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Datasheet for the decision of 26 September 2025

Case Number: T 0883/23 - 3.3.07

Application Number: 16758337.6

Publication Number: 3337478

IPC: A61K31/436, A61K9/127, A61K31/282, A61K31/4745, A61K31/475, A61K31/513, A61K31/519, A61P35/04

Language of the proceedings: EN

Title of invention:

DRUG COMBINATION COMPRISING LIPOSOMAL IRINOTECAN, OXALIPLATIN, 5-FLUOROURACIL AND LEUCOVORIN FOR TREATING METASTATIC PANCREATIC CANCER

Patent Proprietor:

Ipsen Biopharm Ltd.

Opponents:

Sandoz AG
Generics [UK] Limit

Headword:

Liposomal irinotecan drug combination/IPSEN

Relevant legal provisions:
EPC Art. 87(1), 56
RPBA 2020 Art. 12(6)

Keyword:
Priority - same invention (no)
Late-filed evidence - should have been submitted in first-instance proceedings (yes) - circumstances of appeal case justify admittance (no)
Inventive step - (yes)

Decisions cited:
T 1261/21, G 0002/98, T 1472/22, T 2506/12, T 1760/08, T 1409/06, T 0237/15, T 2015/20

Catchword:
The Enlarged Board of Appeal determined in G 2/98 that it is a condition for the compliance with the requirement of "the same invention" that the claimed subject-matter is directly and unambiguously derivable from the earlier application. However, the Enlarged Board did not conclude that the requirement of "the same invention" is necessarily satisfied if this condition is fulfilled, irrespective of any technical information associated with the claimed subject-matter, which is only described in the subsequent patent application.
(see point 1.5 of the decision)

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Case Number: T 0883/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 September 2025

Appellant: (Opponent 1)	Sandoz AG Centralbahnstrasse 4 4051 Basel (CH)
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Appellant: (Opponent 2)	Generics [UK] Limited Building 4, Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
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Respondent: (Patent Proprietor)	Ipsen Biopharm Ltd. Ash Road Wrexham Industrial Estate Wrexham LL13 9UF (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 March 2023 concerning maintenance of the European Patent No. 3337478 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	G. Decker

Summary of Facts and Submissions

I. European patent 3 337 478 ("the patent") was granted with fourteen claims.

Independent claim 1 as granted related to liposomal irinotecan for use in a defined combination treatment of metastatic adenocarcinoma of the pancreas in a patient who has not previously received chemotherapy.

II. Two oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked an inventive step.

Opponent 1 (O1) and opponent 2 (O2) filed appeals against the decision of the opposition division that the patent as amended in accordance with the main request filed on 7 December 2021 met the requirements of the EPC.

Claim 1 of the main request defines:

"Liposomal irinotecan for use in a method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, wherein the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 60 mg/m^2 oxaliplatin,

c. 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil;

wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection."

As indicated in paragraph [0009] of the patent the defined dose of liposomal irinotecan is intended to refer to the amount of irinotecan hydrochloride trihydrate providing an amount of irinotecan encapsulated in the liposome.

The opposition division cited *inter alia* the following documents:

D1: ClinicalTrials.gov archive, History of Changes for Study: NCT02551991, version 1 of 15 September 2015
D2: Annals of Oncology (2014), 25(2), ii105-ii117, oral abstracts, D. Von Hoff et al.,
D3: Cancer Medicine (2015), 4(6), 853-863
D4: Onivyde prescribing information, October 2015
D5: Future Oncology (2016), 12(4), 453-464
D6: Journal of Clinical Oncology (2016), 34, 4(suppl), Abstract TPS482
D7: OncoTargets and Therapy (2016), 9, 3001-3007
D8: Cancer Research (2016), 76, 14(suppl), Abstract 4830
D9: Drug Discovery Today (2012), 17(17/18), 1044-1052
D10: New England Journal of Medicine (2011), 364(19), 1817-1825
D12: British Journal of Cancer (2013), 109(4), 920-925
D13: Cancer Research (2007), 67, 9(suppl), abstract 5648

D14: Cancer Chemotherapy and Pharmacology (2015), 75(3), 579-586
D17: Cancer Research (2006), 66(6), 3271-3277
D18: European Journal of Cancer (2021), 151, 14-24
D19: Declaration of Dr. Bin Zhang, 6 December 2021
D25: Journal of Gastrointestinal Oncology (2011), 2(3), 185-194;
D27: Cancer Research (2014), 74(23), 7003-7013.
D28: Pancreas (2013), 42(8), 1311-1315
D29: Journal of Clinical Oncology (2014), 32, 4(suppl), abstract 275
D30: Journal of Clinical Oncology (2012), 30, 4(suppl), abstract 330
D31: Journal of Clinical Oncology (2014), 32, 4(suppl), abstract 305
D32: Journal of Clinical Oncology (2013), 31, 15(suppl), abstract e15176
D33: Journal of Clinical Oncology (2014), 32, 4(suppl), abstract 256

The opposition division arrived at the following conclusions:

(a) The claimed subject-matter was entitled to the earliest claimed priority.

Documents D1, D4, D5, D6, D7, D8, D18 and D19 were therefore not prior art under Article 54(2) EPC.

(b) Suitable starting points in the prior art were the FOLFIRINOX combination of document D10 as well as a modified version thereof, mFOLFIRINOX as described in document D3.

In view of the experimental results reported in the patent and the results reported in the post-

published documents D18 and D19, the objective technical problem was the provision of a more efficacious treatment of metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy for this condition, which is also acceptably safe and tolerable.

The available prior art reported favourable preclinical and clinical data for liposomal irinotecan. However, no prior art suggested solving the identified technical problem by replacing conventional non-liposomal irinotecan in the FOLFIRINOX or mFOLFIRINOX regimen by liposomal irinotecan, let alone reducing the dosages of liposomal irinotecan to 60 mg/m^2 and oxaliplatin to 60 mg/m^2.

III. The following additional documents were filed during the appeal procedure:

A35: Dean A, et al., "A Randomized, Open-label, Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens versus nab-Paclitaxel Plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma (mPAC)." Poster TPS-48: presented at the Gastrointestinal Cancers Symposium ASCO 2016,
by O1 with the statement of grounds of appeal

A36: Information disclosure statement from the applicant in US Application Number 15809815 dated 13 February 2019,
by the patent proprietor with the reply to the appeals.

IV. With the reply to the appeals, the patent proprietor maintained the main request on which the decision under appeal was based.

V. In its communication pursuant to Article 15(1) RPBA, the Board expressed the preliminary opinion that:

- the subject-matter of the main request did not enjoy the claimed priority,

- document A35 was not to be admitted into the appeal proceedings,

- neither the preclinical results in the patent, nor the post-published evidence from documents D18 and D19 demonstrated any improved tolerability or efficacy of the claimed subject-matter over the modified FOLFIRINOX treatment as known from document D3,

- the claimed invention did not concern a mere dose optimisation, but rather the provision of a dosage regimen for a combination of drugs which had previously not been disclosed to be safe and effective for the treatment of the defined patients.

VI. Oral proceedings were held on 26 September 2025.

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

(a) Priority

The priority applications P1-P7 did not disclose the specific combination of the administration of

60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin as part of an effective and tolerable combination treatment as defined in claim 1 of the main request. The mention of the combination of 60 mg/m^2 of liposomal irinotecan and 60 mg/m^2 oxaliplatin in the earliest priority application (P1) in the context of an outline for a dose escalation/de-escalation study (see P1, paragraph [00288], Table 7) did not provide any pointer towards the defined combination treatment, because this outline included four other dose combinations for liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin, without indication of any preference towards the combination defined in claim 1 of the main request. Moreover, the priority application P1 described a combination of higher doses, 80 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin, as the target of the escalation/de-escalation study of Table 7. Document P1 did furthermore not disclose the results from the escalation/de-escalation study on which the patent relies. The later filed priority applications (P2-P7) did not present any additionally relevant information regarding the combination treatment as defined in claim 1 of the main request.

(b) Admittance of document A35

Document A35 represented a poster describing the protocol of the clinical trial of example 3 of the patent. The poster was published between the filing of the priority applications P4 and P5.

Document A35 was highly relevant to the issue of inventive step, because it presented the same dose-

escalation/de-escalation scheme as Table 7 of the first priority application, including the combination of 60 mg/m^2 of liposomal irinotecan and 60 mg/m^2 oxaliplatin together with 5-fluorouracil and leucovorin as the lowest dose combination. This dose escalation/de-escalation scheme was not revealed in the abstract of document D6 relating to the same clinical trial, which was already part of the appeal proceedings. Moreover, document A35 expressed confidence in the tolerability of at least the lowest dose combination by stating that the object of the dose escalation/de-escalation study was to confirm an appropriate dose to be used in the subsequent efficacy study.

The more complete description of the protocol in document A35 than in the abstract of document D6 did not dramatically alter the objection of lack of inventive step and merely simplified the assessment.

Confronted with document A35, the patent proprietor could not have been taken by surprise, because the authors of the poster were employees of the patent proprietor's predecessor in title.

The document had been particularly hard to retrieve and was eventually obtained from the USPTO after it had been identified in the Information Disclosure Statements (IDS) of the US patents of the patentee. The document was then filed at the earliest opportunity with O1's statement of grounds of appeal

In line with the considerations in T 1472/22, in which evidence of a public prior use was admitted into the appeal proceedings, the theoretical possibility of the retrieval and filing of document A35 at an earlier stage of the proceedings was not a sufficient reason not to admit the document under Articles 12(4) and 12(6) RPBA.

The opposition division decided that the claimed subject-matter enjoyed the relevant priority and that the protocols of the clinical trial as published at a later date in documents D1 and D6 did not form part of the prior art. Insofar as the filing of document A35 did not address an issue that led to the decision under appeal, the circumstances of the appeal case still justified the admittance of document A35, especially since the opponents challenged with their appeals the opposition division's finding on the validity of the priority.

(c) Inventive step - Article 56 EPC

The modified FOLFIRINOX treatment regimen (mFOLFIRINOX), as described in document D3 with reference to document D28 for the first-line treatment of metastatic pancreatic cancer, represented a suitable starting point in the prior art. The differences between the claimed subject-matter and this prior art concerned the replacement of the 180 mg/m^2 conventional non-liposomal irinotecan by 60 mg/m^2 liposomal irinotecan and the reduction of the oxaliplatin dose from 85 mg/m^2 to 60 mg/m^2.

No unexpected advantage concerning the clinical efficacy and tolerability of the combination treatment as defined in claim 1 of the main request had been substantiated. The patent only provided results from a preclinical mouse model with a different dosage regimen and the results reported in document D18 were inconclusive regarding any significant clinical advantage, even when taking the further information from document D19 into account.

The combination treatment as defined in claim 1 of the main request was obvious as a solution to the problem of providing an alternative tolerable treatment. In view of the references to the various possible modifications to the FOLFIRINOX regimen indicated in document D3 itself and the advantageous properties of liposomal irinotecan over non-liposomal irinotecan as described in the reviews in documents D25, D5 and D7 as well as in documents D2, D4, D8, D12, D13, D14, D17 or D27, the skilled person was motivated to replace the non-liposomal irinotecan in the mFOLFIRINOX regimen by liposomal irinotecan. The outline for the clinical trial in document D6, which included a safety run-in to confirm the target dose of oxaliplatin to be used in the efficacy study, further supported this motivation. The efficacy and safety of reduced doses of liposomal irinotecan as compared to conventional irinotecan, described for combination therapy in documents D2 and D4 and for monotherapy in documents D12 and D14, provided guidance for reducing the dose of liposomal irinotecan in replacing non-liposomal irinotecan in the mFOLFIRINOX regimen of document D3. As indicated by documents D3 and D9 and in line with

the considerations in T 2506/12, T 1760/08, T 1409/06 and T 237/15, the reduction of the dose for liposomal irinotecan and oxaliplatin with respect to the doses of irinotecan and oxaliplatin in the mFOLFIRINOX regimen would only concern routine dose optimisation and thus not support an inventive step.

The outline of the clinical trial as disclosed in documents D1 and D6 represented an alternative suitable starting point in the prior art. The objective technical problem concerned the provision of effective and safe first-line treatment for human patients with metastatic adenocarcinoma of the pancreas. The skilled person would consider the dosage regimen defined in claim 1 of the main request an obvious solution in view of the common general knowledge concerning possible modifications to the FOLFIRINOX regimen as described in document D3, the general knowledge from documents D4, D5, D7 and D25, or the information available from documents D2, D8, D12, D13, D14, D17 and D27 regarding the advantageous properties of liposomal irinotecan compared to non-liposomal irinotecan. The reduced doses for the liposomal irinotecan and the oxaliplatin defined in claim 1 of the main request with respect to the conventional FOLFIRINOX regimen resulted from routine dose optimisation.

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

(a) Priority

The priority application P1 disclosed in claim 1 in combination with dependent claims 3 and 20 as well

as in claim 22 a method of treating metastatic adenocarcinoma of the pancreas in a human patient who had not previously received chemotherapy, which involves the administration of a combination of liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil. The priority application P1 further specified in dependent claim 5 the administration of 60 or 80 mg/m^2 liposomal irinotecan, in dependent claim 8 the administration of 60, 75 or 85 mg/m^2 oxaliplatin and in dependent claims 9 and 12 the administration of 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil.

The definition of the administration of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin in claim 1 of the main request did not involve a new selection from two lists, but merely the limitation to one of the six specific dosage combinations defined in claims 5 and 8 of the priority application P1.

Moreover, the priority application P1 disclosed an escalation/de-escalation scheme for a clinical dose finding study, which included the combined administration of specifically 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin together with 400 mg/m^2 leucovorin and 2400 mg/m^2 5-fluorouracil. The outline of this escalation/de-escalation study also included the administration of combinations with higher doses of liposomal irinotecan and oxaliplatin. However, in line with the considerations in T 1261/21, the priority application still provided an adequate pointer towards the dosage regimen of claim 1 of the main request, in particular because the skilled person

would understand that the disclosed combination of lower doses was the most likely to be tolerable.

The subject-matter of claim 1 of the main request was thus directly and unambiguously derivable from the priority application P1. In accordance with the considerations in G 2/98, the claimed subject-matter therefore enjoyed the priority of P1, irrespective of any particular additional technical effects associated with the claimed subject-matter, which were only described in the subsequent application.

(b) Admittance of document A35

Document A35, which was proposed by O1 as an alternative starting point in the prior art, was not to be admitted, because it confronted the patent proprietor with a fresh case on appeal.

Document A36 demonstrated that document A35 was cited in the IDS of 13 February 2019 for a US patent sharing priority with the patent in suit. Document A35 could and should therefore have been filed during the first-instance proceedings.

The patent proprietor could not be assumed to be aware of all publications linked to its predecessor in title and should not be required to respond on appeal to a new attack based on document A35, which was linked to its predecessor in title, Merrimack Pharmaceuticals.

The filing of document A35, which was published after the P1 priority date, did not address any issue that led to the decision under appeal,

because this decision acknowledged that the claimed subject-matter enjoyed the priority of P1.

Document A35 lacked *prima facie* relevance, because it described, like document D6, only the outline for a clinical trial still to be carried out.

(c) Inventive step - Article 56 EPC

The differences between the subject-matter of claim 1 of the main request and the known mFOLFIRINOX regimen described in document D3 involved at least the replacement of the conventional non-liposomal irinotecan by the defined lower dose of liposomal irinotecan and the lower dose of oxaliplatin.

The experimental results reported in the patent and in documents D18 and D19 showed that the differences led to more effective and tolerable treatment. However, even if the objective technical problem was formulated as the provision of a mere alternative treatment, the claimed subject-matter was not obvious in view of the prior art.

Document D3 and documents D28-D33 cited in document D3 did not mention liposomal irinotecan and could thus not provide the skilled person with any suggestion towards the treatment as defined in claim 1 of the main request.

The further cited documents provided no basis for any reasonable expectation that the use of liposomal irinotecan and the reduced doses of irinotecan and oxaliplatin, as defined in claim 1 of the main request, allowed for the effective and

tolerable treatment of the defined group of patients.

Documents D8, D13, D17 and D27 only presented preclinical data without any suggestion regarding the clinically effective and tolerable dosage regimen as defined in claim 1 of the main request. Documents D4, D5, D7, D12 and D25 described the utility of liposomal irinotecan in second-line treatment of advanced pancreatic cancer, but only in the form of monotherapy or combination therapy without oxaliplatin, and at different doses than defined in claim 1 of the main request. The references in documents D5 and D7 concerning the replacement of conventional non-liposomal irinotecan by liposomal irinotecan in the FOLFIRINOX regimen were speculative and left the skilled person without any guidance towards effective and tolerable doses. Document D14 speculated on the potential utility of liposomal irinotecan in combination therapy for solid tumors in general without providing any further guidance on the effective and tolerable dosing as defined in claim 1 of the main request.

Documents D1 and D6 only presented an outline of a clinical trial for exploring the use of liposomal irinotecan in combination with oxaliplatin, 5-fluorouracil and leucovorin. The documents did not describe the doses and administration frequencies and the tolerability and efficacy of the combination treatment remained to be investigated.

Document D9 merely discussed the possibility of using reduced doses of drugs in combination

treatment as compared to the doses of the drugs used in monotherapy in general terms without providing any suggestion towards the effective and tolerable doses as defined in claim 1 of the main request.

The combination of drugs defined in claim 1 of the main request had not been previously disclosed to be tolerable and effective for the relevant treatment. The definition of the doses in claim 1 of the main request could therefore not be regarded as the outcome of mere routine dosage optimisation.

IX. The appellants-opponents requested that the decision under appeal be set aside and that the patent be revoked. The opponents further requested that document A35 be admitted into the appeal proceedings and that the case not be remitted to the opposition division for further examination.

The respondent-patent proprietor requested as a main request that the appeals be dismissed. As an auxiliary measure, it requested that the patent be maintained on the basis of one of auxiliary requests 1 to 3 as filed on 7 December 2021. The patent proprietor further requested that document A35 not be admitted into the appeal proceedings and that the case be remitted to the opposition division if document A35 was admitted into the appeal proceedings and if the Board did not acknowledge entitlement to priority from document P1.

Reasons for the Decision

1. Priority - Article 87(1) EPC

1.1 The earliest priority application (P1) discloses in claim 1 a method for treating pancreatic cancer in a human subject who has not previously received chemotherapy involving the administration of MM-398 liposomal irinotecan, wherein:

- according to dependent claim 3, the liposomal irinotecan is administered in combination with oxaliplatin, leucovorin and 5-fluorouracil,

- according to dependent claim 5 the administered amount of liposomal irinotecan is 60 mg/m^2 or 80 mg/m^2,

- according to dependent claim 8 the administered amount of oxaliplatin is 60 mg/m^2, 75 mg/m^2 or 85 mg/m^2,

- according to dependent claims 9 and 12 the administered amount of leucovorin is 200 mg/m^2 of the (l)-form or 400 mg/m^2 of the (l+d) racemic, and the administered amount of 5-fluorouracil is 2,400 mg/m^2.

- according to dependent claim 20 the pancreatic cancer is metastatic adenocarcinoma of the pancreas.

The independently formulated claim 22 of the priority application P1 defines:

"A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the adenocarcinoma, the method comprising intravenously administering to the patient 80 mg/m^2 of MM-398 liposomal irinotecan, 60 or mg/m^2 [*sic*] oxaliplatin, 200 mg/m^2 of (*l*)-form of leucovorin or 400 mg/m^2 of the (*l+d*) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient." [underlining by the Board]

The priority application P1 describes on page 15 that in the metastatic setting the liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil may be administered beginning on day 1 of a 2-week cycle.

The priority application P1 furthermore presents in paragraph [0288], Table 7, the following scheme for carrying out a dose escalation/de-escalation study involving the combined administration of liposomal irinotecan ("Nal-IRI"), oxaliplatin leucovorin and 5-fluorouracil:

Level	Oxaliplatin		5-FU/LV		Nal-IRI	
	Dose (mg/m^2)[a]	Dose Day[c]	Dose (mg/m^2)[b]	Dose Day[c]	Dose (mg/m^2)	Dose Day[c]
1	60	1, 15	2400/400	1, 15	80	1, 15
-1[d]	60	1, 15	2400/400	1, 15	60	1, 15
2[e]	85	1, 15	2400/400	1, 15	80	1, 15
-2A[d]	75	1, 15	2400/400	1, 15	80	1, 15
-2B[d]	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of nal-IRI; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.

b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion

c Day indicated is part of a 28-day cycle

d Dose levels shaded in grey above are for de-escalation only. Enrollment in these dose levels will only be initiated upon agreement of the Investigators, the Sponsor, and the Medical Monitor.

e Dose level 2 is the target dose for Arm 1, based on Conroy *et al.* [1], and will be used in Part 2 of the study following dose confirmation according to methods described herein .

Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

This dose escalation/de-escalation study is described as Part 1 of a clinical trial for the assessment of the safety, tolerability and efficacy of liposomal irinotecan in combination with other anticancer agents in patients with metastatic pancreatic adenocarcinoma who have not received prior chemotherapy (see P1, paragraphs [00237]-[00575]). The described objectives of Part 1 are (i) the evaluation of the safety and tolerability of the combined administration of liposomal irinotecan, oxaliplatin leucovorin and 5-fluorouracil and (ii) the characterization of dose-limiting toxicities and the determination of the dose to be used in the subsequent stage of the study, Part 2, for the assessment of the efficacy of liposomal irinotecan containing regimens in first-line treatment of metastatic pancreatic cancer patients (see P1, paragraphs [00250]-[00256]).

The priority application P1 does not disclose the outcome of this dose escalation/de-escalation study.

1.2 The method of treating metastatic adenocarcinoma of the pancreas as defined in claim 1 of the main request involves the administration of the antineoplastic therapy consisting of 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil.

The patent (see paragraphs [0138]-[00152]) and the application from which it derives present in Example 4 the results of the dose escalation/de-escalation study for which the priority application P1 only presents the outline. The dose level 1, which involves the administration of the 80 mg/m^2 (salt) dose of liposomal irinotecan (MM-398) in combination with 60 mg/m^2 oxaliplatin together with leucovorin/5-fluorouracil turned out to be not tolerable for human patients. In contrast, the administration of the reduced dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin in combination with 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 leucovorin (dose level -1) was found to be tolerable.

1.3 The Board observes that the dose combination as defined in claim 1 of the main request differs from the combination defined in claim 22 of priority application P1 at least in the lower dose for the liposomal irinotecan, and involves with respect to the definition of the doses in claims 5 and 8 of priority application P1 the selection of 60 mg/m2 liposomal irinotecan and the selection of 60 mg/m2 oxaliplatin.

The above mentioned results from Example 4 of the patent demonstrate that the selected combination of doses for liposomal irinotecan and oxaliplatin defined in claim 1 of the main request was tolerated. At the same time these results show that the alternative dose combinations involving the higher 80 mg/m^2 dose of liposomal irinotecan were not tolerated in humans. These alternative combinations involving the higher liposomal irinotecan dose of 80 mg/m^2 are included by the definition of doses for liposomal irinotecan and oxaliplatin in claims 5 and 8 of priority application P1, but have thus been shown not to be suitable for the use in the therapeutic treatment of the relevant patients in the subsequent application from which the patent is derived. This information concerning the tolerability of the selected dose combination of claim 1 of the main request, as opposed to the intolerable and thus unsuitable alternative dose combinations defined in claims 5 and 8 of priority application P1, was not revealed in the priority application.

1.4 The Board does not recognise that this information is in any way provided by the mere outline for the dose escalation/de-escalation study in priority application P1, which the patent proprietor relied on as a pointer to the subject-matter of claim 1 of the main request with reference to the considerations in T 1261/21.

In T 1261/21 (see reasons 4.2.12), the competent Board considered that a "pointer" in an original disclosure is an implicit or explicit indication or hint towards a combination of features, which demonstrates that this combination of features does not represent an arbitrary combination of features only conceptually comprised, but is actually envisaged in the original disclosure.

However, the competent Board emphasised (see T 1261/21, reasons 4.2.12), that what information a skilled person would directly and unambiguously derive from the original disclosure remains to be assessed on a case-by-case basis.

In the present case, the dose escalation/de-escalation scheme disclosed in paragraph [00288] of priority application P1 includes the option of the administration of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin in combination with leucovorin and 5-fluorouracil as one of five alternative dosage regimens. Priority application P1 (see paragraph [00287]) explains that the dose escalation/ de-escalation study is planned to be carried out starting from the administration of the combination involving 80 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("level 1") and intended to escalate to the combination involving 80 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin ("level 2"). The additionally described de-escalation to 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("level -1") or the alternative combinations with 80 or 60 mg/m^2 liposomal irinotecan and 75 or 85 mg/m^2 oxaliplatin ("level -2A" and "level -2B") are only foreseen in case the combinations of level 1 or level 2 are found to be not tolerable. Priority application P1 thus provides with the outline for the dose escalation/de-escalation study only a conditional proposal for the use of a combination of 60 mg/m2 liposomal irinotecan and 60 mg/m^2 oxaliplatin as part of a study still to be carried out. This conditional proposal cannot be considered to provide any pointer to the combination of 60 mg/m2 liposomal irinotecan and 60 mg/m2 oxaliplatin uniquely tolerable in first-line treatment of patients

with metastatic pancreatic cancer as defined in claim 1 of the main request.

The patent proprietor's argument that the combination involving 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin represented the lowest dose combination in the scheme for the dose escalation/de-escalation study and that the skilled person would therefore understand that this combination was in any case the most likely to be tolerable, only confirms the Board's assessment that the combined selection of the uniquely tolerable doses for liposomal irinotecan and oxaliplatin in the method of treatment as defined in claim 1 of the main request introduces new information that was not disclosed in priority application P1.

1.5 The Board rejects the patent proprietor's argument that the priority application P1 describes the same subject-matter as defined in claim 1 of the main request, which should in accordance with G 2/98 therefore benefit from the priority of P1, regardless of any additional technical effects, such as the results of the dose escalation/de-escalation study, which may have been described only in the subsequent application from which the patent is derived.

According to the established jurisprudence of the boards of appeal, attaining the claimed therapeutic effect is regarded as a functional technical feature of claims in the format of Article 54(5) EPC (see Case Law of the Boards of Appeal of the EPO, 11th edition, 2025, II.C.7.2.2). Notably, the tolerability of the defined treatment is a prerequisite for the therapeutic efficacy (see T 2506/12, reasons 2.8). The tolerability of the dose combination as defined in claim 1 of the main request, as opposed to the intolerability of the

alternative combinations with higher doses of claims 5 and 8 and the dose escalation/de-escalation scheme in priority application P1, is thus a functional technical feature of the subject-matter defined in claim 1 of the main request. As explained in sections 1.1-1.4 above, this feature concerns information which is not directly and unambiguously derivable from priority application P1.

The Board further observes that according to G 2/98 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 (see G 2/98, reasons 9). The Enlarged Board of Appeal thus determined in G 2/98 that it is a condition for the compliance with the requirement of "the same invention" that the claimed subject-matter is directly and unambiguously derivable from the earlier application. However, the Enlarged Board did not conclude that the requirement of "the same invention" is necessarily satisfied if this condition is fulfilled, irrespective of any technical information associated with the claimed subject-matter, which is only described in the subsequent patent application. Notably, the established jurisprudence (see Case Law of the Boards of Appeal of the EPO, *supra*, II.D.4.6) confirms the need for sufficient disclosure of the claimed invention in the priority document.

1.6 During the appeal proceedings, the patent proprietor did not identify any additionally relevant technical

information in the subsequently filed priority applications P2-P7 regarding the tolerability of the combination treatment as defined in claim 1 of the main request that was not present in priority application P1.

1.7 The Board therefore concludes that claim 1 of the main request does not enjoy any of the claimed priorities. Accordingly, documents D1, D4, D5, D6, D7, D8 and D18 as well as document A35, which were published before the filing date of the patent, form part of the prior art.

2. Admittance of document A35

2.1 Document A35 was published between the filing of the priority applications P4 and P5. It represents a poster relating to an outline of the same clinical trial as reported in the abstract of document D6 and the priority application P1. Document A35 provides a more complete description of the outline for the trial than document D6, in particular additionally including the same scheme for carrying out a dose escalation/de-escalation study involving the combined administration of liposomal irinotecan, oxaliplatin leucovorin and 5-fluorouracil as described in paragraph [00288] of the priority application P1.

2.2 Document A35 was filed by opponent O1 with its statement of grounds of appeal and thus represents an amendment to its case. The admittance of this document is therefore at the Board's discretion under Article 12(4) and (6) RPBA.

According to Article 12(6) RPBA, the Board shall not admit requests, facts, objections or evidence which

should have been submitted in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

2.3 In view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner (Article 12(2) RPBA), it is the responsibility of the opponents to file the evidence regarding the prior art on which they intend to rely for their arguments against the maintenance of the patent as granted or as amended according to any of the requests filed by the patent proprietor during the first-instance proceedings. In this context, it is established jurisprudence (see Case Law of the Boards of Appeal of the EPO, *supra*, V.A.4.3.7.n) that new objections or evidence against claims as granted or against claims filed with the reply to the notice of opposition should have already been filed in the opposition proceedings.

According to the submissions of opponent O1, document A35 was retrieved via the Information Disclosure Statements (IDS) of the US patents of the patentee and obtained from the USPTO. As argued by the patent proprietor, document A36 demonstrates that document A35 was indeed provided to the USPTO and listed in the IDS for the US patent application 15809815 (see A36, page 4, entry 23) filed on 13 February 2019.The Board therefore concludes that document A35 was obtainable from the USPTO following the filing of the IDS for the US patent application 15809815 in 2019.

The patent proprietor filed its main request with the reply to the notices of opposition of 7 December 2021. The oral proceedings before the opposition division were held on 24 January 2023. After the filing of the

patent proprietor's main request, the opponents had thus more than a year to file document A35 during the first-instance proceedings.

Document A35 could and should therefore have been filed during the first-instance proceedings.

2.4 The opponents' argument that, in line with the considerations in T 1472/22, the theoretical possibility of the retrieval and filing of document A35 at an earlier stage of the proceedings does not justify the rejection of its admittance under Article 12(4) and (6) RPBA, is not persuasive.

The case of T 1472/22 concerned a decision by the opposition division which was based on an auxiliary request filed by the patent proprietor during the oral proceedings before the opposition division. The competent Board considered that during the first-instance proceedings the opponent had, prior to the oral proceedings, no cause to file its evidence of a public prior use directed against the subject-matter of that auxiliary request (see T 1472/22, reasons 4.2). The Board's conclusion in T 1472/22 (see reasons 4.4), that the purely theoretical possibility of the earlier filing of the evidence was not a sufficient ground for the non-admittance of this evidence under Article 12(4) and (6) RPBA, thus evidently concerned the theoretical possibility to anticipate amendments in auxiliary requests that had not yet been filed by the patent proprietor.

The main request in the present case was, in contrast to the situation in T 1472/22, already filed with the patent proprietor's reply to the notices of opposition, which was more than a year prior to the oral

proceedings held before the opposition division. The considerations in T 1472/22 do therefore not apply in the present case.

2.5 In its decision, the opposition division considered that the subject-matter of the main request enjoyed the claimed earliest priority and therefore concluded that the outline of the trial in document D6 was not prior art. The issues that led to the decision under appeal do therefore not provide any justification for the late filing of a more comprehensive description of the outline of the clinical trial provided in document A35.

According to Article 12(6) RPBA, the circumstances of the appeal case may still justify the admittance of a document into the appeal proceedings, even if the document should have been filed during the first-instance proceedings. During the appeal proceedings, the opponents successfully contested the opposition division's assessment that the subject-matter of the main request enjoyed the claimed earliest claimed priority. Whilst it is due to this circumstance that document A35 could at all be considered as part of the prior art, the Board does not recognise how its conclusion, that claim 1 of the main request does not enjoy the claimed priorities, could in any way justify the late filing of document A35, given the fact that the opponents had challenged the priority claim during the first instance proceedings and should thus have filed document A35 before the opposition division.

2.6 The opponents' argument that document A35 was particularly difficult to retrieve merely explains the late filing of document A35. Notably, the IDS of US patents forming part of the patent family of a patent

in suit represent a known source for the retrieval of potentially relevant documents.

The opponents' further argument that document A35 should not take the patent proprietor by surprise, given that its authors were employees of the patent proprietor's predecessor in title, seeks to justify the late filing of document A35 on the basis of the patent proprietor's presumed knowledge of its publication.

In view of the considerations set out in sections 2.2-2.3 above, neither the explanation provided for the late filing of document A35 nor the assertion that the patent proprietor was already aware of its publication justifies the admittance of document A35.

2.7 The opponents' assertion that the admittance of document A35 merely simplifies, without dramatically altering, the assessment of inventive step, reflects their subjective motivation for the filing of document A35, but offers, from an objective point of view, no justification for the admittance of document A35.

2.8 The Board is furthermore not persuaded by the opponents' argument for the admittance of document A35 based on the pertinence of the information additionally disclosed in document A35, which in their view should be evident from the disclosure of the scheme for the dose escalation/de-escalation study, which corresponds to the scheme as presented in Table 7 of priority application P1 and which is absent in document D6.

In view of the considerations set out in sections 2.2-2.3 above, the asserted *prima facie* relevance of document A35 claimed by the opponents does not suffice

as a justification for its admittance in the appeal proceedings.

The Board is furthermore not convinced of the *prima facie* relevance of the additional information in document A35. Like document D6 and the priority documents, document A35 does not disclose the results from the clinical dose escalation/de-escalation study presented in the patent on which claim 1 of the main request may rely. Moreover, the Board notes that the opponents' argument appears inconsistent with their claim that document A35 does not dramatically alter the assessment of inventive step.

2.9 The Board has therefore not admitted document A35 into the appeal proceedings under Article 12(6) RPBA.

3. Inventive step - Article 56 EPC

3.1 Starting point in the prior art

3.1.1 Claim 1 of the main request relates to the first-line treatment of metastatic adenocarcinoma of the pancreas. As pointed out in section 1.2 above, the patent presents experimental results which demonstrate that the dosage regimen including the administration of 60 mg/m2 liposomal irinotecan, 60 mg/m2 oxaliplatin, 400 mg/m2 (racemic) leucovorin, and 2400 mg/m2 5-fluorouracil as defined in claim 1 of the main request is tolerable, whereas the administration of 80 mg/m2 liposomal irinotecan and 60 mg/m2 oxaliplatin in an otherwise similar dosage regimen is not tolerable in relevant patients.

3.1.2 Document D10 established the so-called FOLFIRINOX regimen as an option for the first-line treatment of

patients with metastatic adenocarcinoma of the pancreas. This FOLFIRINOX regimen involves the administration, every two weeks, of a dose of 180 mg/m^2 conventional irinotecan, 85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin, and 400 mg/m^2 5-fluorouracil as bolus followed by 2400 mg/m^2 5-fluorouracil as slow infusion (see D10, page 1819, section "Treatment").

Document D3 describes modified versions of the FOLFIRINOX regimen of document D10, including the so-called mFOLFIRINOX regimen. In this regimen, the bolus dose of 5-fluorouracil is omitted (see page 855, reference 18 to document D28), which according to the reference to document D28 in document D3 provides improved safety while maintaining efficacy in treatment of pancreatic adenocarcinoma, including metastatic disease (compare D28, title and abstract).

Taking account of the defined purpose of the subject-matter of claim 1, the Board considers the mFOLFIRINOX regimen described in document D3 a suitable starting point in the prior art. The subject-matter of claim 1 of the main request differs from this prior art in the replacement of the 180 mg/m^2 conventional non-liposomal irinotecan by 60 mg/m^2 liposomal irinotecan and the reduction of the oxaliplatin dosage from 85 mg/m^2 to 60 mg/m^2.

3.1.3 Documents D1 and D6 describe the outline for a clinical study to assess the safety/tolerability and efficacy of first-line treatment of patients with metastatic pancreatic cancer involving the combined administration of liposomal irinotecan, leucovorin and 5-fluorouracil, with or without oxaliplatin. Document D6 includes an explicit reference to the FOLFIRINOX regimen as a

standard of care option for first-line treatment of patients with metastatic pancreatic cancer.

The described outline foresees two parts. In part 1 the safety and tolerability of the combination of liposomal irinotecan, leucovorin, 5-fluorouracil and oxaliplatin is to be investigated. Part 2 concerns a randomised efficacy study to compare combinations comprising liposomal irinotecan, leucovorin and 5-fluorouracil with and without oxaliplatin versus the combination of nab-paclitaxel with gemcitabine.

Documents D1 and D6 do not provide any results from the study.

The subject-matter of claim 1 of the main request differs from the information presented in documents D1 and D6 at least in the definition of treatment which is effective and tolerable in the relevant group of patients. Documents D1 and D6 furthermore do not identify the specific dosages intended to be administered in the study to be carried out.

3.2 Objective technical problem

3.2.1 The clinical results reported in the patent demonstrate the tolerability of the treatment as defined in claim 1 of the main request. Moreover, the post-published document D18 confirms the efficacy and tolerability of the defined combination therapy.

Whilst the opponents denied during the appeal proceedings that any particular effect of the subject-matter of claim 1 of the main request had been demonstrated with respect to the mFOLFIRINOX regimen of document D3, the opponents did not contest that the

claimed subject-matter provides effective and tolerable alternative therapy for the defined patients with respect to the known treatment.

Starting from document D3, the objective technical problem may therefore be formulated, at least, as the provision of further first-line chemotherapy for metastatic adenocarcinoma of the pancreas which is effective and tolerable. As documents D1 and D6 do not report any results of the described clinical study, no different formulation of the objective technical problem results when starting from the outline of the study described in documents D1 and D6.

3.3 Assessment of the solution

3.3.1 In view of the identified objective technical problem, the question to be answered is, irrespective of the starting point in the prior art, whether the skilled person would have derived from the prior art a reasonable expectation that the claimed dosage regimen is effective and tolerable in the treatment of the defined group of patients.

3.3.2 Document D3 describes, in addition to the omission of the administration of the bolus of 5-fluorouracil, a variety of further possible modifications, including reductions of the dose of irinotecan (down to 64% = 115 mg/m^2), oxaliplatin (down to 50% = 43 mg/m^2) and the slowly infused 5-fluorouracil (down to 2000 mg/m^2), which retain efficacy and reduce toxicity (see pages 855-856, summarised in Table 2). Document D3 refers in this context to documents D29-D33. However, none of these modifications relates to the use of liposomal irinotecan. Neither document D3 nor the cited documents D29-D33 could therefore have provided the

skilled person with any reasonable expectation that the dosage regimen as defined in claim 1 of the main request, which includes the administration of liposomal irinotecan, would be effective and tolerable.

3.3.3 Documents D8, D13, D17 and D27 report favourable efficacy and tolerability of liposomal irinotecan in preclinical settings. Document D8 refers in this context specifically to combinations of liposomal irinotecan with 5-fluorouracil and oxaliplatin.

Notably, document D17 reports that in normal mice the maximum tolerated dose of liposomal irinotecan is >320 mg/kg, compared to 80 mg/kg for non-liposomal irinotecan (see D17, abstract). However, the phase I clinical study described in document D14 established that the maximal tolerated dose of liposomal irinotecan is 120 mg/m^2, when administered in monotherapy every three weeks to patients with advanced tumors (see D14, abstract). This clinically tolerable dose for liposomal irinotecan is significantly lower than the established dose of conventional irinotecan in the mFolfirinox regimen. Accordingly, it was evident to the skilled person that the favourable tolerability of liposomal irinotecan observed in preclinical settings is not predictive of its tolerability as part of the combination treatment in a clinical setting defined in claim 1 of the main request.

The results from the experiments with liposomal irinotecan in the preclinical settings of documents D8, D13, D17 and D27 did therefore not provide the skilled person with any reasonable expectation that the dosage regimen as defined in claim 1 of the main request would be effective and tolerable.

3.3.4 Document D12 reports positive results from a clinical trial involving the administration of 120 mg/m^2 liposomal irinotecan ("PEP02"/"MM-398") as monotherapy once in three weeks in patients with refractory metastatic pancreatic cancer that had previously received gemcitabine-based therapy (see D12, abstract).

Document D14 presents the results of a Phase I study investigating the toxicity and pharmacokinetics of liposomal irinotecan ("PEP02"/"MM-398") as monotherapy in advanced solid tumor patients. The results include the reported maximum tolerated dose of 120 mg/m^2 for the liposomal irinotecan when administered every three weeks (see D14, abstract) and the AUC of SN-38 (the active metabolite of irinotecan) resulting from administration of the 120 mg/m^2 liposomal irinotan being "roughly" comparable to the AUC resulting from 300-350 mg/m^2 non-liposomal irinotecan (see D14, page 584, left column). Document D14 further states (see D14, page 584, left column): "The lower toxicity profile potentially makes PEP02 a better agent to combine with other cytotoxic agents, i.e., 5-fluorouracil and folinic acid, and/or targeted agents, i.e., bevacizumab or cetuximab for advanced colorectal cancer. However, the optimal dosages of PEP02 for such combinations remain to be determined."

Neither document D12 nor document D14 provide any information as to the tolerability of the combination of liposomal irinotecan with oxaliplatin in addition to 5-fluorouracil and leucovorin (=folinic acid) in patients with metastatic pancreatic cancer, let alone in first-line treatment as defined in claim 1 of the main request. Notably, the documents refer to a tolerable dose of 120 mg/m^2 for the liposomal irinotecan when administered once every three weeks,

which corresponds mathematically to a dose of 40 mg/m^2 once weekly or a dose of 80 mg/m^2 once every two weeks. In contrast, the patent demonstrates that such a dose of 80 mg/m^2 of liposomal irinotecan, administered once in two weeks in combination with oxaliplatin, 5-fluorouracil and leucovorin, is not tolerated, even if the dose of oxaliplatin is reduced to 60 mg/m^2 with respect to its dose of 85 mg/m^2 as typically used in the mFOLFIRINOX regimen.

Documents D12 and D14 do therefore not provide the skilled person with any reasonable expectation that the dosage regimen as defined in claim 1 of the main request would be effective and tolerable.

3.3.5 Document D2 reports positive results from a clinical trial involving the administration of 80 mg/m^2 liposomal irinotecan ("MM-398")in combination with 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 leucovorin once every two weeks to patients with metastatic pancreatic adenocarcinoma after prior gemcitabine-based treatment. Document D4 confirms that the use of such a dose of liposomal irinotecan ("ONIVYDE") in combination with 5-fluorouracil and leucovorin has been approved for the treatment of metastatic adenocarcinoma of the pancreas in patients that have previously received gemictabine-based therapy. Compared to the subject-matter of claim 1 of the main request, the dosage regimen described in documents D2 and D4 involves a higher dose of liposomal irinotacan, but without the administration of oxaliplatin and only as second-line treatment instead of first-line treatment.

The skilled person could therefore, on the basis of documents D2 and D4, not reasonably expect the

treatment as defined in claim 1 of the main request to be effective and tolerable.

3.3.6 The review articles D25, D5 and D7 refer to the known favourable efficacy and tolerability for liposomal irinotecan ("Nanoliposomal CPT-11"/"PEP02"/"MM-398") in a preclinical setting as well as the previously reported positive clinical results obtained with liposomal irinotecan (120 mg/m^2 every 3 weeks monotherapy or 80 mg/m^2 every 2 weeks in combination with 5-fluorouracil and leucovorin) in patients that had previously received gemcitabine-based therapy (see D25, pages 188-191; D5, page 462, D7, see under "Pharmacokenetics", "Preclinical research" and "Clinical trials of Onivyde..."). The treatments described in documents D25, D5 and D7, whether administered as monotherapy or within a combination regimen, involved a calculated dose of 40 mg/m^2 liposomal irinotecan per week instead of a dose of 30 mg/m^2 per week as calculated for claim 1 of the main request. Moreover, the treatment reported in documents D25, D5 and D7 did not include the administration of oxaliplatin.

For the reasons set out in sections 3.3.3-3.3.5 above, this known information did not provide the skilled person with a reasonable expectation that the treatment as defined in claim 1 of the main request would be effective and tolerable.

Document D5 further raises the question whether the optimised pharmacokinetics and safety profile of liposomal irinotecan would make it an ideal substitute for irinotecan in the first-line FOLFIRINOX regimen, which would need to be answered by future clinical trials (see D5, pages 462-463, bridging paragraph).

Document D7 also considers the possibility to use liposomal irinotecan as a safe therapeutic alternative for irinotecan ("could present a safe therapeutic option"; see D7, page 3005, left column) and refers specifically to the study of documents D1/D6 (NCT02552991) as actively recruiting patients (see D7, pages 3005-3006, bridging sentence). However, on the basis of this further speculation in documents D5 and D7, the skilled person could not reasonably expect that the treatment as defined in claim 1 of the main request would be effective and tolerable.

3.3.7 As noted in section 3.1.3 above, documents D1 and D6 merely describe the outline for a clinical trial and do not report any results. The documents indicate that the design of the trial foresees a first stage to investigate the tolerability of combinations of liposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin and to confirm the target dose. The subsequent second stage foresees a comparison of the efficacy of combinations including liposomal irinotecan, 5-fluorouracil and leucovorin, with or without oxaliplatin, against the efficacy of the combination of nab-paclitaxel with gemcitabine in a subsequent stage. However, in the absence of any indication in documents D1 and D6 of actually tolerable doses for the combined administration of liposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin, these documents do not provide the skilled person with any further basis to reasonably expect that the treatment defined in claim 1 of the main request would be effective and tolerable.

3.3.8 The opponents contended that the skilled person would, in view of the positive preclinical and clinical results reported for liposomal irinotecan reported in

the prior art, in any case be motivated to replace conventional irinotecan in the mFOLFIRINOX regimen of document D3 by liposomal irinotecan for the first-line treatment of patients with metastatic pancreatic cancer. The subsequent determination of the effective and tolerable doses, as defined in claim 1 of the main request, would in their view only be a matter of routine dose optimisation. As demonstrated by documents D3 and D9, such dose optimisation was conventional in the prior art and could, in line with the considerations in T 2506/12, T 1760/08, T 1409/06 and T 237/15, not support an inventive step.

However, the motivation to replace conventional irinotecan in the mFOLFIRINOX regimen with liposomal irinotecan cannot realistically be considered in isolation from concerns about the effective and tolerable doses of liposomal irinotecan and the other agents in the resulting combination therapy.

As explained in section 3.3.2 above, document D3 discusses only modifications to the FOLFIRINOX regimen involving dose reductions of conventional irinotecan, oxaliplatin and 5-fluorouracil to improve the tolerability of the original FOLFIRINOX regimen. Consequently, document D3 could not provide the skilled person with any reasonable expectation regarding effective and tolerable doses if the conventional liposomal irinotecan were to be replaced by liposomal irinotecan. Document D9 states in general terms that synergistic drug combinations for cancer treatment can yield favourable outcomes at low doses, which potentially mitigates toxicity and other side effects associated with high-dose monotherapies (see page 1045, right column, and page 1046, right column). Document D9 does thereby not present any further information from

which the skilled person could draw any reasonable expectation regarding effective and tolerable doses in combination treatment as defined in claim 1 of the main request.

The case in T 2506/12 concerned a combination of two drugs which were well tolerated as monotherapies in human patients and which exhibited distinct dose-limiting toxicities across most cancer types (see T 2506/12, reasons 3.12). In contrast, the combination of irinotecan with oxaliplatin, 5-fluorouracil, and leucovorin in the FOLFIRINOX regimen was known to cause problematic side effects, which was why the modified FOLFIRINOX regimens discussed in document D3 were developed in the first place (see D3, page 855, left column). Moreover, the prior art provided the skilled person with no information allowing the assessment of the combined toxicity of liposomal irinotecan with the other components of the FOLFIRINOX regimen, in particular oxaliplatin. Notably, whilst a dose of 80 mg/m^2 liposomal irinotecan in combination with 5-fluorouracil and leucovorin was known to be tolerated in second-line treatment of patients with metastatic pancreatic cancer (see D2 and D4 discussed in section 3.3.5 above), the experimental results in the patent (see Example 4) demonstrated that such a dose of 80 mg/m^2 liposomal irinotecan is not tolerated in a modified FOLFIRINOX regimen, even if the oxaliplatin dose therein is reduced to 60 mg/m^2. The conclusions in T 2506/12 do therefore not further support the opponents' case.

In T 1760/08, T 1409/06 and T 237/15 the competent Boards considered that, in the given situations, the mere optimisation of the dose of a single agent for providing a known or obvious therapeutic did not

involve an inventive step (see T 1760/08, reasons 3.6; T 1409/06, reasons 3.2.1; T 237/15, reasons 4.6.1). However, as explained in T 2015/20, even the provision of an optimised dose of a single agent with regard to efficacy and side effects may, depending on the circumstances, represent the unexpected outcome of a study for finding optimised effectiveness in the absence of side effects, rather than merely the obvious result of routine experimentation (see T 2015/20, reasons 3.5). In the present case, the dosage regimen of claim 1 of the main request involves the combination of four active agents. As pointed out above, the conventional irinotecan with oxaliplatin, 5-fluorouracil and leucovorin in the FOLFIRINOX regimen was known to be associated with problematic side effects, whereas the prior art provided the skilled person with no information regarding the combined toxicity from liposomal irinotecan with the other components of the FOlFIRINOX regimen, in particular oxaliplatin, as defined in claim 1 of the main request. The conclusions in T 1760/08, T 1409/06 and T 237/15 do therefore also not further support the opponents' case.

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request involves an inventive step.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated