit, a reader would understand that the prior docetaxel-based treatment was a prior treatment of the therapeutic indication set out in the claim, i.e. the patients' mCRPC.

Dependent claim 8 was restricted to one of the two alternatives provided in claim 1, namely the combination of cabazitaxel with prednisone.

Added subject-matter (Article 100(c) EPC)

Claim 1 as granted was based on claim 5 as filed when dependent on claims 3 and 1, in combination with page 7, lines 11 to 19 for the feature relating to disease progression during or after treatment with a docetaxel-based regimen.

The invention's key focus on patients with mCRPC who had previously been treated with a docetaxel-based regimen was generally disclosed on pages 1 (lines 5 to 7) and 2 (lines 16 to 20). This provided the context for the cited text passage on page 7.

The terms "docetaxel treatment" and "treatment with a docetaxel-based regimen" would be understood as synonymous, in particular as it was part of the skilled person's common general knowledge that treatment with docetaxel for prostate cancer required co-medication.

Since claim 8 did not, in fact, relate to a triple combination treatment, the opponents' objection on this account under Article 100(c) EPC was unfounded.
The language of claim 8 was, in any case, also present, *verbatim*, in claim 12 of the application as filed.

Sufficiency of disclosure (Article 100(b) EPC)

The clinical data presented in the patent in suit (in particular, in paragraph [0075], Table 2 and Figure 1) confirmed that patients receiving cabazitaxel and prednisone demonstrated longer overall survival than those receiving mitoxantrone and prednisone. This effect was achieved even in patients whose cancer had progressed during docetaxel therapy, the group most resistant to docetaxel. In all patient subsets included in Table 2, the hazard ratio was in favour of cabazitaxel, indicating that these patients were expected to survive for longer if treated with cabazitaxel. These data were confirmed in **D15**, which provided further details on the clinical results.

Contrary to the opponents' view, the data in the patent in suit did not permit the conclusion that therapeutic efficacy could not be achieved in certain patient subsets. The opponents had not provided convincing arguments substantiated by verifiable facts that could raise serious doubt that efficacy would arise in these subsets.

The existence of patient groups where treatment would not be suitable (e.g. owing to contra-indications or severe adverse reactions) did not render a patent claiming a new treatment insufficient. Evidence for the treatment of the patient population in general was sufficient to support a claim under Article 83 EPC.

For any drug, there would be low dosages which were ineffective and high dosages which were toxic. It was not necessary for a medical use claim to expressly exclude such dosages.

Right to priority (Article 87 EPC)

The subject-matter of claim 1 as granted found a basis in claims 6 and 1 of **P1**, claim 6 being dependent on claim 1. This included the feature of disease progression during or after the previous docetaxel-based treatment, which should be considered as implicitly disclosed. Moreover, this feature was explicitly disclosed on page 5 (lines 36 to 38) of **P1**.

Novelty (Articles 100(a), 52(1) and 54 EPC)

The subject-matter of claim 1 as granted was novel over the written disclosure of the cited prior-art documents **D1**, **D2**, **D3**, **D4**, **D6** and **D26** since none of them disclosed the therapeutic efficacy of the claimed cabazitaxel-based treatment. **D4** and **D26** also failed to disclose the co-administration of prednisone or prednisolone.

No evidence had been provided as to the circumstances surrounding the alleged public prior use in any specific instance. Early positive indications might have occurred in patients whose treatment ultimately failed. It could not be ruled out on the basis of the available evidence that any final consultations with individual patients might have taken place only after the conclusion of the study. Furthermore, evidence in a single patient was not evidence of efficacy and safety of a drug in a defined patient population. The opponents had thus not met their burden of proof to show that any disclosure amounting to a direct and unambiguous disclosure of the claimed invention took place before the priority date.

Inventive step (Articles 100(a), 52(1) and 56 EPC)

Document **D7** should preferably be taken as the starting point for the assessment of inventive step.

Irrespective of the starting point under consideration, the technical effect of improved overall survival should always be taken into account in the formulation of the objective technical problem since this was the invention's contribution to the art in a situation where the standard of care at the time (mitoxantrone plus prednisone) was, at best, a palliative therapy.

In any scenario under consideration, the evidence on cabazitaxel in the prior art was not strong enough to create a reasonable expectation of success for the therapeutic use envisaged in claim 1.

As a matter of principle, and contrary to a central argument made by the opponents, the analysis of the pertinent jurisprudence of the boards could not give rise to the conclusion that the mere announcement of a clinical study automatically created a rebuttable presumption that an expectation of success was present. Instead, it was clear that a consideration of the facts and evidence of each individual case was required, which included balancing the positive and negative pointers when determining the expectation of success.

In the case in hand, the background of the TROPIC study did not warrant the conclusion that the study was approved because of a reasonable expectation of success. It could not have been expected that the TROPIC study would meet its primary endpoint of improved survival over the standard of care. At best, there could have been a mere hope of success, which would, however, have been sufficient to swing the risk/benefit assessment in favour of proceeding with the study in a situation where patients had a terminal disease with no approved treatment options available.

The parties' requests

XVIII. The appellants (opponents 1, 2, 5 and 7 to 12) all requested that the decision under appeal be set aside and that the patent be revoked.

XIX. The intervener (opponent 13, party as of right) requested that the patent be revoked.

XX. Opponent 2 also requested reimbursement of its appeal fee pursuant to Rule 103(1)(a) EPC.

XXI. Opponents 2, 9 and 13 furthermore requested that the arguments set out in the patent proprietor's letter of 30 September 2024, paragraphs 11.72 to 11.77, not be admitted.

XXII. The respondent (patent proprietor) requested that the appeals be dismissed and that the patent be maintained as granted

or, in the alternative,

that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 25, all filed with the reply to the appellants' statements setting out the grounds of appeal.

Reasons for the Decision

1. Intervention

1.1 The intervention by a further party (see point XI. above) is in conformity with Article 105(1)a) and Rule 89 EPC.

1.2 The intervener (opponent 13) is party to the appeal proceedings as of right (Articles 105(2) and 107 EPC).

2. Claim construction

Claim 1

2.1 Claim 1 as granted is directed to a further medical use and has been drafted as a purpose-limited product claim in the format according to Article 54(5) EPC. In accordance with the established jurisprudence of the boards, for claims directed to a further medical use, attaining the claimed therapeutic effect is regarded as a functional technical feature of the claim (see **T 609/02**, Reasons 9, and Case Law of the Boards of Appeal of the European Patent Office, 10th edn. 2022, in the following "Case Law", II.C.7.2.1. While the pertinent comments in **T 609/02** relate to claims drafted in the so-called Swiss-type format established by the Enlarged Board in **G 5/83**, they apply equally to claims drafted in the newer format according to Article 54(5) EPC).

In the present case, this therapeutic effect is the treatment of prostate cancer in the specified patient group. Claim 1 as granted specifies in this regard

"for use in treating prostate cancer,

in patients with castration resistant metastatic prostate cancer

who have been previously treated with docetaxel based regimen

and have prostate cancer that progressed during or after said treatment."

2.2 On the definition of the patient group, which was a point in dispute, the board is of the view that a person knowledgeable in the technical field would understand from the wording of claim 1 and in light of the general context set out in the description of the patent in suit that the prior docetaxel-based treatment was for mCRPC, for the following reasons (see points 2.2.1 to 2.2.6).

2.2.1 There is no positive indication in claim 1 that the prior docetaxel-based treatment of patients with mCRPC could have been intended for any therapeutic indication other than the patients' prostate cancer.

The prior docetaxel-based treatment is mentioned specifically in relation to the patients' prostate cancer, namely, prostate cancer that progressed during or after the docetaxel-based treatment.

It would be inferred from the choice of the term "progressed" and from the description of the patients as "patients with castration resistant metastatic prostate cancer who have been previously treated with docetaxel-based regimen" that the mCRPC was pre-existing to the docetaxel-based treatment rather than that it developed or was diagnosed only afterwards, and that the docetaxel-based treatment was intended to counteract progression of the prostate cancer.

On consideration of all aspects, the meaning that suggests itself on reading claim 1 is that the patients of claim 1 are subjects with mCRPC who were previously

treated for this same cancer with a docetaxel-based regimen.

2.2.2 This interpretation is technically sensible, and it is also in line with the general background set out in the description of the patent in suit.

The patent is focused on the treatment of prostate cancer. Docetaxel-based chemotherapy was a known treatment for prostate cancer (see paragraphs [0005] and [0008] of the patent). It was known that cancer may become resistant to taxanes such as docetaxel (see paragraph [0007]). The patent in suit is, accordingly, concerned with providing an option for the follow-on treatment of prostate cancer, especially for "patients not catered for by a taxane-based treatment", in particular patients with castration-resistant metastatic prostate cancer who have previously been treated with a docetaxel-based regimen, "an unmet medical need" (see page 1, paragraphs [0001] and [0008] of the patent in suit).

Thus, the general context provided in the description supports the conclusion that the docetaxel-based treatment referred to in claim 1 was for the patients' prostate cancer. The unmet need is that of treating the prostate cancer as the patients in question were not catered for by the previous docetaxel-based (or taxane-based) treatment.

2.2.3 An alternative setting where the prior docetaxel-based treatment is for an unrelated therapeutic indication (i.e. other than the same prostate cancer that is to be treated with cabazitaxel) is addressed neither in the claims nor in the description.

2.2.4 In these circumstances, the opponents' interpretation that such embodiments are nevertheless claimed appears

arbitrary. It would not occur to a reader as being a technically sensible meaning of the claim since basing a rationale for cabazitaxel-based treatment on the patients' having previously been treated with docetaxel for an unrelated disease is not a logical approach.

2.2.5 While generally established criteria may play a role, such as that features in a claim are to be read in their broadest technically meaningful sense, the meaning of a claim can, ultimately, only be determined in context and on the basis of the circumstances in each individual case (as confirmed in **G 1/24**, Order, cited here as a supplementary reference which is not part of the board's reasoning as it was published after the present decision was taken).

2.2.6 Contrary to the argument presented by opponent 12, the cited jurisprudence on claims referring to the pre-treatment of patients does not establish a mandatory requirement for specific claim language. This jurisprudence, therefore, cannot support a reading of claim 1 where the patient group includes those previously treated with a docetaxel-based regimen against "any" type of cancer. In each of the cases cited by opponent 12 (namely, **T 1491/14**, Reasons 2.2.2; **T 2344/19**, Reasons 3.1; **T 72/18**, Reasons 2.1), the claim under consideration explicitly identified the therapeutic indication for the prior treatment. Consequently, the question of how the therapeutic indication for a prior treatment could be established if not stated explicitly (as in the case in hand) did not have to be addressed. None of the cited decisions contains any general statement that might be understood as defining limiting criteria for identifying the purpose of a prior therapeutic treatment mentioned in a

claim. As a consequence, the cited case law is not relevant to the case in hand.

Claim 8

2.3 Claim 1 specifies that cabazitaxel is to be used "in combination with prednisone or prednisolone". Thus, two alternative options are provided, namely (1) the combination of cabazitaxel with prednisone and (2) the combination of cabazitaxel with prednisolone.

According to dependent claim 8, the compound for use according to any of claims 1 to 7 (i.e. cabazitaxel for use in treating prostate cancer in the specified patient group) is to be used "in combination with prednisone". The effect of this definition in comparison with claim 1 is the deletion of alternative (2). In other words, claim 8 has been restricted to alternative (1), which is the combination of cabazitaxel with prednisone.

Neither the "compound" of claim 1 nor the "use" of claim 1 as referred to in claim 8 include the feature "in combination with prednisone or prednisolone". Thus, also if viewed on the face of the wording alone, claim 8 would not be understood as defining a combination of cabazitaxel with prednisone or prednisolone, in combination with more prednisone, encompassing a triple combination of actives, as asserted by opponent 1.

3. Added subject-matter (Article 100(c) EPC)

3.1 Claim 1 in the application as filed reads as follows:

"1. Compound of formula [followed by the structure formula of cabazitaxel] *which may be in base form or in the form of a hydrate or a solvate, in combination with*

prednisone or prednisolone, for its use as a medicament in the treatment of prostate cancer."

3.2 Thus, claim 1 as filed includes all the technical features of claim 1 as granted except for the definition of the patient group.

3.3 Under the established jurisprudence of the boards, a general disclosure in the description as filed may, as a rule, be combined with claimed embodiments as this does not result in added subject-matter going beyond the content of the application as filed.

3.4 As set out below (see point 3.5), the patient group as defined in claim 1 as granted is generally disclosed in the description of the application as filed. This general disclosure may permissibly be combined with the subject-matter of claim 1 as filed (or, alternatively, with dependent claim 3, which adds the feature that the patients have been previously treated with a docetaxel-based regimen).

3.5 The very first paragraph of the description on page 1 of the application as filed provides general disclosure that the invention is especially for the treatment of patients who are not catered for by a taxane-based treatment, in particular for:

> *"the treatment of patients with castration resistant metastatic prostate cancer who have been previously treated with a docetaxel based regimen, an unmet medical need"*

The third paragraph on page 2 confirms that it is the invention's aim to provide:

> *"a novel therapeutic option for treating prostate cancer, especially for patients who are not catered for by a taxane-based regimen, such as patients*

with castration resistant metastatic prostate cancer who have been previously treated with docetaxel (sold under the brand name Taxotere®) based regimen, an unmet medical need"

The second paragraph on page 3 of the application as filed (see lines 11 to 13) adds that cabazitaxel is preferably administered in combination with a corticoid chosen especially from prednisone and prednisolone - as also required in claim 1 as filed.

Thus, patients with mCRPC who have been previously treated with a docetaxel-based regimen are generally disclosed as being the focus of the invention. The combination of this generally disclosed definition of the targeted patient group with the features of claim 1 as filed does not go beyond the content of the application as filed.

3.6 The further requirement of disease progression during or after the previous docetaxel-based treatment is found in the passage on page 7, lines 12 to 15, of the application as filed, which reads:

"In some aspects of the invention, the patient to be treated has prostate cancer that is resistant to hormone therapy (i.e. hormone refractory) and has previously been treated with docetaxel. In some aspects, the patient has prostate cancer that progressed during or after treatment with docetaxel."

This passage is compatible and consistent with the disclosure in the first paragraph on page 1 and the third paragraph on page 2 since the terms "hormone-refractory prostate cancer" and "castration-resistant prostate cancer" are used as synonyms in the application as filed. This is explicitly stated in the text in the form of a definition (see the definitions

of terms provided in the description as filed, in particular page 5, lines 3 to 4). Also, the patients whose prostate cancer progressed during or after treatment with docetaxel and who are switched from docetaxel to the claimed medication would be patients not catered for by the prior taxane-based treatment.

3.7 The opponents submitted that the passage on page 7 relied on by the patent proprietor was part of an embodiment with further limiting features that were, however, absent from claim 1 as granted. According to the opponents, this omission gave rise to added subject-matter.

In particular, the treatment "with docetaxel" as mentioned on page 7 was restricted by the choice of this wording to docetaxel monotherapy, which was more limited in scope than therapy with a docetaxel-based regimen.

Furthermore, the prior treatment according to page 7 mandatorily involved a cumulative dose of at least 225 mg/m^2 docetaxel since the passage on page 7, lines 12 to 15 (see point 3.6 above), was immediately followed, in lines 15 to 18, by the sentence:

> *"In some aspects, the patient was previously treated with at least 225 mg/m^2 cumulative dose of docetaxel."*

3.8 The board does not find these arguments convincing for the following reasons.

3.8.1 Cumulative dose

The passage on page 7, lines 12 to 19, of the application as filed relates in general to patients previously treated with docetaxel. The passage mentions several additional technical features that may apply in this context, introduced in each case by formulations

such as "In some aspects" or "In a particular aspect". The features relating to disease progression and the minimum cumulative dose of docetaxel are introduced separately, each by the expression "in some aspects". It cannot be inferred from this choice of wording that the features in question are disclosed only in combination. They are instead presented as separate general disclosures. Hence, the cumulative dose of at least 225 mg/m^2 docetaxel is an optional rather than a mandatory limitation, and the fact that this feature is not included in claim 1 as granted does not give rise to added subject-matter.

3.8.2 Monotherapy

Contrary to the opponents' further assertion, the board sees no indication in the passage on page 7 that the previous treatment "with docetaxel" can only be docetaxel monotherapy, as opposed to a docetaxel-based regimen.

Throughout the application as filed, the terms "docetaxel based regimen" or "docetaxel-containing regimen" are typically used where the prior docetaxel-based treatment is discussed (see, for instance, page 1, line 7; page 2, line 19; page 3, lines 8 to 9; page 8, line 9; page 12, line 21; claims 3, 12, 27). As a person skilled in the art would be well aware, this is because the established treatment with docetaxel was not a monotherapy but involved the use of docetaxel in combination with further medication such as estramustine or prednisone (see the application as filed, page 1, lines 35 to 38 and **D14**: page 1, "Indications and Usage").

While the cited passage on page 7 of the application as filed indeed refers to "docetaxel treatment" or "treatment with docetaxel", this would be understood,

in the context of the application and in light of common general knowledge on the clinical treatment of mCRPC, as being used synonymously with "treatment with a docetaxel-based regimen". In the absence of an explicit statement in the text that a reference to monotherapy, excluding the established combination therapies, was intended, the opponents' interpretation that the passage on page 7 relates to an embodiment involving docetaxel monotherapy is not warranted.

3.9 For these reasons, the board arrived at the conclusion that the subject-matter of claim 1 as granted finds a basis in claim 1 of the application as filed combined with the general disclosure in the description on the patient group which is, in particular, to be targeted by the envisaged therapeutic treatment (page 1, first paragraph and page 7, lines 12 to 15).

3.10 Under Article 13(2) RPBA, the board did not admit the submission by opponent 8, presented for the first time at the oral proceedings before the board, that the feature "metastatic" could only be arrived at by carrying out a separate selection from the content of the application as filed, in addition to the further selection steps that were required for combining claim 1 as filed with dependent claims 3 (previous treatment with a docetaxel-based regimen) and 5 (CRPC). However, in any case, this argument could not have succeeded since the board does not rely in its reasoning on the combination of claims 3 and 5, and the definition of the patient group as having mCRPC (thus, metastatic disease) and having been previously treated with a docetaxel-based regimen can be based directly on the general disclosure of this combination of features in the first paragraph of the application as filed.

3.11 In view of point 2.3 above, the objection against claim 8, which was based on a different understanding of this claim, cannot succeed.

3.12 In conclusion, taking into account the opponents' objections, the ground for opposition under Article 100(c) EPC does not prejudice maintenance of the patent as granted.

4. Sufficiency of disclosure (Article 100(b) EPC)

4.1 As set out above, claim 1, being drafted in the format according to Article 54(5) EPC, contains the therapeutic effect as a functional technical feature (see points I. and 2.1 above). This has to be taken into account for the assessment of sufficiency of disclosure.

Also, the requirement of sufficiency of disclosure must be satisfied at the effective date of the patent.

Thus, for the requirement of sufficiency to be met, the suitability of the claimed medication for the claimed therapeutic application must be credible on the basis of the information provided in the patent application as filed, together with the common general knowledge then available to the person skilled in the art (see Case Law, II.C.7.2.1).

4.2 The therapeutic efficacy against mCRPC that had to be rendered credible in the case in hand is that of cabazitaxel when used in the setting defined in claim 1.

4.3 The patent proprietor relied in this regard on data from a phase III clinical study, disclosed in the examples (which are identical in the patent and in the application as filed) and corroborated by a post-published report (**D15**) on the same phase III study,

also known as the TROPIC study. In this study, the patients in the experimental study arm received both cabazitaxel and prednisone, in conformity with claim 1.

4.4 The then-current first-line standard for patients with symptomatic or progressive CRPC, including mCRPC, was docetaxel-based chemotherapy.

Docetaxel-based therapy had demonstrated a survival advantage over the previous standard of care, which was based on mitoxantrone plus corticosteroids. The mitoxantrone-based treatment was known to be of a palliative nature without achieving longer survival times (see the application as filed, page 1, last paragraph; **D7**: page 161, left-hand column, second paragraph and **D105**: abstract and page 54, right-hand column, second paragraph; both **D7** and **D105** being review articles that can be regarded as representative of the skilled person's common general knowledge).

There was, however, no accepted standard of treatment after docetaxel, i.e. in particular for patients with progressive disease after first-line docetaxel. In a selected subgroup of patients, docetaxel re-treatment could be attempted. Mitoxantrone-based treatment (the previous standard of care prior to 2004) had also been used, without a clear advantage (see **D7**: abstract and page 161, line 1 to page 162, right-hand column, third paragraph).

4.5 Example 1 of the application as filed reports data obtained in a clinical study in 755 mCRPC patients whose disease had progressed during or after docetaxel. The patients were randomised to receive 10 mg/day of prednisone with either mitoxantrone (12 mg/m^2) or cabazitaxel (25 mg/m^2), both administered every three weeks. It was found that the combination of cabazitaxel and prednisone had an acceptable safety profile (see

page 14, lines 36 to 37: "a well-tolerated combination with the safety profile of taxanes"). Patients receiving cabazitaxel demonstrated statistically significant longer overall survival compared to mitoxantrone ($p<0.0001$). The median overall survival in the study arm receiving cabazitaxel was 15.1 months versus 12.7 months for the study arm receiving mitoxantrone (control). The hazard ratio was 0.70 (95% CI 0.59-0.83) in favour of cabazitaxel, corresponding to a 30% reduction in risk of death. Benefit was also seen in the subset of patients who were docetaxel refractory and had progressed during docetaxel therapy, i.e. those whose cancer was most resistant to docetaxel (see the application as filed, page 14, line 36 to page 15, line 7 and Figure 1). These and further study results are summarised in Tables 1 and 2 of the application as filed.

4.6 The board is of the view that these data from a phase III clinical study, presented in the application as filed, are sufficient to render the clinical benefit of cabazitaxel credible.

They are also confirmed by the following post-published evidence.

- The journal article **D15** reports on the same clinical phase III study (TROPIC) and provides more detail. Moreover, the authors of **D15** add (see page 1153, right-hand column, last paragraph) that the data obtained in the TROPIC study "support regulatory approval of cabazitaxel in the USA" and that cabazitaxel "will become a standard of care for prostate cancer in this setting" (i.e. mCRPC, after a docetaxel-based regimen).
- **D93** confirms that, based on data from the TROPIC study, cabazitaxel for intravenous use, indicated

in combination with oral prednisone for mCRPC in patients previously treated with a docetaxel-containing regimen, received US regulatory approval under the brand name Jevtana® (see also **D21:** page 4, "Licensing status").

- The assessment report issued by the Committee for Medicinal Products for Human Use of the EMA (European Medicines Agency) concluded that the efficacy of cabazitaxel in combination with prednisone or prednisolone for the treatment of patients with mCRPC (mHRPC in **D21**, see page 3) previously treated with a docetaxel-containing regimen had been established and recommended the granting of a marketing authorisation (**D21:** see page 52, fourth paragraph and page 66, point 2.9).

4.7 The opponents contended that, in view of the disclosure in the application as filed, there would have been doubt that a therapeutic benefit in treating prostate cancer, in terms of efficacy and safety, could be achieved across the scope of patients and possible dosages. This objection related specifically to:

(a) patient subgroups without evidence of a therapeutic effect

(b) patient subgroups affected by adverse events or contraindications

(c) dosage ranges without a therapeutic effect or with unacceptable adverse effects

4.8 These lines of argument are not convincing for the following reasons.

Patient subgroups without evidence of a therapeutic effect

4.8.1 The patient subgroups mentioned in this context by the opponents were:

(i) the subgroup with cancer progression occurring later than three months after the docetaxel-based treatment, in view of inferior median overall survival reported in Table 2

(ii) patients who received a prior cumulative dose of docetaxel lower than 225 mg/m^2, for lack of evidence of the therapeutic efficacy of cabazitaxel-based therapy in this subset

(iii) patients receiving the cabazitaxel-based therapy as a third- or further-line therapy, for lack of evidence in any such setting

4.8.2 In the case in hand, the therapeutic benefit of the cabazitaxel-based treatment in terms of overall survival for the targeted patient population as defined in claim 1 was demonstrated by an adequately powered clinical study, with statistical significance (see points 4.5 and 4.6 above), by comparing the total population in the experimental cabazitaxel arm with the population in the mitoxantrone arm.

This reported outcome is enough to establish sufficiency of disclosure for the treatment and patient group defined in claim 1.

There is no requirement that therapeutic efficacy must also be shown for patient subgroups unless there is a specific, adequately substantiated reason for doubt that the desired efficacy would arise in a particular subgroup. As set out in points 4.8.3 to 4.8.5 below,

the opponents' reasoning on the above-mentioned patient subgroups (i), (ii) and (iii) does not provide an adequately substantiated reason for doubt regarding efficacy in these subgroups.

4.8.3 Subgroup (i)

Table 2 on page 17 of the application as filed provides an analysis of the median overall survival in both study arms and in certain patient subsets.

Table 2

	MP		CbzP		CbzP vs MP
	N (%)	Median OS (mos)	N (%)	Median OS (mos)	HR (95%CI)
ITT	377 (100)	12.7	378 (100)	15.1	0.70 (0.59–0.83)
PD while on D	103 (27)	12.0	113 (30)	14.2	0.65 (0.47–0.90)
PD after last D dose, ≤3 mos	180 (48)	10.3	158 (42)	13.9	0.70 (0.54–0.90)
PD after last D dose, >3 mos	91 (24)	17.7	103 (27)	17.5	0.78 (0.53–1.14)

mos = months
D = Docetaxel

This subgroup analysis shows that patients with disease progression ("PD") during the docetaxel-based treatment or within three months of the last dose of docetaxel showed longer median overall survival ("OS") in the cabazitaxel study arm. This was in line with the finding for the total patient population.

In the patient subgroup where disease progression set in later than three months after the last dose of docetaxel, the median overall survival in the study arm receiving cabazitaxel was about the same as that observed in the mitoxantrone arm (17.5 versus 17.7 months).

However, this result cannot be taken as proving a lack of efficacy in the patient subgroup in question. The median value, representing the midpoint between

the higher and lower halves of a data sample, does not by itself reflect statistical significance and cannot be conclusive in this regard.

The hazard ratios for death in the cabazitaxel group relative to the mitoxantrone group indicated in Table 2 are in line, for each patient subgroup, with the hazard ratio for the overall population (which was significantly below 1, i.e. in favour of cabazitaxel).

However, in the case of the patient subgroup in question, which is smaller than the other two groups, the confidence interval includes the value 1, which means that the hazard ratio (indicated as "0.78 (0.53-1.14)" in the last line of Table 2 and as "0.75 (0.51-1.11)" in the last line of Figure 3 of the application as filed) is not significant. This is not surprising as the study was powered to show a therapeutic benefit in the overall population but not necessarily in smaller subgroups (see **D15**, page 1150:

> *"The study required an estimated sample size of 720 patients (360 per group) to detect a 25% reduction in the hazard ratio (HR) for death in the cabazitaxel group relative to the mitoxantrone group with 90% power").*

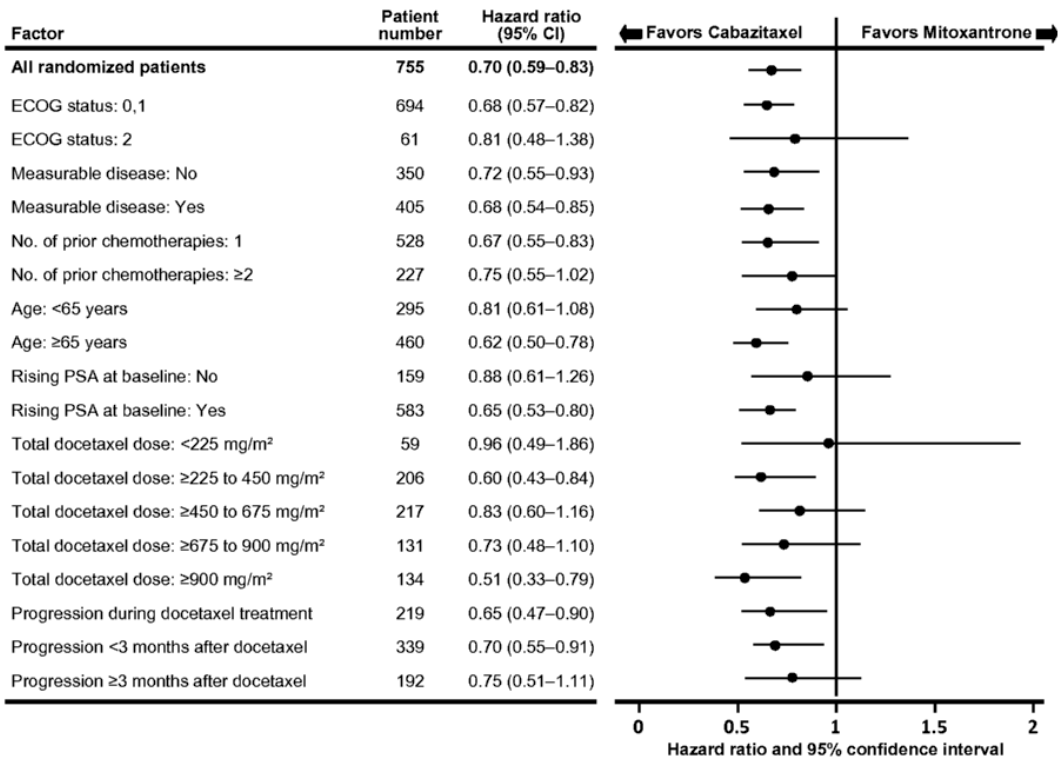
Thus, all that can be said is that the data in Table 2 neither prove nor disprove the therapeutic efficacy of the proposed cabazitaxel-based therapy in the subgroup of patients with cancer progression later than three months after the docetaxel-based treatment.

The finding cannot establish serious doubt regarding the efficacy of the cabazitaxel-based treatment in the patient subgroup in question.

4.8.4 Subgroup (ii)

According to Figure 3 of the application as filed, most of the patients who participated in the clinical study had received a prior cumulative dose of docetaxel of at least 225 mg/m^2. A small subset of 59 patients had received a prior cumulative dose of docetaxel lower than 225 mg/m^2.

FIGURE 3



As set out in **D15** (see page 1149, left-hand column, second paragraph below the box), the reason why only a small group of patients with a cumulative dose of docetaxel lower than 225 mg/m^2 was enrolled was that the inclusion criteria in the study protocol were amended:

"On the basis of emerging guidelines recommending the delivery of 12 weeks of treatment before adjustment of therapy for metastatic castration-resistant prostate cancer, an amendment was made to the study protocol after 59 patients had been enrolled to exclude patients previously receiving a cumulative docetaxel dose lower than 225 mg/m^2."

This was to ensure a sufficient window of drug exposure to docetaxel. Thus, the fact that the inclusion criteria were changed is no indication that a lack of efficacy of the cabazitaxel-based treatment in the patient group in question was expected or had, at that time, been observed.

Like in the case of subgroup (i), the hazard ratio indicated for subgroup (ii) is below 1 but is not statistically significant as the confidence interval crosses the line of unity (see Figure 3).

The same conclusion applies as for subgroup (i) (see also the EMA's assessment in **D21**, page 64, last paragraph: "there is insufficient evidence to conclude that the benefits are lacking in this subgroup"). The opponents failed to provide a substantiated reason why the cabazitaxel-based treatment would not work for patient subgroup (ii). Given that efficacy was demonstrated in the overall population tested, the absence of positive evidence of efficacy in this subgroup does not suffice to establish serious doubt.

4.8.5 Subgroup (iii)

Opponent 5 objected that the study data confirmed at best the effectiveness of cabazitaxel-based therapy as a second-line therapy after docetaxel-based therapy, whereas claim 1 did not limit the line of therapy to a second-line therapy.

In support of this objection, the opponent referred to **D39**, which relates to a study that was undertaken to establish whether taxane-based chemotherapy (including either docetaxel or paclitaxel) was equally effective before and after mitoxantrone-based therapy (see **D39**: page 1236, left-hand column, third paragraph). According to the opponent, this was evidence of an existing concern that efficacy might be reduced or lost depending on the line of treatment in which these drugs were used.

The board understands that the main concern in **D39** was actually to confirm second-line efficacy (see the abstract: "Objectives"). In the outcome, the results observed suggested that taxane-based chemotherapy was indeed active before or after mitoxantrone, and the total progression-free survival and overall survival were equivalent for both sequences (see **D39**: abstract; page 1240, left-hand column: "Conclusions").

Thus, according to **D39**, the hypothesis of differing efficacy was tested, and in the outcome not confirmed, in relation to other taxane drugs (docetaxel and paclitaxel). In the board's view, these facts do not provide a reason for serious doubt about the efficacy of cabazitaxel in settings other than second-line use.

Patient subgroups affected by adverse events or contra-indications

4.8.6 The board sees no merit in the objection that the application as filed should have provided guidance for carrying out a contraindicated use, namely the administration of the cabazitaxel-based therapy to patients with a neutrophil count of $\leq$ 1500 cells/mm^3.

The medical recommendation is not to carry out the treatment if there is a contraindication.

The very fact that the application as filed contains information about possible contraindications (such as a history of severe hypersensitivity reactions, hepatic impairment or a neutropenia with neutrophil count of ≤ 1500 cells/mm^3; see page 8, line 20 to page 11, line 1) is adequate guidance.

4.8.7 In the same way, the information in Example 2, Table 6, on proposed measures and treatment modifications if certain adverse effects occur in patients treated with cabazitaxel constitutes adequate guidance on how to manage these issues (see also page 8, line 20 to page 10, line 37).

4.8.8 The opponents' argument that, in the case in hand, patients affected by contraindications or adverse reactions constitute a sizeable group is not decisive (and also does not change the fact that there is adequate guidance, as set out in points 4.8.6 and 4.8.7 above).

In the case in hand, a relevant proportion of patients appears to benefit from the cabazitaxel-based treatment according to claim 1 as statistically longer overall survival was observed in the cabazitaxel study arm, even if adverse reactions appeared to be more severe than in the control arm. In the field of cancer therapy, it is, however, common that even severe adverse reactions may be tolerated to some extent in exchange for the anticancer efficacy of the chemotherapy drugs (see, for instance, **D21**: point 2.8 on the benefit-risk balance). In the case in hand, the higher rate of treatment discontinuation owing to the occurrence of adverse effects (17.7% in the cabazitaxel arm versus 8.5% in the mitoxantrone arm) is also to be balanced against the lower rate of discontinuation

because of disease progression (47.6% versus 70.8%; see Table 5).

In the claimed clinical setting and with the guidance provided in the application as filed, distinguishing those patients who can be treated with the cabazitaxel-based-regimen from those who cannot, due to contra-indications and severe adverse reactions, is not an undue burden.

Dosage ranges without a therapeutic effect or with unacceptable adverse effects

4.8.9 Claim 1 is intended to define a new treatment option for mCRPC patients in the form of a cabazitaxel-based combination treatment. The fact that this claim does not specify dose limitations does not give rise to the conclusion that the claimed subject-matter is insufficiently disclosed.

It is part of the basic common general knowledge in pharmacy that doses of a medicament below a certain threshold are ineffective and that doses above a certain threshold may be toxic and provoke unacceptable adverse reactions.

Determining the dose range and regimen of a drug that provides safe and effective therapy with minimal adverse effects is a routine task in pharmaceutical development which is solved by carrying out clinical studies. Such a task is not beyond the capabilities of the person skilled in the art. In the case in hand, the application as filed moreover provides guidance by disclosing a suitable dosage regimen for cabazitaxel and prednisone in the context of a phase III clinical study (see point 4.5 above) and by proposing treatment delay and dosage reduction to 20 mg/m^2 cabazitaxel in

the case of adverse reactions (see the application as filed: Table 6).

4.9 To address a further argument submitted by opponent 5, the alleged vagueness of a term such as disease progression does not translate into an objection of insufficiency but rather constitutes an objection under Article 84 EPC for lack of clarity. Since the technical feature relating to disease progression is found in claim 1 as granted, this objection is not open to examination in opposition appeal proceedings (see **G 3/14**, OJ EPO 2015, A102).

In any case, references to cancer progression and progressive disease (as, for instance, in **D7**: abstract and further passages) are standard in the technical field. Disease progression as a term of art would generally be understood to be progression as diagnosed by a clinician with experience in the management of mCRPC.

4.10 For these reasons, the ground for opposition under Article 100(b) EPC does not prejudice maintenance of the patent as granted.

5. Right to priority (Article 87 EPC)

5.1 The opponents argued that the subject-matter of claim 1 as granted was not entitled to the priority date of the first priority application **P1** since it did not relate to the same invention and was the result of an unallowable intermediate generalisation when compared with the content of **P1**.

5.2 As established in Opinion **G 2/98** of the Enlarged Board of Appeal (OJ EPO 10/2001, 413), the requirement for claiming priority of the "same invention" referred to in Article 87(1) EPC means that priority of a previous

application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

5.3 In accordance with this criterion, the question to be answered is whether the subject-matter of claim 1 as granted can be derived directly and unambiguously, using common general knowledge, from the content of **P1**. The board came to the conclusion that this is indeed the case for the following reasons.

5.4 Claim 1 of **P1** reads as follows:

> *"Antitumoral pharmaceutical use comprising cabazitaxel of formula* [followed by the structure formula of cabazitaxel] *which may be in base form or in the form of a hydrate or solvate, intended for treating prostate cancer, especially for patients who are not catered for by a taxane-based treatment, in combination with prednisone or prednisolone."*

5.5 Recasting a claim to a medical use (such as claim 1 of **P1**) in the appropriate format according to Article 54(5) EPC (as employed in claim 1 as granted) is permissible and does not affect the right to priority, i.e. it does not add subject-matter.

5.6 Claim 6 of **P1**, which is dependent on claim 1 of **P1** and further defines the patients as having mCRPC and having been previously treated with a docetaxel-based regimen, thus includes all the technical features of claim 1 as granted, except that it does not explicitly mention

disease progression during or after the previous docetaxel-based treatment.

5.7 The board is, however, of the view (as set out in points 5.8 to 5.12 below) that the feature relating to disease progression is implicit in claim 6 when read together with claim 1 and in light of the description.

5.8 In line with claim 6, the first paragraph on page 1 of **P1** (identical to the first paragraph of the application as filed; see point 3.5 above) confirms that the invention is especially for the treatment of patients who are

> *"not catered for by a taxane-based treatment"*,

and

> *"[i]n particular, (...) patients with castration resistant metastatic prostate cancer who have been previously treated with a docetaxel based regimen, an unmet medical need".*

5.9 The third paragraph on page 2 of **P1** furthermore states that:

> *"The technical problem that the invention intends to solve is that of providing a novel therapeutic option for treating prostate cancer, especially for patients who are not catered for by a taxane-based regimen, such as patients with castration-resistant metastatic prostate cancer who have been previously treated with docetaxel based regimen, an unmet medical need."*

5.10 Thus, an option for follow-on treatment with different medication (namely, cabazitaxel combined with prednisone or prednisolone as claimed) is to be provided especially to patients not catered for by a taxane-based, specifically a docetaxel-based, regimen.

These are patients for whom no sufficient therapeutic benefit was achieved with a docetaxel-based regimen.

5.11 The docetaxel-based regimen would be read, in a technically reasonable sense, as a regimen configured with the medically appropriate dosing and duration for effective treatment.

The population for whom no sufficient therapeutic benefit was achieved may include non-responders with docetaxel refractory disease but also responders who discontinued their docetaxel-based treatment because of contraindications or unacceptable adverse effects.

A person skilled in the art reading **P1** would be well aware that the general approach in medicine would be to provide such follow-on treatment only to patients in need of treatment, in other words those showing disease progression.

The phrasing "not catered for by a taxane-based regimen" (as also used in claim 1 of **P1**) and "unmet medical need" implies, in the context of claim 6, that there is disease progression at some point during or after the previous treatment with a docetaxel-based regimen.

5.12 The board is of the view that a person skilled in the art reading **P1** would understand from the context and phrasing of the relevant text passages (see points 5.8 to 5.11 above) that the phrase "patients who are not catered for by a taxane-based treatment" refers to the preceding docetaxel-based treatment, especially so in the context of claim 6, which is limited to patients with mCRPC having received previous docetaxel-based treatment.

By inferring other hypothetical meanings from the use of the present tense ("are not catered for" instead of

"were not catered for") and the reference to taxane-based treatment in general, opponent 5 over-interpreted the phrasing chosen in **P1** (see point 13 of the letter dated 27 February 2025) and failed to take into account the close connection established in the text with the previous docetaxel-based treatment.

Indeed, the only instance mentioned in **P1** of patients not catered for by a taxane-based treatment is mCRPC patients previously treated with a docetaxel-based regimen, "an unmet medical need". This patient group is mentioned several times in close association with the more generally termed phrase "patients who are not catered for by a taxane-based treatment" and is introduced by the expressions "such as" and "in particular". Thus, the qualification "not catered for by a taxane-based treatment" is disclosed as applying specifically to this patient group.

The use of the present tense "are not catered for" is not in conflict with the understanding that the patients previously treated with a docetaxel-based regimen are currently in need of further treatment options as the treatment with a docetaxel-based regimen did not result in a sufficient therapeutic benefit (see points 5.10 and 5.11 above).

5.13 The implied disease progression during or after the previous docetaxel-based treatment is also mentioned explicitly in the context of the embodiments described on pages 5 to 6 of **P1**, albeit in a more specific setting. However, in view of the considerations set out above, there is no need to rely on this part of the description to arrive directly and unambiguously at the subject-matter of claim 1 as granted.

5.14 At the oral proceedings before the board, opponent 8 presented, for the first time, the objection that the subject-matter as defined in claim 1 as granted was not enabled in **P1** because the part of the disclosure in **P1** that related to experimental data did not restrict the patient population to those having metastatic disease.

5.15 The board did not admit this objection under Article 13(2) RPBA for the following reasons.

5.15.1 Opponent 8, basing its appeal on an objection for lack of inventive step, had not presented any reasoning on the validity of the priority claim in its written appeal submissions. Thus, its submissions at the oral proceedings are an amendment to the opponent's appeal case under Article 13(2) RPBA that should be taken into account only if there are exceptional circumstances justified with cogent reasons.

5.15.2 Further, on the issue of priority, the other opponents had argued that there was a lack of disclosure rather than a lack of enablement in **P1** (see point 5.1 above). Thus, the objection presented by opponent 8 at the oral proceedings is a new line of attack in the proceedings.

5.15.3 The board sees no exceptional circumstance that would have justified taking this new line of attack into account. Opponent 8 submitted that it was presented in reaction to the patent proprietor's submissions on the priority right. However, a party presenting counter-arguments to a given line of attack is not an exceptional circumstance that justifies presenting a different attack at a late stage of the proceedings.

5.16 For the reasons set out above, the board arrived at the conclusion that the claimed subject-matter of current claim 1 finds a basis in the disclosure of **P1** and that priority from **P1** is validly claimed. As

regards the dependent claims, no substantiated objection was submitted.

6. Novelty (Articles 100(a), 52(1) and 54 EPC)

6.1 In the context of their objections of lack of novelty, the opponents cited documents **D1**, **D2**, **D3**, **D4**, **D6**, **D10**, **D15**, **D26** and **D46** as anticipating the subject-matter of claim 1.

*Documents published after the filing date of **P1***

6.2 As a consequence of the finding in section 5 above, document **D10** does not form part of the opposable prior art under Article 54 EPC. This is also the case for documents **D15** and **D46**.

Legal requirements for a finding of lack of novelty

6.3 The requirement for a finding of lack of novelty is that the claimed subject-matter, i.e. the claimed combination of technical features, can be derived directly and unambiguously, either explicitly or implicitly, from a prior-art disclosure under Article 54(2) EPC, account also being taken of the skilled person's common general knowledge at its publication date (see Case Law, I.C.4.1).

In this context, an implicit disclosure means disclosure which the person skilled in the art, using common general knowledge, would objectively consider as the clear and unambiguous consequence of what is mentioned explicitly. An alleged disclosure can only be considered "implicit" if it is immediately apparent to the skilled person that nothing other than the alleged implicit feature forms part of the subject-matter disclosed (see Case Law, I.C.4.3).

6.4 Furthermore, as set out in point 2.1 above, attaining the claimed therapeutic effect in the specified patient group is construed as a functional technical feature of claim 1. This technical feature must be taken into account in the assessment of novelty. As already mentioned, the relevant criterion is not inherency but direct and unambiguous disclosure (see also **T 1859/08**, Reasons 13 and 14, and **T 2506/12**, Reasons 2.6).

*Written disclosure of documents **D4** and **D26***

6.5 Document **D4** reports on a phase I and pharmacokinetic study of cabazitaxel (XRP6258 in **D4**) in 25 patients with different advanced solid tumours, and also summarises previously observed preclinical results. The cytotoxicity (antitumour activity) of cabazitaxel had been compared with that of docetaxel in several murine and human cell lines (see page 723, right-hand column). Furthermore, antitumour activity in human tumour xenograft mouse models had been tested (see page 724, left-hand column). In the phase I study, patients received an i.v. infusion of cabazitaxel every three weeks. Partial responses in two patients with metastatic prostate carcinoma were observed (see page 723: Abstract; page 724, right-hand column, penultimate paragraph; page 727, left-hand column).

6.6 Document **D26** is a review article on tubulin-binding agents. In the section on taxanes, cabazitaxel (XRP6258) is mentioned as one of several new taxanes under development (see **D26**: page 74 and Tables 2 and 3). With reference to **D4** (reference "[23]"), **D26** reports that cabazitaxel was being investigated in phase I studies; that two objective responses, both in CRPC, were seen; and that one of the patients was docetaxel refractory.

6.7 The preclinical *in vitro* and *in vivo* experiments summarised in **D4** do not anticipate the subject-matter of claim 1 since no patients were involved in the experiments.

6.8 The disclosure on the phase I study of cabazitaxel, as described in **D4** and referenced in **D26**, does not anticipate the claimed subject-matter, either, if only because neither document discloses the co-administration of prednisone or prednisolone. This includes the passage in **D4** on "Materials and Methods" for the phase I study, which would mention such co-administration if it formed part of the regular study regimen (see **D4**: page 724, right-hand column, "Drug administration"). Indeed, this passage also states that "[c]orticosteroids were not permitted as prophylactic treatment for nausea and/or vomiting" (see **D4**: page 724, right-hand column, penultimate paragraph). While it might still be considered that a corticosteroid might have been co-administered for a different purpose, this is not derivable from the content of **D4** or **D26**, nor would it be implicit that such a co-administered corticosteroid could only have been prednisone or prednisolone.

*Written disclosure of documents **D1**, **D2** and **D6***

6.9 Documents **D1** and **D6** have the same relevant content. They disclose the set-up for the TROPIC phase III clinical study of cabazitaxel and prednisone in mCRPC with inclusion criteria and primary and secondary objectives, the medication to be administered in the two study arms, and the start date and estimated completion date of the study. The patients had to have been previously treated with a docetaxel-containing regimen. It is also mentioned that the TROPIC study was ongoing/active. No experimental data are disclosed.

Thus, **D1** and **D6** explicitly disclose all the technical features of claim 1 as granted with the exception of the functional feature of the cabazitaxel-based treatment attaining the claimed therapeutic effect.

6.10 Document **D2** provides substantially the same information on the TROPIC study as **D1**. It also discloses the dose of 25 mg/m^2 cabazitaxel every three weeks and provides some additional comments on the technical background (**D2**: page 2, "Technology description" and "Innovation and advantages"), stating that "[c]abazitaxel has shown a promising safety profile and activity in patients progressing after docetaxel therapy."

6.11 The opponents contended that the written disclosure of **D1**, **D2** and **D6** anticipated the subject-matter of claim 1, even though these documents were published before completion of the TROPIC study and did not disclose any study results. The following reasons were given.

6.11.1 Following established case law and in particular **T 158/96**, the announcement of the clinical phase III study implicitly disclosed the effect of cabazitaxel in the relevant patient group because, in the case in hand, the person skilled in the art would have had sufficient information to conclude that the therapeutic efficacy of cabazitaxel was already known from earlier investigations. The review article **D26**, and **D4** referenced in **D26**, could be regarded as representative of the skilled person's common general knowledge in this regard.

6.11.2 **D2**, moreover, explicitly disclosed that the efficacy of cabazitaxel had already been confirmed.

6.12 The board is not persuaded by these arguments for the following reasons.

6.12.1 Contrary to the opponents' view, the additional remark in document **D2**

> *"Cabazitaxel has shown a promising safety profile and activity in patients progressing after docetaxel therapy."*

does not amount to direct and unambiguous disclosure of the therapeutic efficacy of cabazitaxel in the context of the claimed therapeutic use.

This remark is vague as it does not mention a therapeutic indication and does not specify what is meant by the phrase "promising safety profile and activity". Since docetaxel therapy was also indicated in other types of cancer (see **D14**: Indications and Usage), the therapeutic indication of mCRPC is not implicit here (i.e. not the unambiguous consequence of what is explicitly disclosed, see point 6.3 above). The assertion regarding the promising safety profile and activity is not accompanied by verifiable evidence of the facts it is based on, such as a reference to a scientific publication.

The fact that no phase II data for mCRPC and very limited phase I data existed contributes further to the uncertainty. If the remark in question was meant as a comment on the known results from the phase I study (since no other clinical data were known at the time), the facts published about the phase I study are not conclusive in support of therapeutic efficacy in the relevant setting (see point 6.12.6 below and the decision under appeal, reasons 7.20).

There is also no indication in **D2** from which it might alternatively be inferred that the statement in question relates to unpublished preliminary results of

the TROPIC study. Thus, the exact nature of the promising activity mentioned in **D2** cannot be determined. Nor can it be derived that the "promising safety profile and activity" amounts to actual therapeutic utility. By therapeutic utility, the board means adequate efficacy without unacceptable toxicity/ adverse effects (or, in other words, an indication that a workable therapeutic window exists).

Finally, **D2** itself comments on page 4 that the potential or intended impact of the TROPIC study was speculative.

In view of these circumstances, **D2** does not provide direct and unambiguous disclosure of the claimed therapeutic efficacy of cabazitaxel in the relevant setting. **D2**, therefore, discloses no more than **D1**/**D6**, i.e. an announcement of the TROPIC study describing the study's set-up.

6.12.2 Since none of **D1**, **D2** and **D6** discloses any results from the TROPIC study, these documents do not explicitly disclose the functional technical feature of the cabazitaxel-based treatment attaining the claimed therapeutic effect. Thus, the question to be answered is whether there is implicit disclosure of this feature in accordance with the requirements indicated above (see point 6.3). The board is of the view that this is not the case.

6.12.3 The required feature is not implied by the announcement of the TROPIC study. The fact that a phase III study is underway does not, by itself and without further evidence, imply that therapeutic efficacy in the targeted therapeutic indication was established in earlier investigations. In this sense, the announcement of a clinical study is no exception to the general requirements for a direct and unambiguous disclosure,

including "implicit" disclosure, in the context of novelty. Nor would the mere knowledge that the TROPIC study was underway have given the skilled person any certainty as to its outcome, i.e. that the intended therapeutic benefit would arise from the cabazitaxel-based treatment (see e.g. **T 239/16**, Reasons 5.2, page 27, second paragraph to page 29).

6.12.4 In their submissions on implicit disclosure, the opponents relied on the conclusions provided in decision **T 158/96**, which acknowledged the novelty of a further medical use over the disclosure that a clinical study was underway on the basis of two specified conditions.

The case underlying **T 158/96** related to the compound sertraline and its intended therapeutic application in obsessive-compulsive disorder (OCD). The relevant prior art disclosure ("document (5)") showed that sertraline was undergoing clinical phase II studies for OCD but did not report the results of any such investigation. The person skilled in the art reading document (5) had no means of knowing what would be the outcome of phase II. They also had no reasonable ground for assuming that the therapeutic efficacy of sertraline in OCD had already been proven or observed during earlier investigations (phase I/pharmacological or preclinical). Indeed, no reliable model for assessing efficacy in OCD even existed. The board in **T 158/96** (Catchword) therefore concluded:

> *"The information in a citation that a medicament is undergoing a clinical phase evaluation for a specific therapeutic application is not prejudicial to the novelty of a claim directed to the same therapeutic application of the same medicament if such information* [sic] *is plausibly contradicted by the circumstances and if the content of said*

citation does not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect which directly and unambiguously underlies the claimed therapeutic application."

For clarification, the board notes that the reference to "such information" does not appear to be sufficiently precise and might be misleading if only the Catchword of **T 158/96** were to be considered. According to the reasoning provided in the text of the decision, it is actually not the information that the medicament was undergoing a clinical phase evaluation that was plausibly contradicted by the circumstances, but the assumption that its therapeutic efficacy must already have been established in earlier stages of its pharmaceutical development.

In relation to the case in hand, the opponents argued that the condition "plausibly contradicted by the circumstances" was not met. Since the assumption that the claimed therapeutic efficacy had already been established prior to the TROPIC study was not plausibly contradicted by the circumstances, the correct conclusion, according to the opponents, must be that the subject-matter of claim 1 lacked novelty over the disclosure of **D1/D2/D6**.

6.12.5 The board is not convinced by this argument.

In the case underlying decision **T 158/96**, novelty was indeed acknowledged on the basis that the two above-named conditions were met.

However, the condition "plausibly contradicted by the circumstances" is not a necessary requirement. It appears to have been formulated more stringently than necessary in view of the individual set of circumstances of the case underlying decision **T 158/96**.

In particular, the circumstance that no useful assessment method had been available plausibly contradicted, and thereby directly refuted, the argument that the therapeutic efficacy of sertraline in OCD had already been demonstrated.

This is, however, simply a specific instance of the more general condition, also mentioned in **T 158/96** (see points 3.5 and 3.6.2 of the Reasons), that it must be established that the skilled person would not have been in a position to conclude with the required certainty that the relevant therapeutic efficacy had already been shown in earlier investigations. It is, in fact, this broader criterion that is decisive and has to be met as a necessary condition for novelty.

In the case in hand, the evidence relied on by the opponents for common general knowledge on preclinical and clinical data in relation to the targeted therapeutic use would not have led the skilled person to conclude that the therapeutic efficacy required by claim 1 had already been established. The finding that novelty can be acknowledged on this basis is, therefore, in line with the rationale in **T 158/96**.

6.12.6 The board's detailed reasons for this assessment of the available common general knowledge are as follows.

Evidence from phase II

The opponents relied in their submissions on published preclinical data and data from phase I. For the sake of completeness, the board notes that the only phase II assessment that had been carried out for cabazitaxel prior to the TROPIC study concerned breast cancer (see **D13** and the application as filed, page 2, lines 22 to 27). In view of the different patient group, the relevant therapeutic efficacy in mCRPC patients could

not have been derived from the findings on breast cancer.

Evidence from phase I

D4 and **D26** (see also points 6.5 and 6.6 above) summarise the results of a phase I study performed in 25 patients with advanced solid malignancies, including eight cases of prostate cancer.

The patients were treated with cabazitaxel at four dose levels ranging from 10 to 25 mg/m^2 (see **D4**: abstract, Table 1; **D26**: page 75, left-hand column, penultimate paragraph). Partial response was reported in two of the patients with prostate cancer: at the 15 mg/m^2 dose level in a first patient with mCRPC whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol and mitoxantrone, and at the 25 mg/m^2 dose level in a second patient with hormone- and docetaxel refractory metastatic prostate cancer. A minor response not meeting the criteria for a partial response was seen in a third prostate cancer patient (see **D4**: page 727, left-hand column, second paragraph). No information on the other five cases of patients with prostate cancer is provided.

Thus, only the second prostate cancer patient would appear to fall within the definition of the patient group defined in claim 1 and investigated in the TROPIC study. As already mentioned (see point 6.8 above), **D4** and **D26** do not disclose that the patients also received prednisone or prednisolone, so that the treatment regimen in the phase I study was not in conformity with claim 1 and the TROPIC study. Furthermore, the phase I study was not powered to confirm therapeutic efficacy with statistical significance.

The opponents contended that it was the therapeutic activity of cabazitaxel that mattered as this was

independent of the well-known palliative activity of prednisone and prednisolone. They also submitted that the high magnitude of the partial responses in terms of reduction of PSA levels should be taken into consideration. The therapeutic activity of cabazitaxel was derivable from the common general knowledge represented by the data provided in **D26** and **D4** since at least in one relevant individual case in the phase I study, efficacy of cabazitaxel was observed.

The board is of the view that the overall evidence from phase I on efficacy is preliminary and too weak for concluding that there was unequivocal disclosure of therapeutic efficacy.

Firstly, and regardless of the magnitude of the response observed, it is not possible to determine the reasons for a partial response in one single patient as the cancer itself is heterogeneous (see **D58:** point 36) and a variety of other factors (such as previous treatment history, individual spontaneous recovery or medication for individual co-morbidities in typically elderly patients) may affect the manifestation of symptoms and responses to chemotherapy, so that it is not possible to conclude with sufficient certainty that other patients would exhibit an at least similar response to the treatment. The purpose of clinical studies with more than one patient is to establish that the response(s) observed can be attributed to the active substance or regimen under investigation in a statistically relevant way. Based on observations in a single patient, as disclosed in **D4**, the observed responses cannot be regarded as directly and unambiguously attributable to cabazitaxel.

Secondly, the patient in the relevant patient group who showed a partial response was treated at a dose of 25 mg/m^2 cabazitaxel. As pointed out by the patent

proprietor, the abstract of **D4** indicates that the recommended dose for future phase II studies was 20 mg/m^2. This was because at the 25 mg/m^2 dose level the rate of dose-limiting toxicity exceeded the pre-defined limits of tolerability (see **D4**: page 726, paragraph bridging columns). Thus, the only partial response observed in a relevant patient in the phase I study was at a dosage which the authors considered to exceed the limit of tolerability. The concerns over dosage are also taken up in **D26**, which notes that the maximum tolerated dose was reached at 20 mg/m^2 and that the maximum tolerated dose of cabazitaxel (XRP6258) was limited by myelosuppression, which might restrict the extent of tumour cell kill that could be achieved (see **D26**: page 75, left-hand column, penultimate paragraph and paragraph bridging columns).

In view of these considerations, the anecdotal evidence from the phase I study in **D4** and **D26** would not have led the skilled person to conclude, with the required certainty, that the therapeutic efficacy of cabazitaxel relevant to the setting of the TROPIC study and of claim 1 had already been established.

Preclinical evidence

D4 reports on the results of tests in a number of murine and human cancer cell lines, including docetaxel-sensitive cell lines and cell lines with acquired resistance to docetaxel (page 723, right-hand column). None of these cell lines were prostate cancer cell lines.

In human tumour xenograft testing (in mice), a prostate cancer cell line (Du-145) led to positive results (see **D4**: page 724, left-hand column). However, it was not in dispute that this cell line was not resistant to docetaxel.

D4 also reports on human xenograft modelling in three docetaxel-resistant cell lines, none of these being prostate cancer cells, where, furthermore, two of the three resistant xenograft models failed (see **D4:** page 724, left-hand column).

Thus, the known preclinical evidence for prostate cancer was restricted to the Du-145 xenograft.

The board is of the view that the *in vitro* experiments are not relevant as they were not conducted in prostate cancer cells. No conclusion on the effect of the investigated drug on prostate cancer is possible on this basis. The same applies to the xenograft experiments, except for the experiment using the Du-145 xenograft.

The Du-145 xenograft experiment, while in this case based on a prostate cancer cell line, is still a preclinical test based on a model. Its conditions are too far removed from the setting defined in claim 1 and **D1/D2/D6** to permit the conclusion to be drawn, with any certainty, that a safe and effective treatment of human mCRPC patients could be achieved in the setting of the TROPIC study and of claim 1, in human mCRPC patients after prior treatment with docetaxel.

Also, this experiment does not reflect activity in patients where docetaxel therapy has failed.

The person skilled in the art would have been aware that the relevant context of the TROPIC study (which required the patients to have received previous treatment with a Taxotere®-containing regimen and to have a documented progression of disease) was follow-on treatment for patients with disease that had progressed despite docetaxel.

This is evident from the then-current Recommendations of the Prostate Cancer Clinical Trials Working Group

(**D72**). This document, which sets out consensus criteria for prostate cancer studies defined by a committee of international investigators experienced in conducting studies for prostate cancer, may be regarded as forming part of the skilled person's common general knowledge. It reports on the customary design of mCRPC studies as follows (see **D72**, see page 1150, left-hand column, last paragraph):

> *"The demonstration of a survival benefit in a phase III trial and a confirmatory trial led to the approval of docetaxel in 2004. Since then, clinical trials for patients with castrate metastatic disease are being designed in three contexts: before receiving treatment with docetaxel, with agents in combination with docetaxel to improve first-line outcomes, and as second-line treatment for patients with disease that has progressed despite docetaxel."*

Thus, it is clear that the TROPIC study of **D1/D2/D6** addresses the third context, and in particular docetaxel-refractory disease, which is not covered by the Du-145 xenograft experiment. As already mentioned, the xenograft experiments in three docetaxel-resistant cell lines showed mixed results. Thus, the xenograft experiments taken together do not prove efficacy for the core patient group addressed in the TROPIC study and thus do not provide a clear indication that the treatment investigated in the TROPIC study would be effective.

6.12.7 Consideration of the known phase I and preclinical data in combination would not result in a different conclusion.

The circumstances underlying the decision in case **T 1045/21**, mentioned by opponent 8, were different,

since the board concluded that the relevant prior-art document ("D1") disclosed therapeutic efficacy on the basis of the results from a phase II study reported for the entire group of study participants (see Reasons 1.2.6). Only with this background did the board accept that therapeutic efficacy was also credible in the specific case of a single patient who belonged to this group, while the isolated data on this patient could not be regarded as sufficient proof of efficacy (see Reasons 1.2.8).

D4 differs from the prior art examined in **T 1045/21** by not disclosing a conclusive (statistically significant) group result obtained in a clinical study.

6.13 To summarise, documents **D1**, **D2** and **D6** provide neither explicit (see points 6.9, 6.10, 6.12.1 and 6.12.2) nor implicit (see points 6.12.3 to 6.12.7) disclosure of the functional technical feature of attaining the claimed therapeutic effect. As a consequence, the written disclosure of documents **D1**, **D2** and **D6** does not anticipate the subject-matter of claim 1 as granted.

*Written disclosure of document **D3***

6.14 Document **D3** is a blog post commenting on then-current prostate cancer clinical studies in the area of Dallas, Texas. Among others, it mentions cabazitaxel (XRP6258 in **D3**) and a study on cabazitaxel for hormone refractory prostate cancer, as follows (see the second page of **D3**):

> *"XRP6258 is a novel taxane that has been shown to be active in patients with hormone refractory prostate cancer (HRPC) who have failed or progressed after prior therapy with docetaxel (Taxotere) and prednisone, the standard first-line treatment for HRCP. CORT* ["Center for Oncology

Research & Treatment"] *is conducting a study of XRP6258 plus prednisone versus standard mitoxantrone (Novantrone) and prednisone in HRPC patients who have failed prior Taxotere therapy."*

This is, presumably, the TROPIC study, although **D3** does not mention the study phase and does not indicate a name or identification number for the study in question. In addition, information about known risks of cabazitaxel and mitoxantrone is provided in the sentence following the passage cited above.

6.15 The situation in **D3** is similar to that in **D2**, since the document includes a statement on the activity of cabazitaxel.

6.16 The opponents submitted that document **D3** disclosed all the technical features of claim 1 in combination.

The HRPC patients mentioned in **D3** necessarily had to be patients with metastatic disease because chemotherapy with docetaxel was typically only administered in patients with metastatic disease and, at the relevant date, was indeed only approved, in prostate cancer, for CRPC patients with metastatic disease (see **D14:** page 3, point 1.3).

According to the opponents, the statement in the first sentence of the above-cited passage of **D3**, therefore, directly and unambiguously disclosed the therapeutic efficacy of cabazitaxel in the patient group defined in claim 1 as an explicit disclosure.

To satisfy the additional requirement of enablement for this feature, absolute proof was not required. The person skilled in the art would have considered that the pertinent teaching of **D3** was credible, in other words, that the therapeutic efficacy of cabazitaxel was enabled, in light of common general

knowledge, as represented in particular by the review articles **D9** (on molecular mechanisms for docetaxel resistance) and **D26.**

The person skilled in the art would also have inferred that the reference to a clinical study in the second sentence meant the TROPIC study, which involved patients suffering from mCRPC and required the co-administration of prednisone. The therapeutic effect of prednisone was known to be of a palliative nature and should be regarded as separate from the anticancer effect of cabazitaxel.

6.17 The board is of the view that the assertion "has been shown to be active" in the above-cited passage of **D3** does not constitute direct and unambiguous disclosure of the therapeutic efficacy of cabazitaxel in the required clinical setting as it is not specified what kind of activity was shown or how it was shown. As in the case of **D2**, the statement in question is not accompanied by verifiable evidence of the facts it is based on, such as a reference to a scientific publication. There is also no indication in the text that the author based his remarks on unpublished results of the cabazitaxel study which he accessed prior to the publication of the study's results. There is no reason to assume that the first sentence is necessarily linked to the second sentence with the intention of implying such a meaning. A reader of this passage would see two separate statements.

6.18 Since the feature of attaining the claimed therapeutic efficacy in the specified patient group is not directly and unambiguously disclosed by the wording chosen in **D3**, the secondary criterion of enablement for this feature does not have to be addressed.

6.19 By analogy with the reasoning set out in points 6.12.3 to 6.12.7 above in relation to **D1**/**D2**/**D6**, the therapeutic effect cannot be considered to be implicitly disclosed in **D3**, either.

The further review article **D9** mentioned by the opponents as being part of the common general knowledge is concerned with the investigation of molecular mechanisms associated with paclitaxel and docetaxel resistance (see **D9**: abstract). **D9** suggests that cabazitaxel (XRP6258) was considered a possible candidate for overcoming cellular resistance to docetaxel and had entered clinical studies (see **D9**: Table 1, compound 62; page 933, right-hand column, second and third paragraphs) but does not discuss the therapeutic efficacy of cabazitaxel in mCRPC. Thus, the information in **D9** is not more pertinent than the content of **D4**, **D13** and **D26** discussed above.

6.20 For these reasons, the disclosure of **D3** does not anticipate the subject-matter of claim 1.

Public prior use as evidenced by the disclosure of the TROPIC study set-up

6.21 According to the opponents, the TROPIC study itself as described in **D1** (and also in **D2** and **D6**) established a public prior use. This was because of the following particular circumstances: the TROPIC study was an open-label study; it was not a placebo-controlled study; and the patent was based on a broad definition of treatment, so that the disclosure of improvements in any of the parameters (i) PSA level, (ii) tumour level and (iii) pain level was sufficient to anticipate the treatment feature of claim 1.

With regard to the open-label study, the opponents submitted that the patients would have been aware of

whether they were being treated with the study drug. They would have been informed on the progression of their disease and any individual positive effects on their disease symptoms (including PSA count, tumour volume and pain levels, as mentioned in paragraph [0017] and [0072] to [0074] and [0077] of the patent in suit and reported as overall results in Example 1 and in **D15**) - in other words, the effectiveness of their treatment. The patients were not subject to obligations of confidentiality. If even a single patient was made aware that they benefited from effective treatment, this information would have constituted novelty-destroying disclosure. Since the TROPIC study had been completed by the priority date, this disclosure must have taken place by then. Evidence on the information provided to individual patients by clinicians was not necessary for concluding that individual patients in the study arm must have benefited from the cabazitaxel-based treatment. Furthermore, the additional comments in documents **D2** and **D3** (see points 6.12.1 and 6.14 above) were proof that the effective treatment of mCRPC using cabazitaxel and prednisone was becoming known to those engaged in, or otherwise following, the TROPIC study.

6.22 The board is not persuaded by this line of argument. It is established jurisprudence that in order to determine whether an invention has been made available to the public by prior use, the following facts must be proven: (i) the date of prior use ("when"), in order to ascertain its "prior" character; (ii) the object of the use ("what"), in order to examine its relevance, and regarding (iii) the circumstances relating to the alleged prior use ("how" i.e. where, how and by whom the subject-matter was made public through that use) in order to confirm its availability to the public (see

Case Law I.C.3.2.4 a) and IV.C. 2.2.8 i). The board finds that in the present case these requirements are not met and at least (iii) the circumstances relating to the alleged prior use have not been proven. For the following reasons, the evidence relied on for the alleged prior use is not suitable to prove an instance of disclosure of the therapeutic efficacy of the claimed treatment, neither with regard to collective patient data (addressed in point 6.22.2 below) nor to individual patient data (addressed in points 6.22.3 to 6.22.12).

6.22.1 According to **D1**, the start of the TROPIC study was in December 2006. According to **D15** (see abstract), the cut-off for the final analysis was 25 September 2009, i.e. about a month before the filing date of the first priority document **P1** on 29 October 2009 (i.e. the effective date).

6.22.2 It was not shown that collective data from the TROPIC study were part of the public domain before the effective date.

The comments in documents **D2** and **D3** mentioning a "promising activity" of cabazitaxel cannot be taken as evidence that this was the case as there is no indication in these documents that the statements in question were meant to comment on intermediate collective results obtained in the TROPIC study that were increasingly becoming known (as hypothesised by the opponents). This argument remains speculation and is indeed contradicted by the circumstances.

According to the patent proprietor, the clinicians involved in the study were under an obligation of confidentiality, as is customary practice in such cases and as evidenced, for instance, by **D92**, the clinical trial agreement with the author of **D3**, who was an

investigator in the TROPIC study (see sections 4 and 5 on "Confidentiality" and "Publication"). The TROPIC study is identified in **D92** by the protocol number EFC6193 (indicated also in **D1**). No evidence to the contrary was provided.

Regarding the study organisers, **D15** (see the abstract and the paragraph bridging pages 1149 and 1150) reports that "patients and treating physicians were not masked to treatment allocation, but the study team was masked to the data analysis". Only an independent data-monitoring committee received the unmasked results (see **D15**: page 1151, left-hand column, third paragraph). The opponents did not argue that this transfer of information was not confidential.

Thus, the available evidence indicates that the data obtained in the study could only have been analysed and published after completion of the study. No evidence was provided that the study results were publicly disclosed before the first priority date of the patent in suit.

The argument of opponent 1 that the delay of disease progression would have been shared among patients is not supported by evidence of any concrete instance where this occurred. Nor can it be assumed, based on the available evidence, that the patients were in a position to share information on their own clinical state to an extent that a person not bound by confidentiality could gain knowledge of the clinical parameters of a significant number of study participants.

In summary, the alleged public prior use cannot be based on an analysis of collective patient data.

6.22.3 The opponents further relied on the argument that a novelty-destroying public prior use could be established on the basis of the fact that individual patients in the cabazitaxel arm of the study must have been regularly informed about their health status while participating in the TROPIC study (see point 6.21 above). Thus a public prior use would be proven alone by the individual data received by the study participants.

6.22.4 In this context, the opponents submitted that instances of disclosure of treatment in a single case had been recognised in the jurisprudence of the boards as evidence for effective therapeutic treatment.

6.22.5 The board is, however, of the view that the situation underlying **T 1009/97** (cited by opponent 1 as a case in point) was different from the case in hand.

In the case underlying **T 1009/97**, the pertinent prior-art citation (citation "(9)") reported on the treatment of an individual patient, detailing the ineffectiveness of a variety of other medicaments and measures, the recurrence of pain symptoms when the dosage of the relevant effective medication was lowered, and an assessment of its efficacy in this individual case by an experienced clinician. Furthermore, it had not been shown that this assessment was incorrect (see **T 1009/97**, Reasons 5.2, 5.5, 5.6). On this basis, the board in that case concluded that citation (9) should be taken into account for the assessment of novelty and inventive step.

6.22.6 The case in hand differs from the circumstances underlying **T 1009/97** in that the opponents did not provide any evidence of the precise circumstances of an individual case of disclosure to a patient but only derived such a case hypothetically and generically.

This generic construction does not supply sufficient detail for recognising a public prior use (see point 6.22 above).

6.22.7 The circumstances in an individual case being difficult to prove does not mean that such necessary evidence can be dispensed with. In the absence of any supporting evidence, a general allegation that a consultation between a clinician and a patient may have taken place before the priority date is not sufficient as neither the relevant content nor the date of any individual consultation has been established.

6.22.8 Knowledge of the circumstances of disclosure to an individual patient would be necessary to ascertain that a novelty-destroying public prior use indeed occurred, i.e. that it was directly and unambiguously disclosed to this patient before the effective date that in their case, the cabazitaxel-based treatment showed therapeutic efficacy in accordance with claim 1.

6.22.9 What matters in this context is not whether the patient in question could have been under the subjective impression that the treatment with cabazitaxel had been successful, but whether the circumstances of the individual use would have been regarded by a person skilled in the art as sufficiently convincing for concluding that therapeutic efficacy had occurred in this particular case.

6.22.10 While it is undisputed that the patients participating in the open-label study knew about the drug received, i.e. cabazitaxel in combination with prednisone, and that they were also informed about their disease parameters, this is not sufficient to objectively establish efficacy of the treatment. To assess whether therapeutic efficacy was achieved, it would be

necessary to know the specifics of the individual patient, such as information about the symptoms experienced, previous treatment, co-medication, co-morbidities etc., as well as what information about their health status, in terms of individual data, was specifically provided to them, in particular concerning the progression of the disease and estimated life expectancy.

6.22.11 As a general point, therapeutic efficacy in mCRPC is difficult to monitor as there is a lack of meaningful parameters. This is why overall survival (which can, however, only be established by statistical analysis of a patient group, not on the basis of a single case) was regarded as the appropriate primary outcome measure (see **D58**: point 11). In general, it would be difficult to conclude that therapeutic efficacy was achieved on the basis of a single case, i.e. without support of statistical evidence (as seen above in the case of the phase I evidence in **D4**, see point 6.12.6). Various changes in disease manifestations may occur without being clearly indicative of clinical benefit, in particular if based on an isolated report. For instance, as pointed out by the patent proprietor (see **D58**: points 6 to 9), PSA has generally been regarded as an unreliable indicator of drug activity as temporary changes in PSA levels may occur for various reasons. A single consultation in which a physician informed a patient that their PSA level had declined would not be regarded as a clear indication of therapeutic efficacy (see also **D72**: page 1154, right-hand column, second and third paragraph). Moreover, drugs may produce PSA declines without improving survival. In particular, early consultations may not be indicative of an overall benefit. Similarly, tumour reduction may be caused by

various factors and may be of short duration (see also **D58:** point 10).

6.22.12 The absence of a placebo arm in the TROPIC study, which was emphasised by one of the opponents, is not an indication that any improvement observed was necessarily due to the study drug. What can be inferred from the absence of a placebo arm is just that it was not ascertained by statistical means whether any effect observed could be attributed to the drug or might have occurred independently of the drug.

6.22.13 For these reasons, it was not established with the required certainty that the alleged public prior use occurred.

6.23 In conclusion, for the reasons set out in points 6.2 to 6.22.13 above, novelty of the subject-matter of claim 1 is acknowledged (Articles 100(a), 52(1) and 54 EPC). The same conclusion applies to the dependent claims.

7. Inventive step (Articles 100(a), 52(1) and 56 EPC)

7.1 Documents **D1**, **D2**, **D3**, **D4**, **D6**, **D7**, **D37**, **D39** and **D110** were discussed by the opponents as possible starting points for the assessment of inventive step. Three approaches can be identified on the basis of these documents.

The first of these starts from the disclosure of the TROPIC study in documents **D1**, **D2**, **D3**, **D6**, **D7** and **D37**. The board notes that this approach provides two options. Either the experimental study arm (the cabazitaxel arm, preferred by the opponents) or the control arm (the mitoxantrone arm) of the TROPIC study may be taken as the starting point.

The second approach starts from the disclosure of the phase I study results in **D4**.

The third approach starts from established treatment options of mCRPC after treatment with a docetaxel-based regimen as disclosed in **D7**, **D39** and **D110**, namely docetaxel re-treatment (see **D7**: page 162; **D110**: page 24) or mitoxantrone palliative therapy (see **D7**: page 162; **D39**: paragraph bridging pages 1235 and 1236).

7.2 **D10** and **D11**, also proposed by the opponents as possible starting points, cannot be taken into account for the assessment of inventive step since the priority claim based on **P1** is deemed valid (see point 5.16 above).

The experimental arm of the TROPIC study as the starting point

7.3 The pertinent disclosure of **D1**, **D2**, **D3** and **D6** has been summarised above (see points 6.9, 6.10 and 6.14).

7.4 **D7** and **D37** were mentioned by some of the opponents as further disclosure of the TROPIC study (see **D7**: page 163, right-hand column, "Taxanes" and **D37**: page 3948, second paragraph).

7.5 **D3**, **D7** and **D37** do not contain more information about the study protocol than **D1**, **D2** and **D6**. The pertinent disclosure of **D1**, **D2**, and **D6** on the TROPIC study is the same, except that **D2** also discloses the dosage of cabazitaxel in the experimental arm. In the following discussion, the starting point is **D1/D2**. This may be considered representative also of the other prior-art disclosures relating to the TROPIC study cited as possible starting points.

Objective technical problem and solution

7.6 As established above in the section on novelty, the feature distinguishing the subject-matter of claim 1 from the disclosure of the experimental arm of the TROPIC study in **D1/D2** is the effective treatment of the claimed therapeutic indication.

7.7 Since the claim contains the achievement of the therapeutic effect as a functional technical feature, non-working embodiments are excluded. Hence, the opponents' argument that therapeutic efficacy is not achieved across the scope claimed cannot succeed. The issue whether the claimed therapeutic efficacy was sufficiently disclosed has been addressed in section 4.

7.8 On this basis, the objective technical problem is **to put into practice the effective treatment of prostate cancer with cabazitaxel in co-administration with prednisone in patients with mCRPC who have been previously treated with a docetaxel-based regimen and who have prostate cancer that progressed during or after that treatment.**

7.9 The solution to this problem is the subject-matter of current claim 1, which includes attaining the relevant therapeutic effect as a functional technical feature.

Obviousness of the solution

7.10 The issue decisive for obviousness is thus whether the person skilled in the art would have had a reasonable expectation of success with regard to the experimental arm of the TROPIC study.

7.11 The opponents essentially argued that, for a second medical use claim, where the prior art disclosed that a clinical study with the same active agent(s) for the same therapeutic indication had been proposed or was

underway, it was established jurisprudence of the boards that a reasonable expectation of success was generally implied by the mere fact that the study had been authorised, unless there was some evidence of a dissuading teaching in the prior art. In other words, the announcement of a clinical study established a legal presumption of reasonable expectation of success, with the consequence that a patent proprietor had the burden of rebutting such a legal presumption by showing that the skilled person would have been dissuaded by the prior art from following the study protocol with a reasonable expectation of success and so achieve its inevitable outcome.

According to the opponents, this general principle, furthermore supported by general guidelines on clinical studies in oncology (see **D18**), applied in the case in hand.

No dissuading element (negative pointer) was known in the prior art. Rather, in addition to the announcement of the TROPIC study, the available evidence on cabazitaxel would have further incentivised the person skilled in the art to follow the phase III TROPIC study protocol with a reasonable expectation of success.

In this context, the following aspects were mentioned by the opponents as positive pointers.

(a) Cabazitaxel was of the same class as docetaxel (which was known for its efficacy in mCRPC and its superiority in comparison with a mitoxantrone-based regimen) and had, furthermore, been designed to overcome cellular resistance to docetaxel.

(b) The data known from preclinical, phase I and phase II testing were encouraging.

(c) The fact that it was a higher-level (phase III) clinical study that had been approved and that phase II had been skipped would have increased the expectation of success. The skilled person would have considered that a regulator would only progress straight to approval of such a study if it were provided with a significant body of clinical work, which would not necessarily be public, that indicated a positive outcome to be likely.

(d) The person skilled in the art would have inferred that the regulatory agency had been supplied by the study sponsors with additional data in favour of cabazitaxel not publicly available at the time and that this additional information would have contributed to an expectation of success on the part of the regulatory agency (**D15** and **D21** as evidence).

(e) The fact that the study was nearing completion at the priority date of the patent in suit (i.e. that it had not been terminated prematurely) would have increased the skilled person's expectation of success.

(f) Without a realistic expectation of success, the patent proprietor as the study sponsor would not have invested money into the TROPIC study (see **D20:** page 15, where it is reported that the development of cabazitaxel in the treatment of prostate cancer was going to be continued).

7.12 These arguments cannot succeed for the following reasons (seee points 7.13 to 7.16 below).

7.13 The board is of the view that the skilled person's expectation of success has to be considered in particular in relation to the TROPIC study's primary

endpoint, which was overall survival. Success in the context of a clinical study means meeting the primary endpoint.

Starting from the concept of the TROPIC study, including from its experimental arm, the skilled person would still have equated success (in putting the envisaged treatment into practice and solving the objective technical problem) with an increase in overall survival relative to the comparative arm, i.e. with favourable results regarding the primary endpoint.

Thus, to lead to a finding of lack of inventive step, an expectation of success for improved overall survival must have been present.

7.14 The boards have developed a large body of decisions dealing with reasonable expectation of success, including in cases of second medical use where clinical studies were announced in the prior art. This case law mainly focuses on balancing positive and negative pointers. As such pointers are necessarily always linked with the individual circumstances of the case at issue, it cannot be concluded, without taking the circumstances of each case into account, whether there would have been a reasonable expectation of success. Thus the probative value of a clinical study announcement always depends on the particular circumstances of the case.

7.14.1 Thus, and contrary to the opponents' argument (see point 7.11 above), the analysis of the cited jurisprudence of the boards does not lead to the conclusion that ongoing clinical studies automatically establish a legal presumption of success.

A legal presumption, especially if it would override established facts, must be explicitly stated in the law (see also **G 1/23**, Reasons 48, as supplementary

reference which is not part of the board's reasoning as it was published after the present decision was taken).

7.14.2 In principle, the board agrees with the statement in **T 1437/21** that a prior disclosure that an investigational product (i.e. active agent) for use in the treatment of a particular condition is undergoing a clinical study may preclude that a subsequently claimed invention involving this product for use in the treatment of that specific condition is considered to involve an inventive step, even where the results of the study have not been made available to the public (see **T 1437/21**, Reasons 4.3.1, referring to **T 2506/12**, Reasons 3.10 and 3.15; **T 239/16**, Reasons 6.5 and 6.6; **T 1123/16**, Reasons 11; **T 2963/19**, Reasons 4.3.1, which were relied on by the opponents).

7.14.3 However, as also noted in **T 1437/21** (Reasons 4.3.1) and **T 3165/19** (Reasons 22), relied upon by the patent proprietor, this consideration is not absolute but must be understood in the context of the circumstances of the individual cases underlying those particular decisions. For instance, as set out in **T 2963/19** (Reasons 4.3.1), and confirmed in **T 1437/21** (Reasons 4.3.1)

> "*...the approval of a clinical study depends on the assessment of the foreseeable risks to the participants in relation to the anticipated benefit in terms of the relevance of the findings, which does not necessarily imply an expected positive outcome and does not represent a scientific advice on the development programme of the investigational product tested*".

The approval of a clinical study does, therefore, not necessarily imply an expected positive outcome.

7.14.4 As a consequence, the question of whether there was a reasonable expectation of success must be answered on the basis of the specific circumstances of the case. This requires an evaluation of all the facts available at the relevant date of the contested patent, such as the nature of the active agent under investigation, how far the clinical testing of the active agent(s) had advanced and how much was known about the clinical efficacy, safety and potential toxicities of the active agent(s) in the pertinent therapeutic indication.

7.14.5 In this regard, the present board concurs also with **T 1941/21**, in which the board held that inventive step over clinical studies (meaning clinical study anouncements) has to be assessed on a case-by-case basis (see Reasons 1.7.4 and the analysis under points 1.7.1 to 1.7.3) and further that the reasonable expectation of success which "may arise" from the announcement of a clinical study would have to be denied in the presence of negative pointers dissuading the skilled person from pursuing such a study (see in particular Reasons 1.5). The board in **T 1941/21** then goes on to investigate also the possible existence of positive pointers (Reasons 1.5.1 to 1.5.3), which is in agreement with the approach outlined above that all the facts (i.e. negative as well as positive pointers) must be taken into account.

7.14.6 The lack of a general presumption of an expectation of success had already been emphasised in **T 1806/18** (Reasons 7.21), in which the board stated that

> *"[t]he fact that a clinical study is announced in a prior-art disclosure does not automatically mean that its outcome was predictable and that a reasonable expectation of success had to be*

acknowledged. Whether this is indeed so, depends on the facts and circumstances of each case."

7.14.7 As explained in the following, the considerations in the decisions cited by the opponents regarding the expectation of success in view of the disclosure of clinical study announcements are, as in the above decisions relied upon by the proprietor, evidently linked to the further circumstances of each case, in particular the nature of the active agent under investigation and the pertinent therapeutic indication.

7.14.8 **T 239/16** concerns a claim directed to zoledronic acid for use in a method of treating osteoporosis in which the period between administrations of this active agent was about one year.

Prior-art document "(55)" (see Reasons 5.2) related to the set-up of a pertinent clinical study but did not disclose any data from this study.

Document (55) was deemed to not be novelty-destroying as it neither explicitly nor implicitly disclosed achieving the relevant therapeutic effect (Reasons 5.2 and 5.3).

In the context of obviousness, the skilled person's expectation of success for the relevant study arm (administration at intervals of one year) was of interest.

The board in **T 239/16** undertook a detailed analysis of what was known in the art for the agent under consideration and for related actives (see Reasons 6.5 and 5.2). This anaysis revealed positive pointers to the expected efficay of zoledronic acid (see Reasons 5.2). Following from the analysis of the prior art described in the preceding paragraphs, the board came to the view that zoledronic acid was expected to

behave, in principle, in the same way as other agents of the bisphosphonate class, and that the possibility of persistent effects lasting at least 12 months was being discussed. Thus, it was due to the particular circumstances of the case that the board concluded (Reasons 6.5, first two paragraphs) that the person skilled in the art would have entertained an expectation of success for the once-yearly study arm, and that negative pointers would have been required to dissuade the skilled person from this expecation.

The factual situation in **T 239/16** was different from that in the case at issue. This was about a particular dosage regimen of an active agent (zoledronic acid) belonging to a class of compounds with well-established efficacy in treating the claimed thrapeutic indication (osteoporosis). It is to be noted here that the therapeutic indication in case **T 239/16** is a chronic disease, and that the related actives (i.e. other bisphosphonates) differ from zoledronic acid merely in their potencies. Thus, other than in the present case, the data available for the active under consideration was rather solid. In contrast, the case in hand relates to a new cancer drug used in a new indication, and the situation is complicated by the further issue of resistance to taxanes.

7.14.9 For the same reason, namely the individual aspects relevant for the assessment of the presence of a reasonable expectation of success, the present case differs from the situation underlying the decision in **T 2506/12**. The claimed subject-matter concerned a combination treatment of two drugs, and the relevant prior art disclosed that a clinical phase I study was ongoing to assess the combination treatment. Each of the two drugs was known to have efficacy in the therapeutic indication (ovarian cancer). The relevant

question was thus merely to confirm the usefulness of the drug combination and for this reason the board concluded that, in the absence of contrary information on file, there was no reason for the skilled person to expect the combination to fail (see Reasons 3.10 to 3.12 and 3.15).

7.14.10 As stated above, the board is in agreement with the principles that can be derived from the body of case law discussed above (points 7.14 to 7.14.10) and for this reason does not follow **T 96/20**, where the board held differently that the announcement of a detailed safety and efficacy clinical study protocol for a particular therapeutic and disease alone provided the skilled person with a reasonable expectation of success of this particular therapeutic, unless there was evidence to the contrary in the state of the art (Reasons 9). There was however no detailed discussion regarding this aspect and the potential impact of positive and negative pointers.

7.14.11 On account of these considerations and having in mind the objective technical problem as formulated above, the crucial issue in the assessment of inventive step starting from the experimental arm of the TROPIC study thus remains whether, in view of the available information in the prior art, the skilled person had a reasonable expectation that cabazitazel in combination with prednisone would be effective to improve overall survival (see point 7.13 above).

7.15 To return to the case in hand, the following applies in respect of the positive pointers mentioned by the opponents (see point 7.11 above).

7.15.1 Pointer (a)

The fact that cabazitaxel was of the same class as docetaxel would, in general, have dissuaded the skilled person from expecting an increase in overall survival for a patient group that had progressed during or after docetaxel treatment. While cabazitaxel had indeed been designed with a view to overcoming resistance to docetaxel, the available data were not yet clear enough to predict that this effect would indeed be achieved.

7.15.2 Pointer (b)

As can be seen from the analysis of the disclosure of documents **D4** and **D26** (see point 6.12.6 above), the data from the preclinical phase were sparse and incomplete. No relevant cell lines had been tested *in vitro,* and the results of the xenograft experiments were mixed. The phase I clinical data were furthermore not of the type to allow any insights on a possible increase in overall survival. As overall survival is linked to type of cancer and stage of disease progression, a phase II clinical study on breast cancer cannot be taken into account as a matter of principle. This is not remedied by the somewhat vague remark in **D7** (page 163, right-hand column, "Taxanes")

> *"A phase II trial with XRP6258 has not been performed in patients with CRPC; however, given its activity in the docetaxel refractory setting described above, this agent in currently being investigated on a phase III multi-center, randomized superiority trial comparing 3-weekly XRP6258 with prednisone to mitoxantrone with prednisone in patients with castrate* [sic] *resistant metastatic prostate cancer previously treated with docetaxel-containing treatment."*

It cannot, in any case, be derived from this statement that activity in breast cancer would translate to activity in prostate cancer.

7.15.3 Pointer (c)

Under usual circumstances, the fact that a phase III clinical trial is carried out might indeed provide a pointer indicating a successful development path of a new drug/new drug application (see **D18**).

D18 is written on the basis of a standard clinical study development programme, which includes a phase I study, followed by a phase II study to assess dosage and efficacy, followed by a "confirmatory" phase III study in a large population to confirm the efficacy demonstrated in the phase II study.

However, in the case in hand, the usual path of drug development is only poorly reflected. As set out above, preclinical and early clinical data (**D4, D26**) are limited. Also, no relevant data from a phase II clinical study are available. No phase II study in mCRPC was carried out. The phase II study in breast cancer (see **D13**) was not followed by a phase III study as this line of development was discontinued (see **D20**). Thus, the TROPIC study cannot be considered a confirmatory study as earlier data are lacking and indeed only a single patient in the population to be treated had been reported in phase I (see **D4**). Again, each case has to be assessed based on its circumstances. No automatic inference can be drawn.

7.15.4 Pointer (d)

In addition to the fact that both **D15** and **D21** are post-published, neither document discloses the information based on which the regulatory authorities approved the phase III clinical study. While **D21** indicates that

"non-clinical and clinical data based on applicants' own tests and studies" were submitted, the nature and content of these data are not mentioned (see **D21:** page 4).

Given that the majority of phase III clinical studies fail, it would amount to speculation to hypothesise how the risk assessment in one particular case, here the TROPIC study, would have been carried out by the regulatory authorities.

Thus, the opponents' argument that the person skilled in the art would have inferred that the regulatory authorities, at the time of approving the TROPIC study, must have had knowledge of additional unpublished experimental evidence in favour of therapeutic efficacy cannot succeed, as no such inference could have been drawn with any certainty on the basis of the known facts.

Confidential data may of course be the foundation of a rationale under which a clinical study is carried out. However, this is irrelevant in the context of assessing inventive step because such data, due to their confidential nature, were not available to the skilled person. The skilled person could thus not have taken them into account.

In addition, the alternative explanation provided by the patent proprietor is plausible and cannot be ruled out, namely that the extremely poor prospects for patients with mCRPC, especially docetaxel-refractory mCRPC, was a major factor in the TROPIC study being permitted to proceed. The risk/benefit assessment would have been strongly in favour of proceeding with the study. Patients had a terminal disease and had no approved treatment options available. The *de facto* standard treatment was a highly toxic chemotherapy with no clear data on a palliative effect, whereas the

potential benefits to the patients of a positive finding in the study were significant. Phase I toxicity studies had been completed and the risks would have appeared manageable. Even a hope of succeeding would have been sufficient to swing the assessment in favour of proceeding with the study (see the patent proprietor's reply to the statements setting out the grounds of appeal, points 10.9 and 10.68 to 10.74).

7.15.5 Pointer (e)

The fact that a study is nearing completion *per se*, in the absence of knowledge of the parameters selected for monitoring, is neither a positive nor a negative pointer when assessing expectation of success. Again, the particularities of the disease and patient group may play a crucial and decisive role. In the case in hand, no information is on file regarding the work of the data-monitoring committee, the timing of interim reviews and the predetermined criteria on which such interim reviews would have been based.

7.15.6 Pointer (f)

Similarly as in the case of pointer (d), no particular inference could have been drawn from the fact that the patent proprietor decided to continue the development of cabazitaxel for mCRPC rather than breast cancer (as announced in **D20**). It is not unusual that clinical studies of new anticancer agents fail. It is not known what factors and priorities might have played a role in this business decision and the underlying financial risk/benefit analysis.

7.16 In conclusion, the facts brought forward by the opponents as positive pointers would not have given rise to a reasonable expectation of success. In the absence of a reasonable expectation of success, the

claimed subject-matter involves an inventive step in the setting starting from the experimental arm of the TROPIC study.

The control arm of the TROPIC study as the starting point

7.17 The control arm of the TROPIC study may be considered as an alternative starting point in the assessment of inventive step.

Objective technical problem and solution

7.18 In this case, the distinguishing feature of claim 1 is the choice of medication (cabazitaxel plus prednisone instead of mitoxantrone plus prednisone).

7.19 Mitoxantrone was known to not increase survival and to only have a palliative effect (see **D7:** page 162; **D105:** page 54, right-hand column, second paragraph). As acknowledged above in the section on sufficiency of disclosure, the claimed cabazitaxel-based regimen (corresponding to the experimental arm in the TROPIC study) was found to provide an advantage in overall survival in comparison with the mitoxantrone-based regimen.

7.20 The objective technical problem can, therefore, be defined as **providing an anticancer agent for co-administration with prednisone, for improved treatment of prostate cancer in patients with mCRPC who have been previously treated with a docetaxel-based regimen and who have prostate cancer that progressed during or after that treatment.**

7.21 The solution to this problem is the subject-matter as defined in claim 1.

Obviousness of the solution

7.22 While **D1/D2** discloses cabazitaxel-based treatment in the experimental study arm, the person skilled in the art would not have entertained a reasonable expectation of success for the cabazitaxel-based regimen, as set out above (see points 7.10 to 7.16).

7.23 The conclusion is, therefore, the same, whether the starting point is the experimental arm or the control arm of the TROPIC study, and the claimed subject-matter would not have been obvious to the person skilled in the art.

The phase I study results as the starting point

7.24 The pertinent disclosure of **D4** has been summarised above (see points 6.5 and 6.12.6). The closest starting point within the phase I study is the report about the sole study participant who meets the definition of the patient group according to current claim 1 (see **D4**: page 727, left-hand column).

Objective technical problem and solution

7.25 As set out above (see point 6.12.6), based on the facts of the case in hand, the observed changes in the health status of the only patient of the phase I study who meets the definition of the patient group in current claim 1 cannot be attributed with certainty to therapeutic efficacy of cabazitaxel. Thus, the subject-matter of claim 1 differs from the pertinent disclosure of **D4** by two technical features, namely the co-administration of prednisone or prednisolone and the effective treatment of mCRPC in the claimed patient group (see points 6.8 and 6.12.6 above).

7.26 On this basis, the objective technical problem is to be defined as **providing a cabazitaxel-based treatment of prostate cancer in patients with mCRPC who have been previously treated with a docetaxel-based regimen and who have prostate cancer that progressed during or after that treatment.**

7.27 The solution to this problem is the treatment as defined in current claim 1.

Obviousness of the solution

7.28 As mentioned before (see points 6.12.6 and 6.16 above), the co-administration of corticosteroids such as prednisone and prednisolone was commonly known and practised for its palliative effect. For instance, prednisone was co-administered also with mitoxantrone (see **D7**: page 161, left-hand column, second paragraph in combination with reference [4]) and with docetaxel (see **D14**). Hence, this technical feature cannot provide a contribution to inventive step. In particular, it was also known that the co-administration of prednisone and cabazitaxel was being envisaged in the TROPIC study (**D1/D2**). In this context, it may be added that a person skilled in the art tasked with the objective technical problem defined above would have identified and consulted documents announcing a phase III study with the same purpose.

7.29 Thus, an inventive step can only be acknowledged if the skilled person would have had a reasonable expectation of success for achieving effective treatment of mCRPC by cabazitaxel in the relevant patient group.

7.30 In this regard, the patent refers to various parameters for response to treatment (see paragraphs [0006] and [0074] and Table 1). Not only death (or overall

survival) but also decline in PSA levels, tumour size or pain are mentioned as responses to be considered.

7.31 For overall survival, the reasoning set out above regarding the skilled person's expectations for the primary endpoint of the TROPIC study applies (see points 7.10 to 7.16).

7.32 For analogous reasons, owing to the erratic way in which the development of cabazitaxel for mCRPC took place and the resulting paucity of prior data for cabazitaxel in prostate cancer, especially mCRPC, the person skilled in the art would have had no reasonable expectation of success with regard to other parameters potentially reflecting treatment response. To recapitulate:

- No dedicated pre-clinical *in vitro* data for prostate cancer cell lines existed.
- Xenograft testing was carried out in various models, only one model was based on prostate cancer, and activity was retained in only one of the three docetaxel-resistant xenografts (which was not for prostate cancer).
- In the phase I study, which did not focus on prostate cancer and was not powered to show therapeutic efficacy, cabazitaxel was administered to patients having a variety of different solid tumours. The starting point in the prior art is the data reported in **D4** for the only patient in the phase I study meeting the definition of the patient group in claim 1, hence, anecdotal evidence.
- After the phase I study, no phase II study was carried out in prostate cancer, and, for unknown reasons, cabazitaxel was not taken forward in

breast cancer after a phase II study in breast cancer.

- A phase III study for cabazitaxel-based treatment in mCRPC had then been approved but the results were not yet known.

Prior to the publication of the results of the TROPIC study, the person skilled in the art would, therefore, not have disposed of any convincing evidence pointing to the therapeutic efficacy of cabazitaxel in the relevant therapeutic indication and patient group. As set out above, the isolated fact that a clinical study had been approved does not permit the conclusion that the regulators must have entertained a reasonable expectation of success. This is especially so in the circumstances of the current case where the TROPIC study was, according to all evidence, not based on the usual clinical upscaling and it could not be inferred from the known facts that therapeutic efficacy had been established in advance. Speculation about the potential existence of confidential additional data is not relevant, since the assessment of inventive step requires that the person skilled in the art would only have proceeded on the basis of established facts and publicly available data.

7.33 The conclusion is thus, also in this scenario, that there was no reasonable expectation of success and that the person skilled in the art could at most have entertained a hope to succeed in solving the objective technical problem.

Docetaxel-based re-treatment or mitoxantrone-based treatment as the starting point

7.34 For the assessment starting from a mitoxantrone-based treatment, the same considerations apply as set out above for the approach starting from the control arm of the TROPIC study (see points 7.17 to 7.23; if parameters other than overall survival were to be considered, see points 7.29 to 7.33).

7.35 For the assessment starting from docetaxel-based re-treatment, the following applies:

7.35.1 The review **D7** (page 162, left-hand column) teaches that docetaxel re-treatment was considered a reasonable option in a subgroup of patients who previously tolerated and responded to first-line docetaxel therapy. This corresponds to patients with disease progression after prior docetaxel-based treatment.

7.35.2 The objective technical problem(s) in view of this starting point is thus to be defined as **providing an alternative treatment for mCRPC patients with disease progression after docetaxel-based therapy** and **providing an effective treatment for mCRPC patients with disease progression during docetaxel-based therapy**.

7.35.3 The solution is the cabazitaxel-based treatment as defined in claim 1.

7.35.4 For the reasons provided in points 7.13 to 7.23 and in points 7.28 to 7.33) above, the person skilled in the art would have had no reasonable expectation of success for achieving an effective treatment in the relevant patient group but, at most, a hope to succeed.

Conclusion on inventive step

7.36 For the reasons set out above, the subject-matter of claim 1 involves an inventive step within the meaning of Article 56 EPC. The same conclusion applies to the dependent claims.

8. Request for non-admittance of arguments (Article 12(4) RPBA)

8.1 The arguments set out in the patent proprietor's letter of 30 September 2024 (i.e. the reply to the appeals), paragraphs 11.72 to 11.77, are presented in section 11 of that submission, which is entitled "Auxiliary Requests", in the context of novelty and inventive step. They relate to those auxiliary requests that include the limiting feature that the patients experienced disease progression during the docetaxel-based treatment (see point 11.62 of the same letter).

8.2 As these arguments play no role in the board's decision, it is not necessary to address their admittance.

9. Admittance of documents filed in appeal

9.1 **D110**, by reason of having been filed with opponent 13's notice of intervention, is part of the proceedings.

9.2 As regards the documents newly filed in the course of the appeal proceedings (see point XIII. above), the board does not need to provide reasons on their admittance. Firstly, their admittance was not explicitly objected to. In addition, some of these documents merely reflect the skilled person’s common general knowledge, which was not in dispute. Other

documents are not addressed in the board's reasoning because their disclosure was not deemed crucial.

9.3 With particular reference to **D112** (Tribunal Judiciaire de Paris, 3ème chambre, 2ème section, Jugement N°RG 21/06416-N°Portalis 352J-W-B7F-CUMKO, in Accord v Sanofi, 6 September 2024), the Boards of Appeal may in principle take into consideration decisions and opinions given by national courts in interpreting the law (see **G 5/83**, Reasons 6 and **G 2/12**, **G 2/13**, Reasons V.(2)). Nevertheless, such considerations do not exonerate a board from its duty as an independent judicial body to interpret and apply the EPC and to decide in last instance in patent granting matters. Thus, national decisions are elements to be taken into consideration by the Boards of Appeal but are not binding on them. In this sense they may have persuasive effect. Within this framework, the board has carefully taken into account the findings of the French Court (**D112**). However in view of the reasoning set out above, the board cannot share the conclusions reached by the French Court for inventive step.

10. Reimbursement of the appeal fee (Rule 103(1)(a) EPC)

10.1 Opponent 2 requested the reimbursement of its appeal fee pursuant to Rule 103(1)(a) EPC due to a substantial procedural violation under Article 113(1) EPC.
The opponent contended that the decision under appeal failed to address several of its arguments, specifically those based on **T 1806/18**, **D18** and **D21** and mentioned in sections 3.3, 4.2, 4.3 and 4.4 of its statement setting out the grounds of appeal.

10.2 Under Rule 103(1)(a) EPC, reimbursement of the appeal fee is only applicable if the appeal is deemed allowable and the reimbursement is equitable by reason

of a substantial procedural violation, in the sense that a causal link must exist between the alleged procedural violation and the appealed decision that necessitated filing an appeal (see also Case Law, V.A.11.7.1).

10.3 In the current case, the criteria for reimbursement are not met.

10.4 Firstly, the appeals were dismissed, so there is, in any case, no basis for reimbursement.

10.5 In addition, the board is also of the view that there was no substantial procedural violation.

10.5.1 The protection of the right to be heard under Article 113(1) EPC requires that the decision contains at least some reasoning on crucial points of dispute, in order to give the party concerned a fair idea of why its submissions were not considered convincing and to enable it to base its grounds of appeal on relevant issues. It is essential that the deciding organ demonstrably heard and considered the party's submissions. In particular, a decision must show that all potentially refutative arguments adduced by a party are actually refutable (see Case Law, III.B.2.4.2). However, provided that the reasons given enable the parties concerned to understand whether the decision was justified or not, the deciding organ is under no obligation to address each and every argument presented by the party concerned (see Case Law, III.B.2.4.3 and V.B.4.3.10).

10.5.2 The board finds that the above-mentioned arguments of opponent 2, even if not addressed explicitly, were indeed covered by the opposition division's reasoning concerning inventive step in the decision under appeal. E.g., the opposition division, despite not individually

addressing decision **T 1806/18** (which provides comments on decision **T 239/16**), discussed a number of decisions, including **T 239/16** itself, on the relevance of the existence of clinical studies for the assessment of the criterion of reasonable expectation of success. It also discussed several circumstances which were submitted as indicators of an expected favourable outcome of the TROPIC study. In the opposition division's view, these were more than counterbalanced by dissuading facts pertinent to the TROPIC study, so that a separate discussion was not necessary. Similar considerations apply to any arguments based on **D18** and **D21**.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated