

***CSPC Pharmaceutical Group Limited, et al.
v. Ipsen Biopharm Ltd.
IPR2025-00505***

Oral Argument - May 19, 2026

**Petitioners' Oral Argument
Demonstratives**

The Challenged Claims of the '552 Patent

Methods of treating metastatic pancreatic cancer in a human who has not previously been treated with an anti-cancer agent (first-line treatment) with a specific combination of chemotherapy drugs:

- (1) 60 mg/m² of liposomal irinotecan,
- (2) 60 mg/m² oxaliplatin,
- (3) 400 mg/m² of leucovorin, and
- (4) 2400 mg/m² of 5-fluorouracil ("5-FU").

But PO did not invent this combination of drugs to treat first line metastatic pancreatic cancer.

By this time, the **gold standard** for treating first line metastatic pancreatic cancer patients was already something called FOLFIRINOX, which is short for **F**olonic Acid (leucovorin), **5-FU**, **i**rinotecan, and **o**xaliplatin, which was disclosed in the prior art by Conroy and its protocol/appendix, and Mahaseth.

Challenged Claims v. FOLFIRINOX

Claim 1	FOLFIRINOX (Conroy and Mahaseth)
<p>1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:</p> <ul style="list-style-type: none">a. 60 mg/m² of liposomal irinotecan,b. 60 mg/m² oxaliplatin,c. 200 mg/m² of the (1)-form of leucovorin or 400 mg/m² of the (I+d) racemic form of leucovorin, andd. 2,400 mg/m² 5-fluorouracil; <p>to treat the metastatic adenocarcinoma of the pancreas in the human patient.</p>	<p>A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:</p> <ul style="list-style-type: none">a. 180 mg/m² of irinotecan,b. 85 or 60 mg/m² oxaliplatin,c. 400 mg/m² of racemic form of leucovorin,d. 2,400 mg/m² 5-fluorouracil; <p>to treat the metastatic adenocarcinoma of the pancreas in the human patient. (Conroy and Mahaseth each teach the discontinuation of the 400 mg/m² bolus of 5-FU.)</p>

Challenged Claims are liposomal irinotecan applied to FOLFIRINOX

But much was already known about liposomal irinotecan

Claim 1	Bayever
<p>1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:</p> <p>a. 60 mg/m² of liposomal irinotecan, b. 60 mg/m² oxaliplatin, c. 200 mg/m² of the (I)-form of leucovorin or 400 mg/m² of the (I+d) racemic form of leucovorin, and d. 2,400 mg/m² 5-fluorouracil;</p> <p>to treat the metastatic adenocarcinoma of the pancreas in the human patient.</p>	<p>A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:</p> <p>a. 60 or 80 mg/m² of liposomal irinotecan, b. 400 mg/m² of racemic form of leucovorin, c. 2,400 mg/m² 5-fluorouracil;</p> <p>to treat the metastatic adenocarcinoma of the pancreas in the human patient.</p>

Challenged Claims are obvious over the combination of FOLFIRINOX and Bayever

PO tries to complicate the issues by saying that the POSA would be confronted with making 4 simultaneous changes over the prior art which were unpredictable.

But that is not reasonable and not how the POSA would confront this issue.

The single combination of FOLFIRINOX (Conroy and Mahaseth) with Bayever discloses every element of the Challenged Claim.

Challenged Claims	Prior art
Methods of treating metastatic pancreatic cancer in a human who has not previously been treated with an anti-cancer agent (first-line treatment) with a specific combination of chemotherapy drugs:	FOLFIRINOX and Bayever each teach this.
(1) 60 mg/m2 of liposomal irinotecan,	Bayever teaches this.
(2) 60 mg/m2 oxaliplatin,	FOLFIRINOX teaches this.
(3) 400 mg/m2 of leucovorin, and	Bayever and FOLFIRINOX each teach this.
(4) 2400 mg/m2 of 5-fluorouracil (“5-FU”).	Bayever and FOLFIRINOX each teach this.

There was strong motivation to combine these references

- Although the gold standard, FOLFIRINOX was known to have liabilities based on its toxicity
- Liposomal irinotecan was developed to be a better irinotecan to provide better efficacy with less toxicity
- Prior art references (Saif and Ko) specifically suggested replacing irinotecan with liposomal irinotecan in FOLFIRINOX

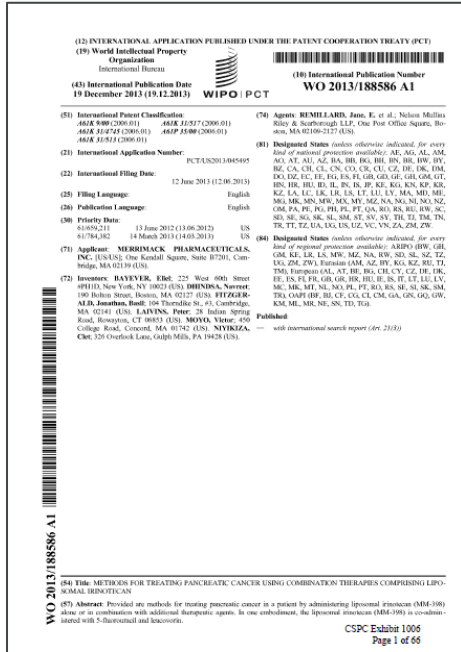
FOLFIRINOX was known to have liabilities based on its toxicity

Mahaseth (Ex. 1005) at 1: “The FOLFIRINOX regimen was associated with significantly higher toxicity including myelosuppression, fatigue, diarrhea, and vomiting. The trial included a heavily selected group of patients with relatively younger age, an excellent performance status, and a high proportion of tumors in the pancreatic body or tail. The toxicity profile and the patient selection raised the concerns whether the results of the trial would be generalizable to a nontrial setting and to patients who have tumors in the pancreatic head requiring biliary stents.”

Ratain Declaration (Ex. 1002) at ¶67: “However, FOLFIRINOX had its drawbacks, including the potential for life-threatening (and even fatal) toxicity, yet with only a small proportion of patients surviving even two years. (Ex. 1003, FIG. 1A; Ex. 1041, Table 1.) For example, FOLFIRINOX was associated with high rates of severe and life-threatening diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory neuropathy. (Ex. 1003 at 8; Ex. 1041 at 3; Ex. 1042 at 1.) Given these toxicities, a POSA was motivated to modify FOLFIRINOX. In fact, modifications to FOLFIRINOX were common. (See, e.g., Ex. 1041, Ex. 1042.)”

’552 Patent (Ex. 1001) Background (col. 1:50-57): “During the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (FOLFIRINOX). However, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status (i.e. ECOG performance score of 0 or 1).”

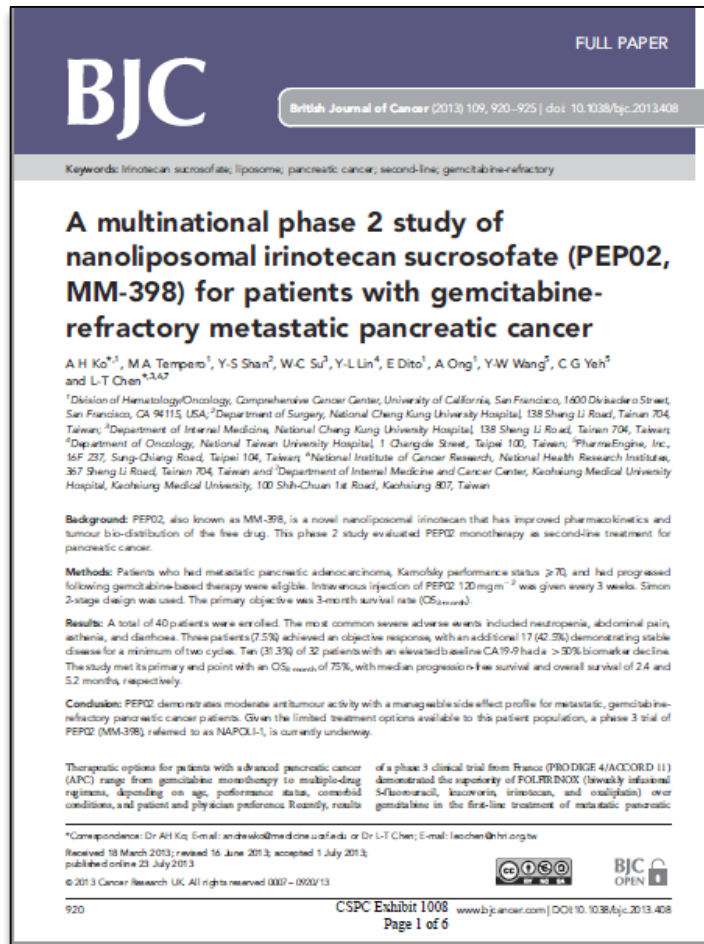
Liposomal irinotecan was developed to be a better irinotecan to deal specifically with toxicity issues



Bayever (Ex. 1006)

- “Combination therapies including folinic acid (leucovorin or levoleucovorin), 5-fluorouracil, and irinotecan (FOLFIRI), **folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX)**..are also used to treat some pancreatic cancers.” *Id.* at 1 (emphasis added).
- “The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug...These drug properties contribute to the **marked heterogeneities in efficacy and toxicity** observed clinically with irinotecan. *Id.* at 2 (emphasis added).
- “Thus, there is an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer. **The disclosed invention addresses this need and provides other benefits.**” *Id.* at 2-3 (emphasis added).
- “This stable liposomal formulation of irinotecan has **several attributes that may provide an improved therapeutic index**. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process This local bioactivation is believed to result in **reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor.**” *Id.* at 9. (emphasis added).

Ko et al. (2013)



Ko (Ex. 1008)

“PEP02 (also known as MM-398) is irinotecan sucrosfate encapsulated in a liposome drug delivery system. This stable nanoliposomal formulation has been shown in preclinical studies to improve pharmacokinetics and tumour bio-distribution of both irinotecan and its active metabolite SN-38 when compared with the free form of the drug, with less accumulation in many of the target organs associated with toxic side effects. PEP02 also demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model (Hann et al, 2007).” *Id.* at 2.

Phase 2 study. “The study met its primary end point with an OS3-month of 75%, with median progression-free survival and overall survival of 2.4 and 5.2 months, respectively.” *Id.* at 1.

“Additional studies may explore **this drug’s potential role in the first-line setting and as part of combination regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.**” *Id.* at 5. (emphasis added).

Saif et al. (2014)



Saif (Ex. 1007)

Phase III study: “On May 1st, 2014, Merrimack Pharmaceuticals, Inc. (Cambridge, MA, USA) announced that the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and leucovorin alone [1].” *Id.* at 1.

“The results of the NAPOLI-1 study are exciting, as currently FDA has approved no regimen for secondline treatment of pancreatic cancer. While it offers a new regime for our patients, the study also brings new questions such as:

1. Reformulation of an old drug can produce different results. This is in consistency with the results of nab-paclitaxel and gemcitabine study, which tested a new form of paclitaxel and produced positive outcome. [2]
2. Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment? [3, 4]
3. It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398. However, bone marrow toxicity has to be borne in mind.” *Id.* (emphasis added).

Dr. Ratain's Expert Declaration



Dr. Mark Ratain

Expert Declaration
(Ex. 1002) at ¶¶ 235-236

Petition (Paper 1) at 32, 42.

235. First, a POSA would have been motivated to use liposomal irinotecan (MM-398) in place of the free irinotecan in Conroy/FOLFIRINOX. As an initial matter, Patent Owner admits that irinotecan and liposomal irinotecan are, from a qualitative safety standpoint, considered similar. (Ex. 1015 at ¶¶ 231-235; *see also id.* at 225 (admitting they similarly lack drug interaction with 5FU/LV); Ex. 1006 at 21 (same).) Therefore, a POSA would have considered this substitution. Ko and Saif, discussed in Sections VIII (E-F) above, also support this understanding and/or provide a POSA with additional motivation to combine, i.e., they suggest studying and/or replacing free irinotecan with liposomal irinotecan. Consistently, Saif also specifically states that because of these encouraging results of using MM-398 in second-line therapy, “it seems **logical** to test this drug/regimen further: **will it be worth replacing irinotecan in FOLFIRINOX with MM-398.**” (Ex. 1007 at 1 (emphasis added).) As with Saif, Ko also suggested that given the emergence of FOLFIRINOX as a first-line standard in advanced pancreatic cancers, MM-398 should be further explored in the first-line therapy setting. (Ex. 1008 at 5.)

236. In addition, Bayever suggests such a substitution and provides even further motivation to combine, as Bayever and other prior art disclosed evidence of superiority of liposomal irinotecan to irinotecan. (*See* Ex. 1006 at 11, 19-21, 25; Ex. 1008 at 2-5; Exs. 1058-1059.) Bayever suggests its liposomal formulation of irinotecan “has several attributes that may provide an improved therapeutic index,” therapeutic synergy, or “superior outcome.” (*Id.* at 5, 10, 16.) Bayever disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims (60 mg/m²) along with the same claimed doses of leucovorin (i.e., 200 mg/m² of the (1)-form or 400 mg/m² of the (1+d) racemic form) and 5-FU (i.e., 2,400 mg/m²). (*Id.* at 4, 6, 14-15, 26-27, 32-33, 39-42, 54, 63.)

There was a reasonable expectation of success

- FOLFIRINOX (Conroy and Mahaseth) was the “gold” standard of care for treating first-line metastatic pancreatic cancer patients.
- Liposomal irinotecan (Bayever, Ko, and Saif) was shown to have superior preclinical and clinical properties over free irinotecan.
- Ko (2013) – Phase II clinical study showing that liposomal irinotecan improved OS.
- Saif (2014) – Phase III clinical study showing that liposomal irinotecan improved OS.
- Oberstein applied an overly strict standard: whether it was “more likely than not” that a POSA would expect a benefit that is “statistically significant” when “compared to the old regimen.” (Ex. 1210 at 335:14-356:10.)
- The Board has rejected such “mistaken” assertions that the expectation be tied to “more favorable results.” *Celltrion*, IPR2017-01095, Paper 60 at 55. “[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” *Id.* (quoting *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)).
- Where each component of the claimed invention had known efficacy to treat the condition recited in the claim, there is a reasonable expectation of success. *See Nalpropion Pharms., Inc. v. Actavis Lab’ys FL, Inc.*, 934 F.3d 1344, 1354-56 (Fed. Cir. 2019) (finding reasonable expectation of success when both drugs in combination treatment were known to affect the endpoint and combination and dose ranges taught or suggested in art).

Conroy and its Protocol/Appendix disclose that patients received 60 mg/m² of oxaliplatin

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

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ABSTRACT

Background
Data are lacking on the efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer.

Methods
We randomly assigned 342 patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating a greater severity of illness) to receive FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area, irinotecan, 180 mg per square meter, fluorouracil, 400 mg per square meter, and leucovorin, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 2-hour continuous infusion, over 2 weeks) or gemcitabine at a dose of 1000 mg per square meter weekly for 7 of 10 weeks and then weekly for 3 of 4 weeks. Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival.

Results
The median overall survival was 11.3 months in the FOLFIRINOX group as compared with 8.8 months in the gemcitabine group (hazard ratio for death, 0.59; 95% confidence interval, 0.43 to 0.81; P<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 5.3 months in the gemcitabine group (hazard ratio for disease progression, 0.65; 95% CI, 0.57 to 0.75; P<0.001). The objective response rate was 51.6% in the FOLFIRINOX group versus 9.6% in the gemcitabine group (P<0.001). More adverse events were noted in the FOLFIRINOX group. Sixty of 169 patients in this group had febrile neutropenia. At 6 months, 13% of the patients in the FOLFIRINOX group had a deleterious deterioration of the quality of life versus 6% in the gemcitabine group (hazard ratio, 0.45; 95% CI, 0.30 to 0.70; P<0.001).

Conclusions
As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status. (Funded by the French government and others; ClinicalTrials.gov number, NCT00120843.)

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CSPC Exhibit 1003
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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.

		Irinotecan	Oxaliplatin	Fluorouracil
Granulocytes < 1.5 x 10 ⁹ /L	Hold treatment until granulocytes ≥ 1.5 x 10 ⁹ /L (one or two weeks if necessary).	1 st occurrence: reduction of dose to 150 mg/m ² 2 nd occurrence: maintain the dose at 150 mg/m ²	1 st occurrence: no reduction of dose 2 nd occurrence: reduce the dose to 60 mg/m ²	1 st occurrence: delete bolus 5FU

Platelets < 75 x 10 ⁹ /L	Hold the treatment until recovery (platelets ≥ 75 x 10 ⁹ /L).	1 st occurrence: no reduction of dose 2 nd occurrence:	1 st occurrence: reduce the dose to 60 mg/m ² 2 nd occurrence:

Diarrhea grade 3-4 or Diarrhea + fever and/or neutropenia grade 3-4	1 st occurrence: reduce the irinotecan dose to 150 mg/m ² and delete the bolus 5FU dose 2 nd occurrence: reduce also the oxaliplatin dose to 60 mg/m ² and reduce the dose of continuous 5FU to 75 % of the original dose

Febrile neutropenia Grade 4 neutropenia during more than 7 days Grade 3-4 thrombocytopenia	1 st occurrence: reduce the dose of irinotecan to 150 mg/m ² and delete the bolus 5FU dose 2 nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m ² 1 st occurrence: reduce the oxaliplatin dose to 60 mg/m ² and the continuous 5-FU dose to 75 % of the original dose

Based on certain adverse events (like haematological toxicities, neutropenia, diarrhea), patients were given dose reductions of oxaliplatin from 85 mg/m² to 60 mg/m². Ex. 1004, 16-18, Ex. 1017, 3-7; Petition (Paper 1) at 16.

“The median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, **78%**, and 100%.” Ex. 1003 at 4 (emphasis added); Petition (Paper 1) at 15.

Dr. Ratain's Expert Declarations



Dr. Mark Ratain

“For example, Conroy disclosed that a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m² oxaliplatin was used in the study, indicating in many patients a lower dose of oxaliplatin was administered. (Section VIII.A; Ex. 1003 at 4.) The Conroy Protocol also disclosed a dose reduction of oxaliplatin to 60 mg/m² oxaliplatin for toxicity. (Ex. 1004 at 16-18, 27.) A POSA who reviewed the results of Conroy stating that the median dose intensity of oxaliplatin was 78% and the fact that the Conroy Protocol disclosed numerous dose reductions of oxaliplatin to 60 mg/m² oxaliplatin in the event of certain toxicity incidents would have concluded **that a significant portion of patients undergoing the FOLFIRINOX trial were administered oxaliplatin 60 mg/m².**” Ratain Expert Declaration (Ex. 1002) at ¶241 (emphasis added); Petition (Paper 1) at 16.

“In fact, I further explained that the Conroy Protocol disclosed reducing the dose of oxaliplatin from 85 mg/m² to 60 mg/m² based on known toxicities and that this was ‘consistent with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m² dose and indicate **that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m² based on various toxicity events.**’” (*Id.* at ¶ 105.) Supplemental Ratain Declaration (Ex. 1200) at ¶9. (emphasis added); Petition (Paper 1) at 16.

Declaration of Ipsen's Expert – Dr. Oberstein



Dr. Oberstein admits that dose reductions of oxaliplatin to 60 mg/m² occurred and were reported in Conroy and its Appendix/Protocol.

“At most, Conroy’s disclosure of median relative dose intensity indicates that dose reductions occurred.” Ex. 2076 (Oberstein Decl.) at ¶153; POR (Paper 21) at 30.

“Accordingly, all patients in the FOLFIRINOX arm received an 85 mg/m² dose of oxaliplatin; **only patients with specific toxicity events received a lower dose of oxaliplatin.**” Ex. 2076 at ¶153 (emphasis added); POR (Paper 21) at 30-31.

“In my opinion, a POSA would understand Conroy, Conroy Protocol, and Conroy Appendix, as a whole, to teach the efficacy and safety of the study regimen, **which comprised a starting dose** of 85 mg/m² – not the 60 mg/m² oxaliplatin dose given in adverse toxicity events....” Ex. 2076 at ¶160 (emphasis added); POR (Paper 21) at 30-31.

But the Challenged Claims are not limited to “starting doses.” Claim 1 requires administration of the claimed therapy “once every two weeks,” and dependent claims 5 and 11 require administration of the claimed drugs on “on days 1 and 15 of a 28-day treatment cycle.”

PO admitted that Challenged Claims are not limited to starting doses: “Ipsen does not argue that the claimed treatments are ‘limited to...just a starting dose.’...Rather, Ipsen argues...**that the claimed treatments comprise at least the recited starting doses** with subsequent dose reductions contemplated by the specification.” PO Sur-Reply (Paper 38) at 15.

Challenged Claims are not limited to “starting doses”

1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (1)-form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

5. The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

- After two weeks, dose can be reduced to practice this claim.
- After one full treatment cycle (28 days), dose can be reduced to practice this claim.
- This is not a method of treatment where the patient is only given one starting dose.
- That is not how chemotherapy works.
- Claims may comprise a starting dose, but it also covers subsequent doses.
- Prior art which discloses a species within a genus still renders it obvious.

Petitioners' Reply (Paper 32) at 3-4, 12.

Original claim 1 during prosecution

1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:

- a. 60 mg/m² of liposomal irinotecan,
- b. **60 or 85 mg/m² oxaliplatin**,
- c. 200 mg/m² of (l)-form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Patent Owner eliminated the higher oxaliplatin dose through the following amendment: “60 ~~or 85~~ mg/m² oxaliplatin” element to try to overcome the obviousness rejection over Conroy (Ex. 1084 at 287).

Exhibit 1084 at 60; Petition (Paper 1) at 11-12.

That is why the specification has many instances of oxaliplatin being administered at 85 mg/m², and even administered at 85 mg/m² and then reduced to 60 mg/m² because of toxicities.

Oxaliplatin

Grade 2,
persistent:
Reduce dose
from 85 mg/m²
to 60 mg/m² or
from 60 mg/m²
to 45 mg/m²
Grade 3,
recovers prior to
next cycle:
Reduce dose
from 85 mg/m²
to 60 mg/m² or
from 60 mg/m²
to 45 mg/m²
Grade 3,
persistent:
Discontinue
therapy
Grade 4:
Discontinue
therapy

'552 patent (Ex. 1001)
at Table 3, col. 32.

Dr. Ratain's Expert Opinion



Dr. Mark Ratain

Reducing the dose of oxaliplatin from 85 mg/m² to 60 mg/m² because of toxicity concerns was well within the POSA's routine skill.

"In addition, because a POSA would have been motivated to substitute MM-398 for the free irinotecan in FOLFIRINOX, an effective but toxic regimen, a POSA would have been cautious about oxaliplatin dosing. A POSA would therefore have considered lowering the oxaliplatin dose through routine optimization...Based on the disclosures in the prior art, a POSA would have understood that doses of oxaliplatin in the range of 60-80 mg/m² were generally considered both therapeutically effective and tolerable, each of which would be less toxic than the 85 mg/m² FOLFIRINOX dose. Because most dosing is done in increments of 5 mg/m², a POSA would have a limited number of tolerable doses to choose from and found any dose within that range an obvious choice. In addition, a POSA would have been aware of the 60 mg/m² dose of oxaliplatin disclosed in the Conroy protocol. (See Section VIII.B.) A POSA would have been motivated to select a dose that had already been used or tested. (See id; see also Section VIII.H (also disclosing a 60 mg/m² dose of oxaliplatin). Moreover, a POSA would have understood that other art, like Cantore, showed or suggested that these lower dose regimens, including a 60 mg/m² dose of oxaliplatin along with 60 mg/m² irinotecan, were found to be safe and effective in metastatic pancreatic cancer patients."

Dr. Ratain's Opinions are consistent with the Board's definition of "treat" and "treating"

"[T]reatment' would have more than a *de minimis* therapeutic benefit of efficacy for the patient being treated...To the extent the Patent Owner's position would require some particular degree of clinical efficacy, however, we do not find that position supported by the evidence. We need not address the exact degree of benefit or efficacy obtained, as the level of clinical efficacy is not a claim limitation." Institution Decision (Paper 13) at 14.



139. I use the terms "treat" and "treating" in a similar way in my own every day practice. When administering "treatment" to metastatic pancreatic cancer patients, the goal is always that such treatment will have more than a *de minimis* therapeutic benefit or efficacy for that patient. While some patients may not receive a therapeutic benefit, the intention behind any treatment is for such benefit to occur.

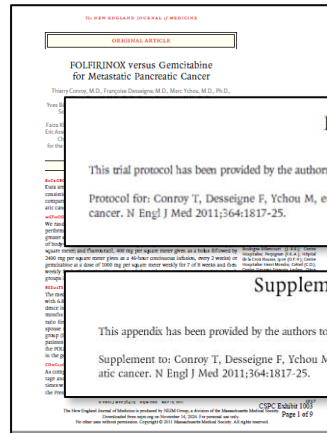
Oberstein Declaration
(Ex. 2076) at ¶139; POR
(Paper 21) at 9-10.



"[T]he terms 'treating' and 'treat' are well-understood terms in the medical community. Treating a patient is always performed in an attempt, or with the intent, to cause therapeutic improvement in the patient."

Ratain Declaration (Ex. 1002) at ¶¶ 18-20; Petition (Paper 1) at 27.

PO and Oberstein erroneously apply an anticipation standard to try to divide and conquer



Protocol

This trial protocol has been provided by the authors to give readers additional information about the trial.

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Supplement to: Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-25.

For Conroy and its protocol/appendix, where is liposomal irinotecan?



For Bayever, Ko, and Saif, where is oxaliplatin?

- PO and Oberstein resort to a piecemeal application of obviousness by looking at references in isolation to argue against a motivation to combine or reasonable expectation of success.
- They argue that a particular prior art reference, such as Bayever, Ko, or Saif, does not disclose the claimed oxaliplatin dose.
- They argue that Conroy does not disclose liposomal irinotecan.
- Too rigid - obviousness does not rely on a single reference disclosing all elements.
- The Board correctly acknowledged that *KSR* demands that “the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” Paper 13 at 37 (quoting *KSR*, 550 U.S. at 416).

PTAB has invalidated combination cancer treatment patents where each of the claimed drugs within the combination was already known to treat cancer

- *Genome & Co. v. Univ. of Chi.*, PGR2019-00002, Paper 40 at 44 (PTAB Apr. 14, 2020) (“Given the teachings of the reference that both [agents] exhibit an anti-tumor effect, we agree with Petitioner that it would have been obvious to combine the two agents to treat cancer.”);
- *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01168, Paper 59 at 23 (PTAB Oct. 31, 2018) (holding the claimed method simply adds rituximab to the Moreau regimen and “amounts to no more than ‘the predictable use of prior art elements according to their established functions.’”);
- *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 60 at 55 (PTAB Oct. 4, 2018) (method to treat low grade NHL with rituximab and CVP chemotherapy found obvious where claim simply substituted one known and useful chemotherapy for treating NHL for another).

This case is not about simultaneously substituting 4 new elements; these are dosing claims

As Dosing Claims, the Challenged Claims are particularly vulnerable to obviousness

Pfizer v. Apotex, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (claims are obvious “when the optimization of a range or other variable within the claims [] flows from the ‘normal desire of scientists or artisans to improve upon what is already generally well known’...our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious”).

Genentech, Inc. v. Sandoz Inc., 55 F.4th 1368 (Fed. Cir. 2022) (“varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice.”).

Amgen Inc. v. Sandoz Inc., 66 F.4th 952, 968 (Fed. Cir. 2023) (“Varying dose in response to the occurrence of side effects is well-known and obvious to the skilled artisan.”).

ImmunoGen, Inc. v. Vidal, 653 F. Supp. 3d 258, 294 (E.D. Va. 2023) (claims found obvious because the POSA could change the dose to avoid known toxicities).

Ipsen and Oberstein Admit that Dose Modifications to FOLFIRINOX were routine in the prior art



“Overall, the studies of the modified FOLFIRINOX regimens demonstrate that clinicians were willing to make modifications to the original regimen for each of the four components, including oxaliplatin and leucovorin, in order to address toxicity concerns or to treat sensitive patient populations, provided efficacy was maintained.” Oberstein Decl. (Ex. 2076), ¶ 61; POR (Paper 21) at 5.

Oberstein Declaration’s Appendix B (exemplary prospective and retrospective studies evaluating modified FOLFIRINOX regimens) showed over a dozen examples of modified reduced dose regimens that were published or being conducted prior to the August 21, 2015 effective filing date of the Challenged Claims. Ex. 2076, Appendix B; Petitioner’s Reply (Paper 32) at 7.

APPENDIX B

Reference Name and Year Published	Regimen Administered	Modification From Standard FOLFIRINOX	Treatment Administered In Prior / Award-Like Patients	Conclusion
Prospective Studies				
Valleri 2012				
James 2014				
Shen 2016				
Troiano 2017				
Li 2017				
Chen 2018				

Reference Name and Year Published	Regimen Administered	Modification From Standard FOLFIRINOX	Treatment Administered In Prior / Award-Like Patients	Conclusion
Falkner-Hewes 2010	Oxaliplatin 55 mg/m ² Irinotecan 180 mg/m ² Leucovorin 400 mg/m ² 5-FU (bolus) 2,400 mg/m ² 5-FU (bolus) 0 mg/m ²	Reduced 5-FU (bolus)	First-line and second-line patients	"In the subgroup analysis defined by Irinotecan, no observed differences between Best. The most interesting finding is that when DSI values were <2.3 x 10 ⁹ , there were no differences between treatment received. In contrast, in the group of patients with DSI ≥2.3 x 10 ⁹ , we observed a larger OS with mFOLFIRINOX therapy."
Talbot 2011	Oxaliplatin 55 mg/m ² Irinotecan 180 mg/m ² Leucovorin 400 mg/m ² 5-FU (bolus) 2,400 mg/m ² 5-FU (bolus) 0 mg/m ²	50 mg reduced irinotecan Reduced 5-FU (bolus)	First-line	"The results of this study suggest that DSI may be useful in appropriately selecting patients who would benefit from FOLFIRINOX therapy as a more intensive than less intensive regimen." "In conclusion, we demonstrated that the prognosis of PC with peritoneal metastases was significantly improved over time with the advent of the novel combination chemotherapy regimen (OXF and mFPC). These two regimens showed a satisfactory radiologic tumor response, OS, and QOL, and were identified as an independent prognostic factor for OS."
Shen 2011	Oxaliplatin 55 mg/m ² Irinotecan 180 mg/m ² Leucovorin 400 mg/m ² 5-FU (bolus) 2,400 mg/m ² 5-FU (bolus) 0 mg/m ²	50 mg reduced oxaliplatin 50 mg reduced irinotecan Reduced 5-FU (bolus)	First-line	"In summary, we demonstrated the prognostic value of alpha-1B for both locally advanced PDC and advanced PDC. Data ID-1 was a potential marker of predicting chemotherapy response. Patients with higher alpha-1B will benefit from mFOLFIRINOX treatment. The alpha-1B test positively correlated with better OS, and was correlated with the degree of tumor ARF associated with tumor progression."

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Ipsen Ex. 2076, Page 198 of 198

New Eng J Med. 2010; 363:1111-1120. DOI: 10.1056/NEJMOA090457	
ORIGINAL ARTICLE • PANCREATIC TUMORS	
FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma	
Ernst Scharf, MD, Alexander D'Amico, MD, Ellen M. O'Reilly, MD, Maria A. Lavery, MD, Karen A. Goodman, MD, Richard Kim, MD, PhD, Laura H. Tang, MD, PhD, Michael G. Haskins, MD, Michael J. D'Amico, MD, Ronald P. DeMatteo, MD, J. Peter Kline, MD, William R. Jarnagin, MD, and Peter J. Allen, MD	
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY	
ABSTRACT Background: Reports show that FOLFIRINOX (despite for pancreatic ductal adenocarcinoma [PDAC]) results in objective response rates that are 10-fold higher than those of other regimens. The only agent to cause response and toxicity in this study was irinotecan. A patient subgroup response was observed in 25% of all patients, which was associated with ability to perform resection ($p < .004$). The median overall survival time was 11 months for the group that did not undergo resection. Conclusions: Nearly one-third of the patients who had been initially identified as having stage 3 pancreatic adenocarcinoma and had been treated with FOLFIRINOX responded radiographically and underwent resection.	
A recently completed phase 3 randomized trial for stage 4 pancreatic ductal adenocarcinoma (PDAC) identified FOLFIRINOX as superior to gemtuzumab in terms of radiographic response together with improved progression-free and overall survival. Patients who received FOLFIRINOX experienced a 10% to 15% objective response rate compared with 0% to 5% for gemtuzumab. The results of this study, which consisted of patients with stage 3 PDAC, were consistent with the results of the phase 3 trial. Conclusions: Nearly one-third of the patients who had been initially identified as having stage 3 pancreatic adenocarcinoma and had been treated with FOLFIRINOX responded radiographically and underwent resection.	
This study was presented at the American College of Surgeons Annual Meeting, October 10 to 15, 2010, San Francisco, CA.	
Disclosures: Supplementary material: The online version of this article (available at http://dx.doi.org/10.1056/NEJMOA090457) contains supplementary material, which is available to authorized users.	
© Society of Surgical Oncology 2010 DOI: 10.1007/s12032-010-9450-7 Published online: 12 June 2010 P. J. Allen, MD e-mail: allen@mskcc.org	
CSCC Exhibit 1216 Page 1 of 10	

Over 100 Memorial Sloan Kettering patients treated between 2010-2013 who received a reduced “starting dose,” “instituted at the discretion of the treating medical oncologist” of “80% of that used in [Conroy]”. Sadot (Ex. 1216) at 2; PO Sur-Reply (Paper 38) at 13.

Ratain did not employ “Impermissible Hindsight”



Q. And why did you start with FOLFIRINOX?

A. Because, in reading the claims, I said this is FOLFIRINOX but with the substitution of liposomal irinotecan.

Q. Okay. So you chose to start with FOLFIRINOX because of its similarity to the claims in the '552 patent, correct?

A. That's right.

Ex. 2073 at 27:6-13.

This is not impermissible hindsight.

“Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant’s disclosure, such a reconstruction is proper.” *In re McLaughlin*, 443 F.2d 1392,1395 (C.C.P.A. 1971) (emphasis added).

PO misunderstands what “Impermissible Hindsight” means – it does not mean that hindsight is always impermissible – hindsight is permissible as long as it does not rely only on applicant’s disclosure which was not already known in the art.

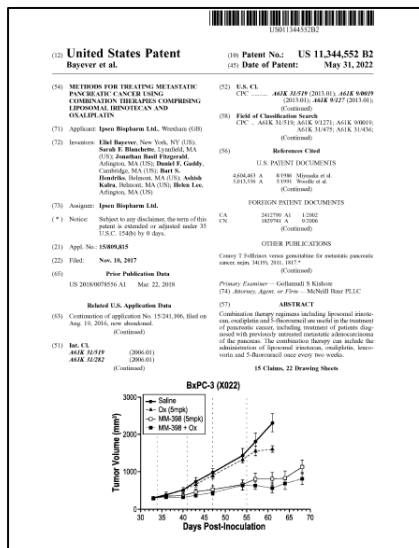
Ratain merely testified that the POSA would recognize that the claims substantially matched the prior art



- Of course, the POSA is supposed to have knowledge of the claims.
- Otherwise, how does one even make an obviousness analysis?
- The POSA is supposed to know what the invention is in order to evaluate whether it is obvious or not – the POSA is not going to start with prior art unrelated to the claims, such as radiation therapy or gene therapy as PO suggests.
- That is exactly how Patent Examiners evaluate pending claims for obviousness.

- *Micron Tech., Inc. v. Yangtze Memory Techs.*, IPR2024-0078, 2026 WL 30880, *20 (PTAB Jan. 5, 2026) (in rejecting PO’s hindsight argument and holding claims obvious, “Petitioner has referred to the [patent’s] claims, not its disclosure, to guide its assertions”);
- *Samsung Elecs. Co., Ltd. v. Netlist, Inc.*, IPR2022-00062, 2023 WL 5110321, *14 (PTAB May 8, 2023) (“We agree with Petitioner that Patent Owner’s assertion takes Petitioners’ expert’s testimony out of context, and that [Petitioners’ expert] made the combination from the point of view of a [POSA], and then considered whether the combination satisfied the claim language.”).

PO should not be allowed to immunize its Patent from prior art challenges based on FOLFIRINOX just because PO discussed FOLFIRINOX in the Background



“During the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (FOLFIRINOX). However, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status...Although the FOLFIRINOX regimen has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011, there are some concerns about the toxicity associated with FOLFIRINOX...Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules.” ’552 patent (Ex.1001), col. 1:50 – 2:6.

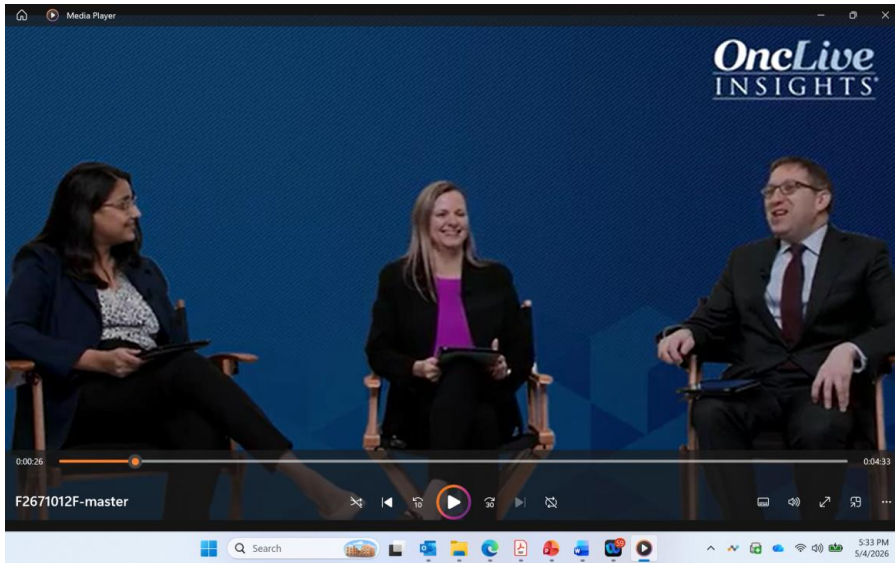
That FOLFIRINOX being prominently discussed in the Background of the ’522 patent does not remove it from the POSA’s obviousness analysis as impermissible hindsight.

That make no sense and just rewards POs who want to preemptively immunize their patents from the closest prior art.

“[T]he fact that the inventor made the claimed invention for the same reason motivated by the prior art is evidence **that the invention was obvious, not that the petitioner relied on hindsight-bias.**” *Samsung Elecs. Co., Ltd. v. Huawei Techs. Co., Ltd.*, IPR2017-01487, 2018 WL 6519544, *16 (PTAB Dec. 10, 2018) (emphasis added).

ASCO 2025 Updated OS Analysis Panel Interview

Featuring Paul E. Oberstein MD, Priyadarshini Pathak MBBS, and Tara E. Seery MD



“Correct. 100%, Umm and the comparison of course in that study [NALIRINOX] was gem nab-pac, not gemcitabine alone but I would say unlike the earlier PRODIGE [FOLFIRINOX] trial it was a larger more global more general population involved in this study so a much more heterogeneous group of patients both for the treatment and for managing side effects that makes an impact. Umm, but outside of that the regimes are quite similar there was modifications in the dosage of oxaliplatin and 5-FU compared to the original one but you know the schedule otherwise for patients was quite similar.” Panel Interview with Dr. Oberstein (Ex. 1211) at 1:31 minute:second (emphasis added); Petitioners’ Reply (Paper 32) at 1-2.

Exhibits 1211-1213.

“Yeah. And the original FOLFIRINOX I don’t think any of us use, it was challenging all of us have now use the modified version with the slightly lower the risk.” Dr. Seery

“Nobody can tolerate the full dose of FOLFIRINOX.” Dr. Pathak

“I’m impressed with those patients that initially enrolled.” Dr. Seery

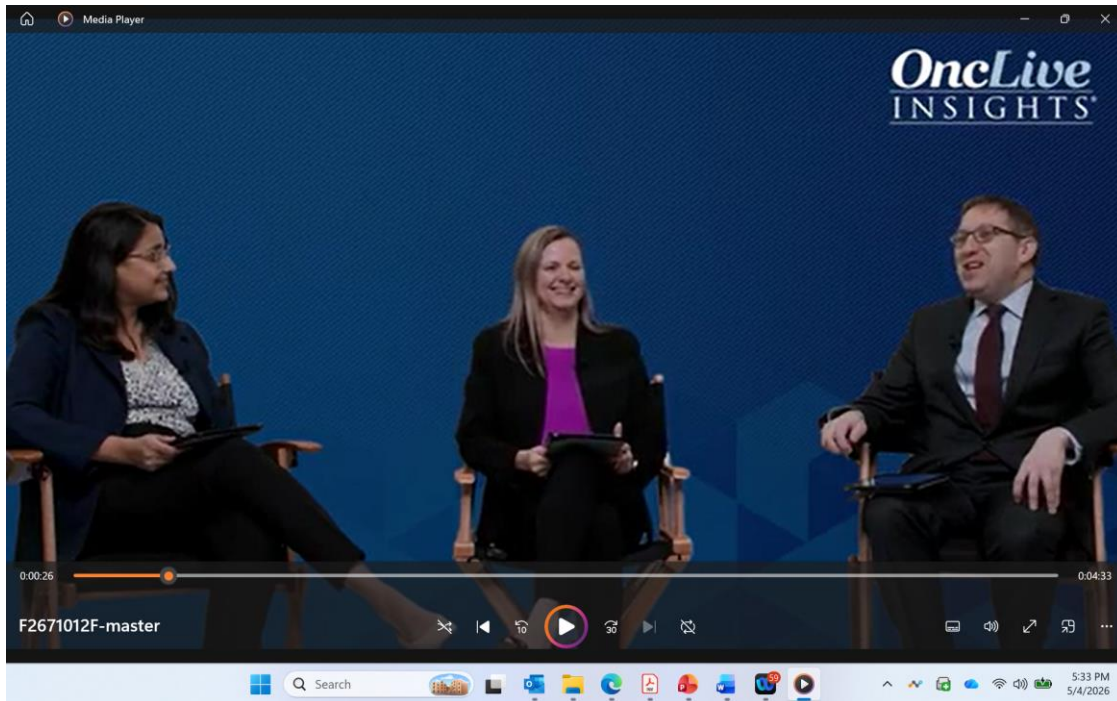
“I agree, I agree.” Dr. Pathak

Ex. 1211 at 2:05 minute:second; Ex. 1213 at 1-2; Paper 32 at 1, 21-22.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

ASCO 2025 Updated OS Analysis Panel Interview

Featuring Paul E. Oberstein MD, Priyadarshini Pathak MBBS, and Tara E. Seery MD



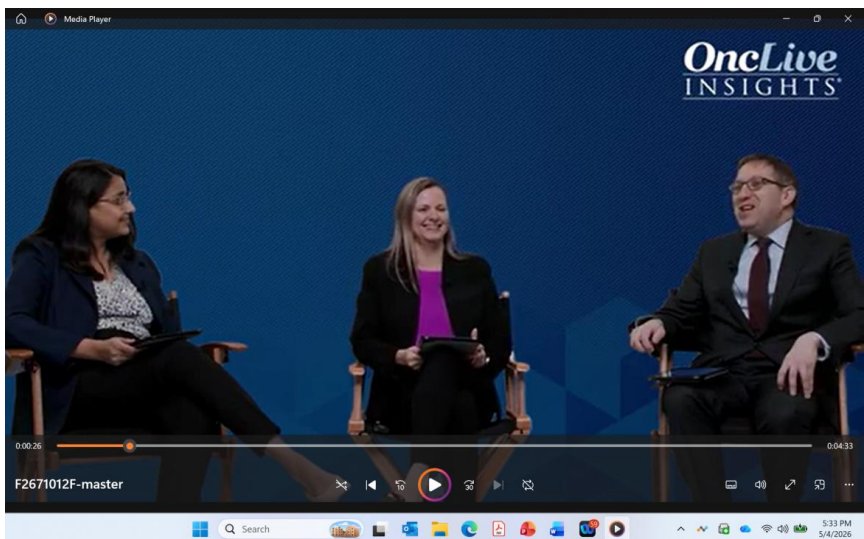
- When not testifying on behalf of PO, Dr. Oberstein publicly stated that the regimens of NALIRIFOX (Challenged Claims) and FOLFIRINOX were “quite similar.”
- All panelists emphasized the fact that the original FOLFIRINOX required dose reductions.
- Dose modifications are routine in pancreatic cancer treatment.

Exhibits 1211-1213; Petitioners’ Reply (Paper 32) at 1-2, 21-22.

ASCO 2025 Updated OS Analysis Panel Interview

Featuring Paul E. Oberstein MD, Priyadarshini Pathak MBBS, and Tara E. Seery MD

Dose modifications are routine in pancreatic cancer treatment.



“And basically the message there, which I think is very similar to what we see in practice, is that if we modify doses and we can keep patients on longer they’re going to sometimes to do better. And so it really I would say that’s our practice it gives us a lot of reinforcement to do that which is that the key thing here is not necessarily being too strong, too aggressive on day one, it’s keeping patients on treatment if it’s working. Right. And I think for a large number of patients it is working and we get a high response rate. And the question then becomes how do you stay on trial, well not on trial, how do you stay on treatment outside of the trial. And what they showed at GI ASCO is that with dose modifications in both liposomal irinotecan and oxaliplatin, patients who were able to modify and stay on trial seem to do much better.”

Ex. 1211 at 3:46 minute:second; Ex. 1213 at 2-3; Petitioners’ Reply (Paper 32) at 7, 22.

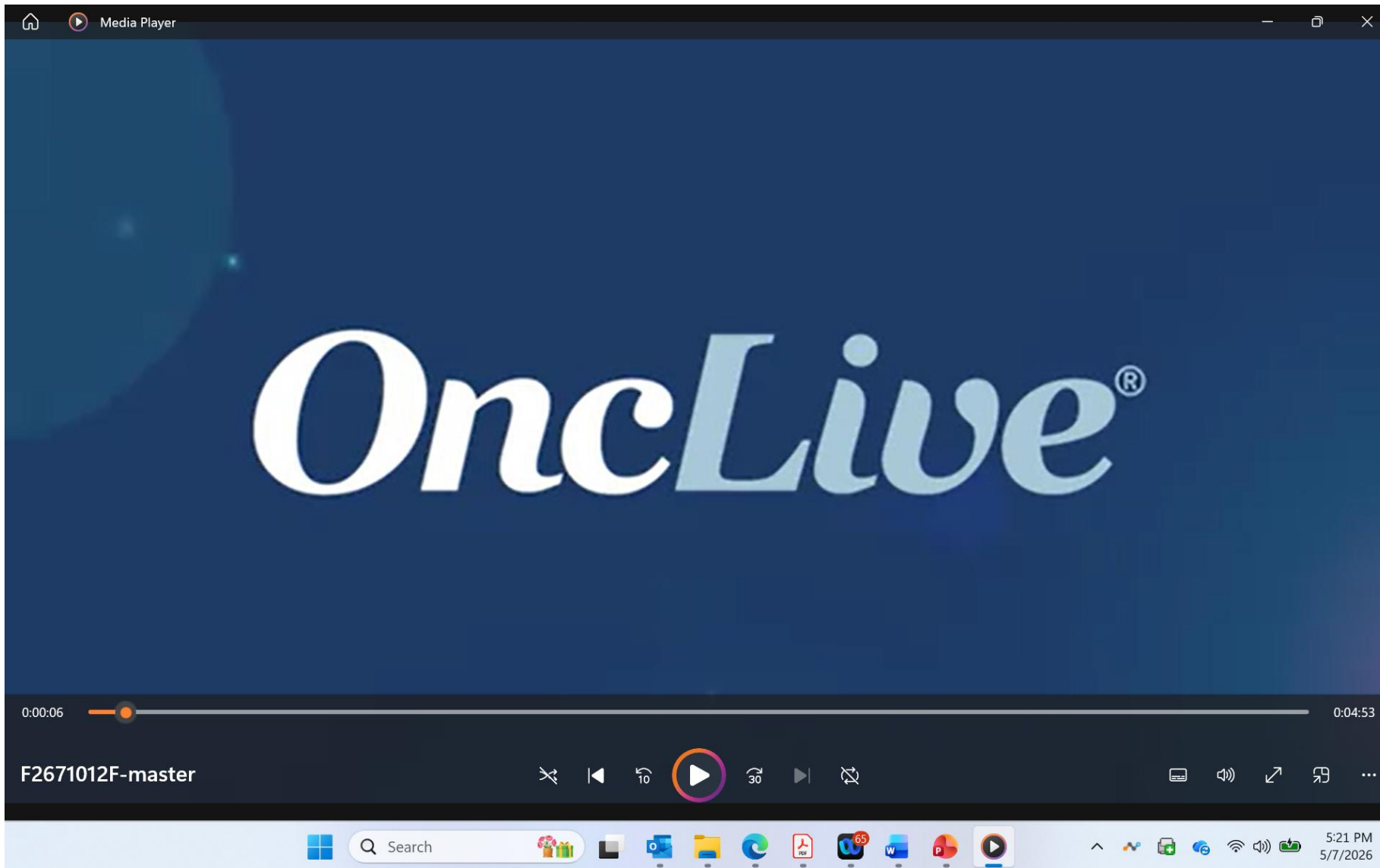


Exhibit 1211; Petitioners' Reply (Paper 32) at 1-2, 22.

Dr. Oberstein lacks credibility



When testifying for PO	What he says publicly
Prior art does not teach the modifications to FOLFIRINOX to arrive at the Challenged Claims. Ex. 2076 at ¶20.	NALIRIFOX (regimen of the Challenged Claims) and FOLFIRINOX are “quite similar.” Ex. 1211 at 1:31.
POSA would administer the maximum tolerated dose when treating first-line pancreatic cancer and not practice dose reductions. Ex. 2076 at ¶¶50, 245.	“[T]he message there, which I think is very similar to what we see in practice, is that if we modify doses and we can keep patients on longer they’re going to sometimes do better. And so it really I would say that’s our practice it gives us a lot of reinforcement to do that which is that the key thing here is not necessarily being too strong, too aggressive on day one.” Ex. 1211 at 3:46.
Most clinicians “would be reluctant to make exchanges that would dilute” the benefit seen with FOLFIRINOX. Ex. 1210 at 309:18-24.	Participates in a panel where the consensus was “Nobody can tolerate the full dose of FOLFIRINOX” and that no one uses the original FOLFIRINOX. Ex. 1211 at 2:05.

- PO pays Oberstein tens of thousands of dollars a year outside of his role as an expert witness, most of which relate to promoting NALIRIFOX (regimen of the Challenged Claims). \$54,000 - \$63,000 in payments in 2024 alone before this IPR challenge. Ex. 1214, 1-7; Ex. 1210, 36:13-39:18, 45:7-46:21.
- Oberstein’s prescribing of NALIRIFOX has grown substantially in the last two years and is now one of his most prescribed treatments. Ex. 1210, 80:5-81:16, 317:22-318:3.

Petitioners’ Reply (Paper 32) at 1-4.

Count 2: Claims 2, 7, and 15 are obvious

Claims	Prior Art
2. The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.	Same prior art as to Count 1, in addition to Masi (Ex. 1012 at 5), which discloses that irinotecan should be administered prior to oxaliplatin in FOLFOXIRI regimen, and Ginocchi (Ex. 1016 at 1), which applied a modified FOLFOXIRI regimen that administered the irinotecan before the oxaliplatin) to metastatic pancreatic patients. Administering oxaliplatin 2 hours after liposomal irinotecan would have been routine optimization.
7. The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.	Same reasons as claims 1 and 2, and the fact that Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen with leucovorin immediately preceding it and that Bayever also discloses that 5-FU is administered last with leucovorin immediately preceding it.
15. The method of claim 1, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.	Same reasons with respect to claims 1 and 2, and the fact that Bayever discloses administering dexamethasone, which is a corticosteroid, and an anti-emetic to the patient prior to the antineoplastic therapy. (See Ex. 1002, ¶¶310-311; Ex. 1006 at 4-6, 33-35 Claims 9, 18.)

Claim Requirements

12. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

- a. 60 mg/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (1)-form of leucovorin or 400 mg/m² of the (1+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

- Claims require
 - Treatment of a patient
 - Precise dosages
 - Fixed schedules
- Benefits must come from these claimed parameters

Numerous Objections and Patent Owner's Unexpected Results Argument

- The '552 Patent claims were rejected no less than 5 times over several years, based in part on the teachings of Conroy (Ex. 1003) and Bayever (Ex. 1006).
- Patent Owner then raised an unexpected results argument, relying on Wainberg (Exs. 1018-1019) and got claims allowed.
- Evidence does not support unexpected results.

Office Action Summary		Application No. 15/809,815	Applicant(s) Bayever et al.	
		Examiner GOLLAMUDI S KISHORE	Art Unit 1612	AIA (FITF) Status Yes
<p align="center">– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –</p> <p>Period for Reply</p> <p>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.</p> <ul style="list-style-type: none">- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). <p>Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</p> <p>Status</p> <p>1) ☒ Responsive to communication(s) filed on 02-25-2021. ☐ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on ____.</p> <p>2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.</p> <p>3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.</p> <p>4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i>, 1935 C.D. 11, 453 O.G. 213.</p> <p>Disposition of Claims*</p> <p>5) ☒ Claim(s) <u>1,4-15, 18-19 and 21-23</u> is/are pending in the application. 5a) Of the above claim(s) ____ is/are withdrawn from consideration.</p> <p>6) ☐ Claim(s) ____ is/are allowed.</p> <p>7) ☒ Claim(s) <u>1,4-15, 18-19 and 21-23</u> is/are rejected.</p> <p>8) ☐ Claim(s) ____ is/are objected to.</p> <p>9) ☐ Claim(s) ____ are subject to restriction and/or election requirement</p> <p>* If any claims have been determined allowable, you may be eligible to benefit from the Patent Prosecution Highway program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.</p> <p>Application Papers</p> <p>10) ☐ The specification is objected to by the Examiner.</p> <p>11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).</p> <p>Priority under 35 U.S.C. § 119</p> <p>12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</p> <p>Certified copies:</p> <p>a) ☐ All b) ☐ Some** c) ☐ None of the:</p> <p>1. ☐ Certified copies of the priority documents have been received.</p> <p>2. ☐ Certified copies of the priority documents have been received in Application No. ____.</p> <p>3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</p> <p>** See the attached detailed Office action for a list of the certified copies not received.</p> <p>Attachment(s)</p> <p>1) ☐ Notice of References Cited (PTO-892)</p> <p>2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)</p> <p>3) ☐ Interview Summary (PTO-413)</p> <p>4) ☐ Other: ____</p> <p>Paper No(s)/Mail Date ____</p> <p>U.S. Patent and Trademark Office PTOL-326 (Rev. 11-13)</p> <p align="right">Office Action Summary Part of Paper No./Mail Date 20210707</p>				

What “Unexpected Results” Requires

Legal Nexus for Evidence

A legally sufficient nexus must directly link unexpected results to the novel elements of the claimed invention.

Identification of What Was Expected

A showing of what was expected by a persons of ordinary skill in the art is required as a benchmark.

Difference in Kind Requirement

Unexpected results must show a qualitative difference, not just incremental or predictable improvements.

No Evidence of Nexus

- Patent Owner makes no serious nexus arguments

Further, the evidence of record establishes nexus. There is no dispute that the NALIRIFOX regimen comprises the '552 patent's recited components and doses. *See* Paper 21 at 6-8; Ex. 2076 at ¶¶ 65-68. CSPC's arguments to the contrary appear to rest on claim-construction arguments that are unsupported by the record. *See* Paper 32 at 21-22. CSPC appears to assume a claim construction that would preclude any modification of the recited doses during the course of treatment. *See id.* (arguing that "the claims require specific doses of four drugs two weeks apart."). For reasons already discussed, this argument ignores the intrinsic record and *unrebutted* expert testimony on how a POSA would understand the claimed treatment methods. As explained *supra*, a POSA would

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understand the recited treatment methods to comprise at least the recited starting dose, with subsequent dose modifications permitted.

Table. Summary of Clinical Trials Characteristics

Trial name	NAPOLI 3 ⁵	ACCORD 11 ¹	MPACT ²	HALO ¹⁴	RESOLVE ¹⁵	AVENGER500 ¹²	CanStem111P ¹³
ClinicalTrials.gov Identifier	NCT04083235	NCT00112658	NCT00844649	NCT02715804	NCT02436668	NCT03504423	NCT02993731
Study timeframe	February 2020 to July 2022	December 2005 to October 2009	May 2009 to April 2012	March 2016 to December 2018	May 2015 - October 2018	November 2018 to January 2022	January 2017 to February 2019
Publication year	2023	2011	2013	2020	2021	Presented at ASCO 2022	2023
Geographic area	Global	France	Global	Global	Global	Global	Global
Blinding	Open-label	Open-label	Open-label	Double-blind	Double-blind	Open-label	Open-label
Randomization	1:1	1:1	1:1	2:1	1:1	1:1	1:1
Primary end point	OS	OS	OS	OS	OS, PFS	OS	OS
Secondary end points	PFS, ORR	PFS, ORR, safety, QOL	PFS and ORR	PFS, ORR, safety	ORR, CA 19-9 response, QOL, safety	PFS, DOR, QOL, safety	PFS, DCR, ORR
Total patients enrolled, No.	770	342	861	492	424	528	1134
Experimental group	NALIRIFOX (n = 383)	FOLFIRINOX (n = 171)	GEM-NABP (n = 431)	PEGPH20 + GEM-NABP (n = 327)	Ibrutinib + GEM-NABP (n = 211)	Devimistat + FOLFIRINOX (n = 266)	Napabucasin + GEM-NABP (n = 565)
Details	Liposomal Irinotecan 50 mg/m ² + oxaliplatin 60 mg/m ² + LV 400 mg/m ² + fluorouracil 2400 mg/m ² over 46 h; every 15 d	Irinotecan 180 mg/m ² + oxaliplatin 85 mg/m ² + LV 400 mg/m ² + fluorouracil bolus 400 mg/m ² + 2400 mg/m ² over 46 h; every 15 d	GEM 1000 mg/m ² + NABP 125 mg/m ² ; Days 1, 8, 15, and every 28	3.0 µg/kg of PEGPH20 as IV infusion, 2/wk for wk 1-3 of cycle 1, then 1/wk for wk 1-3 of cycle 2 and beyond in combination with GEM-NABP	Ibrutinib 560 mg once daily + Gem 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and 28	Devimistat 500 mg/m ² on days 1 and 3 + Irinotecan 140 mg/m ² + oxaliplatin 65 mg/m ² + LV 400 mg/m ² + fU bolus 400 mg/m ² + 2400 mg/m ² over 46 h; every 15 d	Napabucasin 240 mg 2/d + GEM 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and every 28
Control group	GEM-NABP (n = 387)	GEM (n = 171)	GEM (n = 430)	GEM-NABP (n = 165)	GEM-NABP (n = 213)	FOLFIRINOX (n = 262)	GEM-NABP (n = 569)
Details	GEM 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and every 28	GEM 1000 mg/m ² ; cycle 1: weekly (7 of 8 wk); cycle 2 onward: days 1, 8, 15, and every 28	GEM 1000 mg/m ² ; cycle 1: weekly (7 of 8 wk); cycle 2 onward: days 1, 8, 15, and every 28	GEM 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and every 28	GEM 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and every 28	Irinotecan 180 mg/m ² + oxaliplatin 85 mg/m ² + LV 400 mg/m ² + fluorouracil bolus 400 mg/m ² + 2400 mg/m ² over 46 h; every 15 d	GEM 1000 mg/m ² + NABP 125 mg/m ² ; days 1, 8, 15, and every 28
Treatment duration	Until disease progression or unacceptable toxic effects	6 mo recommended for patients who had a response, continuation and/or reintroduction allowed	Until disease progression or unacceptable toxic effects	Until disease progression or unacceptable toxic effects	Until disease progression or unacceptable toxic effects	Until disease progression or unacceptable toxic effects	Until disease progression or unacceptable toxic effects
Time since metastatic disease diagnosis	≤6 wk	Not specified	≤6 wk	Not specified	≤6 wk	Not specified	Not specified
Type of metastatic lesions	RECIST criteria, version 1.1	RECIST criteria, version 1.0	RECIST criteria, version 1.0	RECIST criteria, version 1.1	RECIST criteria, version 1.1	RECIST criteria, version 1.1	RECIST criteria, version 1.1
Other relevant criteria	NA	NA	NA	Hyaluronan-high tumors, defined as ≥50% hyaluronan staining in the ECM of tumor samples	NA	NA	NA
Neoadjuvant or adjuvant chemotherapy	Allowed (>12 mo before trial treatment)	Not allowed	Fluorouracil or GEM as radiation sensitizer in the adjuvant setting (>6 mo before trial treatment)	Allowed (>6 mo before trial treatment)	Not allowed	Allowed	Not allowed
Age limit	None	76 y	None	None	None	75 y	None

Abbreviations: ASCO, American Society of Clinical Oncology; CA 19-9, carbohydrate antigen 19.9; DCR, disease control rate; DOR, duration of response; ECM, extracellular matrix; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GEM, gemcitabine; LV, leucovorin; NA, not applicable; NABP, nab-paclitaxel;

NALIRIFOX, fluorouracil, leucovorin, liposomal irinotecan and oxaliplatin; ORR, overall response rate; OS, overall survival; PEGPH20, pegvorhyaluronidase alfa; PFS, progression free survival; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours.

NAPOLI-3 Dose Reductions Break Nexus

CONCLUSIONS

- This *post hoc* analysis investigated the demographic and clinical characteristics and dosing patterns among long-term survivors from North America treated with NALIRIFOX in NAPOLI 3.
- A substantial proportion of long-term survivors had ≥ 3 metastatic sites at baseline, but they otherwise had a good clinical profile: younger (vs typical mPDAC diagnosis), few tumors in the head or tail of the pancreas, a good performance status and reasonably low CA 19-9 levels.⁷
- Dose reductions and/or treatment delays occurred in the majority of long-term survivors, enabling prolonged exposure, high cumulative doses of both liposomal irinotecan and/or oxaliplatin drugs and an overall mOS of 19.5 months.
- Owing to the small sample size, these results should be interpreted with caution.

Treatment patterns among long-term survivors

- Most long-term survivors experienced dose reductions and dose delays of both liposomal irinotecan (66.7% and 86.7%, respectively) and oxaliplatin (80% both) (Table 3).

Table 3. Treatment patterns among long-term survivors treated with NALIRIFOX at North American centers in NAPOLI 3

Treatment characteristic	OS ≥ 18.0 months (n = 15)	ITT (n = 120)
Liposomal irinotecan		
Dose reduction, n (%)	10 (66.7)	63 (52.5)
Dose delay, n (%)	13 (86.7)	84 (70.0)
Duration of exposure, weeks		
Median (IQR)	65.1 (40.1–89.0)	23.1 (10.9–44.8)
Cumulative dose, mg/m ²		
Median (IQR)	1229.4 (821.9–1513.9)	429.3 (202.7–860.1)
Oxaliplatin		
Dose reduction, n (%)	12 (80.0)	72 (60.0)
Dose delay, n (%)	12 (80.0)	83 (69.2)
Duration of exposure, weeks		
Median (IQR)	39.9 (26.6–76.4)	21.8 (10.9–37.6)
Cumulative dose, mg/m ²		
Median (IQR)	962.3 (655.0–1470.3)	481.9 (242.7–920.9)

IQR, interquartile range; ITT, intention-to-treat; OS, overall survival.

Oberstein Confirms Lack of Nexus

Q. Okay. Do you offer any opinions about the nexus related to unexpected results and the claims?

MS. MURPHY: Objection to the extent it calls for a legal conclusion.

A. I don't believe I did that.

Q. Do you know how many patients received a dose reduction in their second treatment?

A. I do not.

Q. That patients who are younger, fitter and have --

A. Low CNT-9 seem to do better. I shouldn't say seem to do better. Seem to be patients who have long-term survival.

Q. So the subset that were younger and fitter also received dose reductions; is that correct?

A. That's correct. That is what it says.

- Confirms he offers no opinion on nexus
- Admits evidence does not indicate how many patients received a dose reduction during second treatment
- Younger, fitter patients with lower antigens skewed survival stats, i.e., they received dose reductions and had longer survival

No Conclusive Evidence of Treatment

Oberstein further confirms any "benefit" for any one patient cannot be known for sure.

Rather, the "goal" is to provide benefit.

A. So if a patient sits down in front of me and I say to them I want to treat you with NALIRIFOX, the goal of that treatment is to provide benefit to the patient. Yes.

Q. So how do you know if those patients received any benefit from the prescribed regimen?

A. So, again, this is what statistics in populations could do. It can tell you what is the significant differences between groups at a certain level. If you had a small study or single arm study, it is hard to do that. With a randomized controlled trials you can make -- sometimes you can make those conclusions.

Q. But when it comes to a particular individual, you are prescribing the regimen because you think it works for a general population, but you don't know that it is going to work for that particular individual, correct?

A. I mean I think we don't know for sure. We have evidence based on large Phase III trials, and that is what guides our experts and us and a POSA to determine the best treatment for a patient, but without randomized Phase III had trials it is hard to say.

Results Were Not Unexpected

- Patent Owner must first show what properties were expected and then provide an evaluation of the significance and kind of results achieved.
 - *Pfizer v. Apotex*, 480 F.3d 1348, 1371 (Fed. Cir. 2007); *Bristol-Mers Squibb Co. v. Teva Pharms., USA, Inc.*, 752 F.3d 967, 977 Fed. Cir. 2014); *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F.Supp.2d 305, 348 (D. Del.).
- Patent Owner offers no evidence regarding a POSA's expectations.

Testimony on Unexpected Results Is Not Unrebutted

- Ratain offered testimony about a POSA's awareness of modified FFX regimens with comparable efficacy.

113. Second, Mahaseth confirmed that by eliminating the 5-FU bolus, and thereby decreasing the dosage of 5-FU by 400 mg/m², the modified regimen improved on FOLFIRINOX's overall efficacy. (Id. at 4.) For instance, Mahaseth

found that the modified regimen months and overall survival (OS) 7.3 months (PFS) and 6.7 months

deleting the bolus and administering prophylactic pegfilgrastim, (3) and substantial dose reductions: with median relative doses of 57-100%. (Id. at 4-5.) Conroy 2013 further notes that despite these modifications, efficacy was maintained, response rates remained promising, and/or that patients achieved disease control. (Id.)

144. Like other references discussed herein, Ko found that the liposomal irinotecan formulation may reduce toxicity while increasing efficacy of antitumor activity when compared to first-line FOLFIRINOX.

103. A POSA would have been very familiar with the FOLFIRINOX regimen at the time of the alleged invention and aware of studies on the efficacy, safety, and tolerability of FOLFIRINOX and modifications thereto.

107. Mahaseth et al. "Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma," was published in Pancreas in November 2013 (Ex. 1005). I understand that Mahaseth is

Petition (Paper 1) at 7-8, 14, 16-17, 22, 24, 43; Exhibit 1002, ¶¶103, 107, 113, 144, 149, 156.

Improved Tolerability and Maintained Efficacy Were Expected

- No dispute that reducing dose would reduce toxicity.
- Evidence suggests efficacy could be maintained.

“In this single institution retrospective study, the use of modest dose attenuations of FOLFIRINOX in conjunction with growth factor support, was associated with improved tolerability compared to full dose FOLFIRINOX as reported by Conroy et al. Our findings suggest that these modest dose attenuations do not reduce the efficacy of FOLFIRINOX in metastatic pancreatic cancer patients. Moreover, the efficacy of FOLFIRINOX in locally advanced disease was comparable to its efficacy in metastatic disease.”

“We observed activity and acceptable toxicity in carefully selected patients treated with FFX at 80% dose intensity and routine use of growth factor support. Treatment with FFX resulted in median OS of > 1 year in pts with stage IV PAC and is an active front-line regimen.”

“Compared to full-dose FOLFIRINOX, our modified regimen resulted in lower haematological but only marginally improved non-haematological toxicity rates, with comparable efficacy outcomes. Prospective studies are required to validate these findings.”

“In spite of dose reductions, FOLFIRINOX was found to be very effective. Rates of response were similar to the ACCORD study with more than 70% of patients having at least stable disease on therapy. Similar response rates were seen in non-metastatic patients who were not included in the ACCORD trial. In fact, 8

Dose Reductions in FFX – Common and Comparable

- MSK treated 106 pancreatic cancer patients between 2010 and 2013 where the “starting dose” of FFX was “80% of that used” in Conroy.
- Dose reductions were still required for 45% of patients.
- No grade 4 or 5 toxicity was recorded and the median OS was 11 months.

Petitioners’ Reply (Paper 32) at 7-8, 23; Exhibit 1216 at 1.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma

Eran Sadot, MD¹, Alexandre Doussot, MD¹, Eileen M. O'Reilly, MD², Maeve A. Lowery, MD², Karyn A. Goodman MD³, Richard Kinh Gian Do, MD, PhD⁴, Laura H. Tang, MD, PhD⁵, Mithat Gönen, PhD⁶, Michael I. D'Angelica MD¹, Ronald P. DeMatteo, MD¹, T. Peter Kingham, MD¹, William R. Jarnagin, MD¹, and Peter J. Allen, MD¹

¹Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; ²Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; ³Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; ⁴Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY; ⁵Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; ⁶Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Background. Reports show that FOLFIRINOX therapy for pancreatic ductal adenocarcinoma (PDAC) results in objective response rates two to threefold higher than those of other regimens. This study aimed to assess response and resection rates for locally unresectable (stage 3) patients initially treated with induction FOLFIRINOX.

Methods. The institutional cancer database was queried for patients treated with induction FOLFIRINOX therapy between 2010 and 2013. Patients were included in the study if they were treated at the authors' institution for stage 3 PDAC (locally unresectable) that had been adjudicated at a weekly multidisciplinary tumor board.

Results. The study identified 101 patients. The median age was 64 years (range 37–81 years), and the median follow-up period was 12 months (range 3–37 months). The patients received a median of six cycles (range 1–20 cycles) of induction FOLFIRINOX. No grade 4 or 5 toxicity was recorded. At the initial restaging (median of 3 months after diagnosis), 23 patients (23 %) had developed distant

metastases, 15 patients (15 %) had undergone resection, and 63 patients (63 %) had proceeded to chemoradiation. In the group of 63 patients who had proceeded to chemoradiation (median of 9 months after diagnosis), an additional 1 patient (16 %) had undergone resection, and 5 patients (5 %) had developed metastases. A partial radiographic response was observed in 29 % of all the patients, which was associated with ability to perform resection ($p = 0.004$). The median overall survival time was 11 months for the group that progressed with FOLFIRINOX and 26 months for the group that did not progress.

Conclusion. Nearly one third of the patients who had been initially identified as having stage 3 pancreatic adenocarcinoma and had been treated with FOLFIRINOX responded radiographically and underwent tumor resection.

A recently completed phase 3 randomized trial for stage pancreatic ductal adenocarcinoma (PDAC) identified FOLFIRINOX as superior to gemcitabine in terms of radiographic response together with improved progression-free and overall survival.¹ Patients who received FOLFIRINOX experienced a 32 % objective response rate (ORR) compared with 9 % in the gemcitabine arm of the study, which correlated with survival benefit (median overall and progression-free survival, 11 and 6 versus 7 and 3 months, respectively).

Retrospective studies of patients with both borderline resectable PDAC (stages 1 and 2) and stage 3 disease (locally unresectable) also have suggested an ORR of approximately 30 % with FOLFIRINOX.^{2,3} The reported ORR from non-FOLFIRINOX regimens has generally been in the range of 10 %, including the results of a phase

This study was presented at the American College of Surgeons Annual Clinical Congress, October 26–30, 2014, San Francisco.

Electronic supplementary material The online version of this article (doi:10.1245/s10434-015-4647-4) contains supplementary material, which is available to authorized users.

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Published Online: 12 June 2015

P. J. Allen, MD
e-mail: allenp@mskcc.org

Liposomal Irinotecan (MM-398/CPT-11/PEP02) Also Expected to Increase Efficacy

- Exhibited “greatly enhance[d] antitumor efficacy”
- “Demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan” in pancreatic cancer mouse model
- “Superior activity over irinotecan”

The screenshot displays the article navigation and abstract for a paper in the British Journal of Cancer (BJC). The article title is "Abstract A41: Sustained intratumoral activation of MM-398 results in superior activity over irinotecan demonstrated by using a systems pharmacology approach." The authors listed are Jaeyoon Kim, Eiel Bayever, Peter Laivins, Clet Niyikiza, Ulrik Nielsen, Jonathan Fitzgerald, Ashish Kalra, Milind Chalisahar, Stephan Klinz, Nancy Paz, Bart Hendriks, Daryl Drummond, Dmitri Kirpulin, and Victor Moyo. The abstract text describes the development of a mechanistic pharmacokinetic (PK) model of MM-398 and free-irinotecan to predict both plasma and intratumoral levels. The model was trained with PK and biodistribution data from mice bearing HT-29 xenografts, which were administered intravenously with varying doses of MM-398 or free-irinotecan. The model simulations predicted that MM-398 resulted in equivalent SN-38 exposure (area under curve, AUC) in tumor at a five-fold lower dose than free-irinotecan. However, an in vivo animal activity study showed that 15-fold lower dose of MM-398 was sufficient to yield equal growth inhibition of HT-29 xenografts, which reveals the limit of relating simple AUC based exposure to in vivo tumor response. While intratumoral SN-38 exposure from free-irinotecan was limited to the first 48 hours after dosing, MM-398 maintained high levels of SN-38 throughout the week long time window. Further studies are needed to confirm these findings in clinical trials.

Petition (Paper 1) at 2, 8, 10; Exhibit 1002, ¶91; Exhibits 1008, 1058, 1059.

Difference in Degree, Not Kind

- Patent Owner relies exclusively on Oberstein's testimony to "the claimed methods provide comparable efficacy with an improved toxicity profile" was a "difference in kind." POR (Paper 21) at 52.
- Oberstein confirms: the claimed invention is nothing more than "the same outcome but slightly better or the same end point" and **not** "a step forward, some innovation."

Oberstein testimony:

Q. What is your understanding of difference in kind?

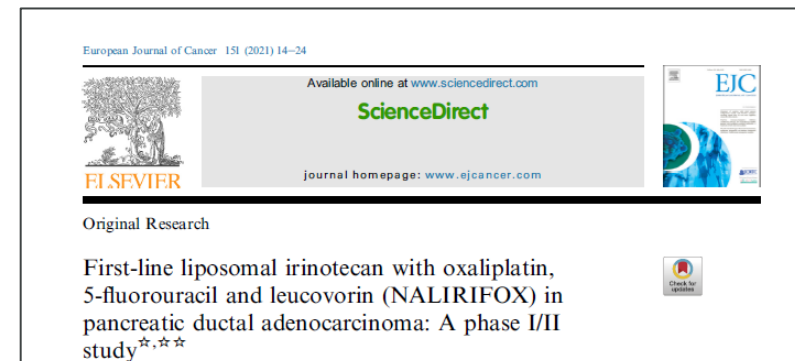
A. Again, I think it depends very much on the context, but I might understand difference in kind as being the same outcome but slightly better or the same end point maybe.

Q. Okay. What is your understanding of difference in degree?

A. So I understand difference in degree to be I would say greater than difference in kind and have to have some step forward, some innovation. That is just more than just a little bit more.

Wainberg Does Not Support Unexpected Results Argument

- Patent Owner does not
 - Cite to or refer to Wainberg references
 - Dispute that Wainberg cautions there were “limitations inherent in [Wainberg’s] study design,” including small population size and differences in disease stage, disease type, and patient ages between NALIRIFOX and FOLFIRINOX studies mean the two “cannot be reliably compared” and that comparisons between the studies “cannot be made”
 - Dispute other more recent studies lack Wainberg’s inherent limitations or demonstrate a lack of NALIRIFOX advantage



The safety of NALIRIFOX cannot be reliably compared with that of established therapies without head-to-head studies. However, no unexpected safety outcomes were apparent based on the known safety

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Available online 4 May 2021

Limitations inherent in the present study design include the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomised design; and the absence of a control group. Although only patients with adequate performance status were included, similar restrictions were used in PRODIGE 4 [5].

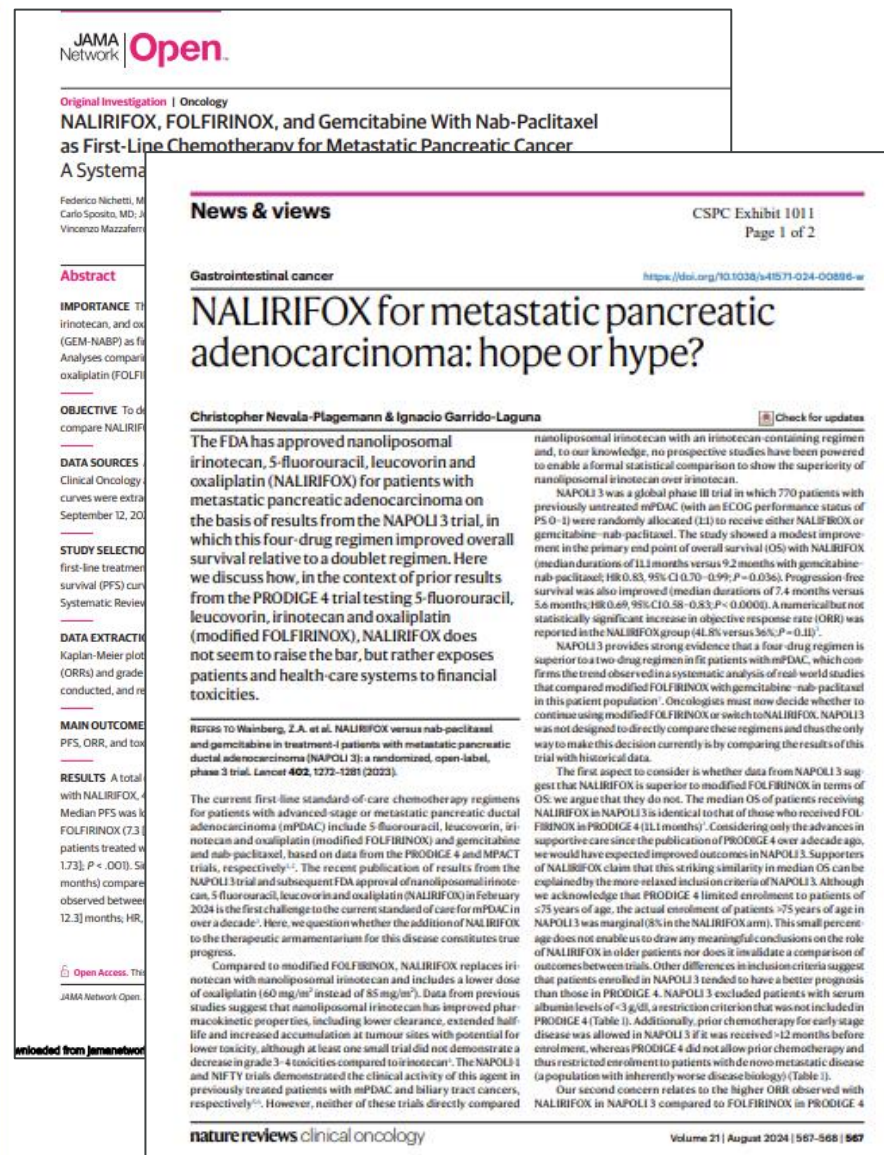
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No Advantage to NALIRIFOX over FFX

- Ipsen admits comparison between NALIRIFOX and FFX is “not possible”
- Industry literature finds
 - “No difference” or lower overall survival with NALIRIFOX (11.1 months) compared to FOLFIRINOX (11.7 months)
 - NALIRIFOX is “not clinically [or] statistically significant”
 - NALIRIFOX is a “financial toxicity” and “more costly”

Petitioners’ Reply (Paper 32) at 25; Exhibits 1010-1011, 2032-2033.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



Notable Lack of Clinical Advantage to NALIRIFOX

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NCCN

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NCCN Guidelines Version 2.2025

Pancreatic Adenocarcinoma

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[Discussion](#)

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

• Consider evaluational geriatric assessment (see [NCCN Guidelines for Older Adult Oncology](#)).

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	<ul style="list-style-type: none">• FOLFIRINOX (category 1) or modified FOLFIRINOX^{9,5}• Gemcitabine + albumin-bound paclitaxel⁶ (category 1)• NALIRIFOX^{4,7} (category 1) <p>Only for known <i>BRCA1/2</i> or <i>PALB2</i> mutations:</p> <ul style="list-style-type: none">• FOLFIRINOX (category 1) or modified FOLFIRINOX^{9,5}• Gemcitabine + cisplatin^{8,9}	<ul style="list-style-type: none">• Gemcitabine (category 1)• Gemcitabine + erlotinib^{9,11} (category 1)• Gemcitabine + capecitabine¹⁰• Gemcitabine + albumin-bound paclitaxel + cisplatin^{14,15}• Fluoropyrimidine + oxaliplatin<ul style="list-style-type: none">▶ CapeOx¹² (category 2B)▶ OFF¹³ (category 2B)• GTX¹⁶ (category 2B)	<ul style="list-style-type: none">• Entrectinib (if <i>NTRK</i> gene fusion-positive)• Larotrectinib (if <i>NTRK</i> gene fusion-positive)• Repotrectinib (if <i>NTRK</i> gene fusion-positive)²¹• Pembrolizumab²² (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])• Selpercatinib (if <i>RET</i> gene fusion-positive)• Dabrafenib + trametinib (if <i>BRAF</i> V600E mutation-positive) (category 2B)^{19,20}

NCCN finds NALIRIFOX regimen “does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX” for both locally advanced and metastatic disease.

- NALIRIFOX (liposomal irinotecan in combination with 5-fluorouracil/leucovorin plus oxaliplatin) is a US Food and Drug Administration and European Medicines Agency approved first-line (1L) treatment option for mPDAC,^{4,5} based on the results of the phase 3 NAPOLI 3 trial (NCT04083235).⁶
- At a median follow-up of 16.1 months, mOS in NAPOLI 3 for the NALIRIFOX treatment arm was 11.1 months;⁶ the characteristics of long-term survivors in NAPOLI 3 have not been previously reported.

- NALIRIFOX (liposomal irinotecan in combination with 5-fluorouracil/leucovorin plus oxaliplatin) is a US Food and Drug Administration and European Medicines Agency approved first-line (1L) treatment option for mPDAC,^{4,5} based on the results of the phase 3 NAPOLI 3 trial (NCT04083235).⁶
- At a median follow-up of 16.1 months, mOS in NAPOLI 3 for the NALIRIFOX treatment arm was 11.1 months;⁶ the characteristics of long-term survivors in NAPOLI 3 have not been previously reported.

14 A. So in the NAPOLI-3 trial you
15 mean?

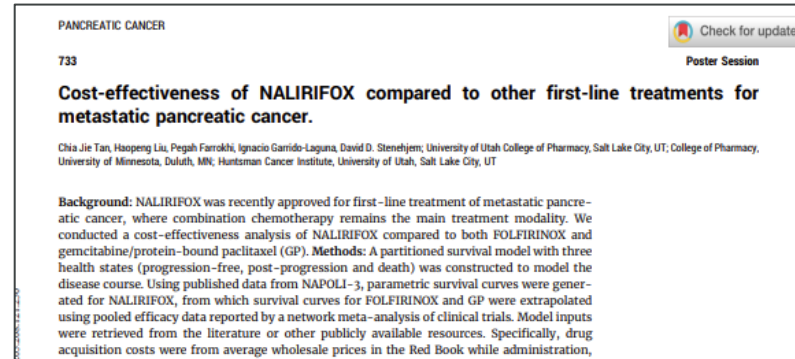
17 A. So I think the trial had 11.1 --
18 I think 11.1 month median survival on
19 11.0. One of those two.

21 A. So that is the same number

22 Conroy reported from their trial.

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Incremental Cost Effectiveness Ratio



otherwise. Results: The overall cost associated with NALIRIFOX was \$129,314, followed by GP (\$104,593) and FOLFIRINOX (\$41,528). Among the 3 regimens, NALIRIFOX incurred the highest treatment-related cost (\$105,533) but the lowest adverse effects management cost (\$16,541). On average, patients on NALIRIFOX gained a total of 1.14 life years (LY) or after adjusting for utility, 0.86 QALY. FOLFIRINOX led to 1.09 LY or 0.82 QALY while GP resulted in 0.99 LY or 0.75 QALY. Due to its higher cost and lower survival benefit, GP was dominated by FOLFIRINOX. Compared to FOLFIRINOX, the incremental cost-effectiveness ratio (ICER) of NALIRIFOX was \$1,952,062/QALY. In our sensitivity analysis, the probability of NALIRIFOX being cost-effective was 0% at all conventional ICER thresholds up to \$200,000/QALY. Conclusions: Due to the high drug acquisition cost, the ICER of NALIRIFOX far exceeds currently acceptable thresholds for economic value and NALIRIFOX is considered not cost-effective. This is despite that in our model among first line treatments for metastatic pancreatic cancer, NALIRIFOX was associated with reduced costs for managing adverse effects. Research Sponsor: None.

CSPC Exhibit 1217
Page 1 of 1

Reliance on *Allergen* is Misplaced

- No arguments or evidence the prior art taught away from combination or the claimed invention
- No arguments or evidence that safety concerns or side effects from FOLFIRINOX “caused many patients to discontinue treatment.”
 - Even today, Oberstein continues to prescribe FOLFIRINOX