

***CSPC Pharmaceutical Group Ltd., et al.,
v.
Ipsen Biopharm Ltd.,***

**IPR2025-00505
U.S. Patent No. 11,344,552**

**Patent Owner Ipsen's Hearing Demonstratives
May 19, 2026**

Onivyde for Metastatic Pancreatic Cancer



Metastatic pancreatic cancer patients face median survival times under 12 months and only about 2% surviving five years after diagnosis.

Ex. 2076 at ¶ 47



In the NAPOLI 3 trial, the NALIRIFOX regimen demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival compared with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma who had not previously received treatment in the metastatic setting. The observed

Ex. 2032 at 6; Paper 21 at 5-7; Ex. 2076 at ¶ 67

'552 Patent

(12) United States Patent and Trademark Office
Bayever et al.

(54) METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

(71) Applicant: Ipsen Biopharm Ltd., Wrexham (GB)

(72) Inventors: Eliel Bayever, New York, NY (US); Sarah F. Blanchette, Lynnfield, MA (US); Jonathan Basil Fitzgerald, Arlington, MA (US); Daniel F. Gaddy, Cambridge, MA (US); Bart S. Hendriks, Belmont, MA (US); Ashish Kalra, Belmont, MA (US); Helen Lee, Arlington, MA (US)

(73) Assignee: Ipsen Biopharm Ltd.

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 15/809,815

(22) Filed: Nov. 10, 2017

(65) Prior Publication Data
US 2018/0078556 A1 Mar. 22, 2018

Related U.S. Application Data
(63) Continuation of application No. 15/241,106, filed on Aug. 19, 2016, now abandoned.
(Continued)

(51) Int. Cl.
A61K 31/519 (2006.01)
A61K 31/282 (2006.01)
(Continued)

CPC: A61K 31/519; A61K 9/1271; A61K 9/0019; A61K 31/475; A61K 31/436;
(Continued)

(56) References Cited
U.S. PATENT DOCUMENTS
4,604,463 A 8/1986 Miyasaka et al.
5,013,556 A 5/1991 Woodie et al.
(Continued)

FOREIGN PATENT DOCUMENTS
CA 2412799 A1 1/2002
CN 1829741 A 9/2006
(Continued)

OTHER PUBLICATIONS
Conroy T. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *nejm*, 34(19), 2011, 1817.*
(Continued)

Primary Examiner — Gollanudi S Kishore
(74) Attorney, Agent, or Firm — McNeill Baur PLLC

(57) ABSTRACT
Combination therapy regimens including liposomal irinotecan, oxaliplatin and 5-fluorouracil are useful in the treatment of pancreatic cancer, including treatment of patients diagnosed with previously untreated metastatic adenocarcinoma of the pancreas. The combination therapy can include the administration of liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil once every two weeks.

15 Claims, 22 Drawing Sheets

BxPC-3 (X022)

Days Post-Inoculation	Saline (mm³)	Ox (5mpk) (mm³)	MM-398 (5mpk) (mm³)	MM-398 + Ox (mm³)
30	~200	~200	~200	~200
35	~400	~400	~400	~400
40	~800	~600	~500	~500
45	~1200	~800	~600	~600
50	~1600	~1000	~700	~700
55	~2000	~1200	~800	~800
60	~2400	~1400	~900	~900
65	~2500	~1500	~1000	~1000

'552 Patent

METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN

The invention claimed is:

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:

- 60 mg/m² of liposomal irinotecan,
 - 60 mg/m² oxaliplatin,
 - 200 mg/m² of the (1)-form of leucovorin or 400 mg/m² of the (1+d) racemic form of leucovorin, and
 - 2,400 mg/m² 5-fluorouracil;
- to treat the metastatic adenocarcinoma of the pancreas in the human patient.

CSPC's Expert: No Opinion on "Treatment"

Petition & Ratain Decl.
Jan. 17, 2025

**Petitioner &
Dr. Ratain:**

Alternate
constructions
of "treatment"

"attempting to cause a
therapeutic improvement
but not requiring actual
efficacy

OR

"requir[ing] a showing
of clinical efficacy"

Paper 1 at 26-30;

Ex. Ex. 2076 at at ¶¶ 49-50; Paper 1
at 36; Ex. Ex. 2076 at at ¶¶ 216-226

Institution Decision
Aug. 14, 2025

Board

Did not adopt
Petitioner's
construction and
construed
"treatment":

"the 'treatment' would have
more than a *de minimis*
therapeutic benefit or
efficacy for the patient
being treated"

Paper 13 at 13-14

Patent Owner's Response
Nov. 10, 2025

**Ipsen &
Dr. Oberstein**

Applied Board's
construction:

"I adopt the PTAB's claim
interpretation ruling for
purposes of the opinions
set forth herein."

Ex. 2076 at ¶ 136

Petitioner's Sur-Reply
Feb. 11, 2026

Petitioner

No expert
declaration
applying the
Board's
construction

Paper 32

Ground 1

Grounds and Challenged Claims

- CSPC challenges all claims of the '552 Patent on three grounds as follows:

Ground	Claims	Basis	Asserted Prior Art
1	1, 3-6, 8-14	103	Conroy, Conroy Protocol, Conroy Appendix, and Mahaseth in combination with Bayever, Saif, Ko, and Cantore
2	2, 7, and 15	103	Ground 1 in addition to Masi and Ginocchi
3	1-15	103	Grounds 1 and 2 in addition to Carnevale and Dean

Pet. at 6.

Patent Owner's Expert: Dr. Paul Oberstein



Dr. Paul Oberstein



- Service Chief, Gastrointestinal Medical Oncology Program
- Co-Director, Pancreatic Cancer Center
- Associate Professor, Dept. of Medicine at NYU Grossman School of Medicine
- Fellowship in Hematology and Oncology, Columbia Presbyterian Medical Center
- Residency in Internal Medicine, Temple University Hospital
- MD, Ohio State University

Procedural History

Jan. 17, 2025

- Petition (Paper 1)
- Ratain Declaration (Ex. Ex. 2076 at)

May 23, 2025

- Ipsen's request for DD (Paper 8)
- Ipsen's POPR (Paper 9)

Jun. 23, 2025

- Petitioner's Response to request for DD (Paper 10)
- Supplemental Ratain Declaration (Ex. 1200)

Jul. 16, 2025

DD decision (Paper 11)

Aug. 14, 2025

Institution decision (Paper 13)

Nov. 10, 2025

- Ipsen's Patent Owner's Response (Paper 21)
- Oberstein Declaration (Ex. 2076)

Feb. 11, 2026

- Petitioner's Reply to Patent Owner's Response (Paper 33)
- **NO SUPPORTING EXPERT DECLARATION**

2025

2026

Dr. Oberstein's Opinions Are Unrebutted

- Non-obviousness under Board's construction of "treatment"
- No motivation to make all four (4) FFX modifications
 - POSA would have considered efficacy in addition to toxicity
 - POSA would understand that lower doses may compromise efficacy
- Conroy does not teach claimed dose of oxaliplatin
 - The claimed doses are starting doses
- No reasonable expectation of successful "treatment"
 - Early-phase or preclinical data not predictive of success
 - Unpredictability/low probability of success in the field
- Unexpected results support obviousness
 - NALIRIFOX is an embodiment of the invention
 - Invention improved tolerability without sacrificing efficacy

Paper 38 at 3-4, 11-13, 16, 18-19, 20-22

No Motivation to Modify FOLFIRINOX

Unrebutted: The Claimed Doses Are Starting Doses

The invention claimed is:

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 (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.

'552 Patent at Claim 1

Other dose reduction schedules are provided Tables 1B-1E below. When the starting (initial) dose of MM-398 is 60 mg/m², 5FU 2400 mg/m², LV(1+d) 400 mg/m² and Oxaliplatin is either 85 mg/m² OR 60 mg/m², then the first dose reduction in response to a grade III or IV hematotoxicity is preferably a 25% dose reduction for each of the MM-398, 5-FU and Oxaliplatin doses for each administration of the antineoplastic therapy. For persistent toxicities

'552 Patent at 13:38-45

The starting dose of ONIVYDE will be 60 mg/m², 5FU 2400 mg/m², LV 400 mg/m² and Oxaliplatin either 85 mg/m² or 60 mg/m². Dose reduction will be 25% reduction in all agents for any grade III-IV Hematotoxicity. For persistent toxicities despite the first dose reduction, and additional 25% dose reduction in all agents will occur. Further toxicity will then lead to discontinuation from trial.

'552 Patent at 30:5-11

CSPC Argues Obviousness of Four Changes to FFX

Conroy ("FOLFIRINOX")		'552 Patent ("NALIRIFOX")
180 mg/m ² irinotecan	1. New, different drug	60 mg/m ² liposomal irinotecan
85 mg/m ² oxaliplatin	2. New dose of a new, different drug	60 mg/m ² oxaliplatin
400 mg/m ² bolus, followed by 2,400 mg/m ² infusion of 5-flourouracil	3. Dose reduction of oxaliplatin	2,400 mg/m ² of 5-flourouracil
400 mg/m ² leucovorin	4. Dose reduction of 5-FU (bolus dose removal)	200 mg/m ² of <i>L</i> -form of leucovorin or 400 mg/m ² of racemic (<i>L</i> + <i>D</i>) form of leucovorin

E.g., Paper 38 at 5-6

Toxicity Concerns Would Not Have Motivated All Four Changes

1. Dr. Ratain's opinions are rooted in hindsight
2. The Conroy References nor any other art suggest preemptive reduction of oxaliplatin from 85 mg/m² to 60 mg/m²
3. The Prior Art as a whole would not have directed a POSA to make all four, distinct proposed modifications
4. The alleged properties of liposomal irinotecan would not have motivated a POSA to arrive at the claimed invention

E.g., Paper 21 at 24-26, 26-32, 32-35, 36-41

Dr. Ratain's Analysis Was Hindsight-Driven

It is hindsight to begin with the claimed invention

“Obviousness ‘cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention”

Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc., 725 F.3d 1341, 1352 (Fed. Cir. 2013) (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998))

Dr. Ratain's Analysis Was Hindsight-Driven

It is hindsight to begin with the claimed invention



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

Q. Why were you looking at a publication that was specifically teaching dropping the fluorouracil bolus?

A. Because, one, when I read the specification, they made a point of that, the patentees.

And, two, because I was aware that it's – it's been dropped from the FOLFIRINOX regimen by the vast majority of clinicians.

Ex. 2073 at 35:12-36:5

Paper 38 at 24-26 (citing, *inter alia*, Ex. 2073 at 27:6-13, 35:12-36:5)

Dr. Ratain's Analysis Was Hindsight-Driven

It is hindsight to begin with the claimed invention



Q. And then for Cantore, why did you select Cantore?

A. I have to refresh my memory on Cantore. I believe that was one of the ones that was after the 2015 priority date. It would be helpful if I could look at that document, Counsel.

* * *

So this regimen, Cantore, it discloses just the use of two of the drugs, irinotecan and oxaliplatin, but it's a much older reference. So it's part of the ancestry, so to speak, of FOLFIRINOX, and that's why I looked at it. It also -- **counsel asked me are there any references to specifically disclose an oxaliplatin dose of 60 milligrams per meter squared, and so I found this regimen.**

And so it's part of the history here, and it also has that specific dose.

Ex. 2073 (Ratain) at 39:24-41:16

Paper 21 at 26 (citing, *inter alia*, Ex. 2073 at 39:24-41:16)

The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

FOLFIRINOX Is Defined As Including 85 mg/m² Oxaliplatin

- Dr. Ratain only relies on the Conroy References for providing the motivation to reduce oxaliplatin dose to 60 mg/m²
- Conroy defines FOLFIRINOX as comprising 85 mg/m² oxaliplatin

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; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at a dose of 1000 mg per square meter weekly for 7 of 8 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.

Ex. 1003 at 1

Paper 21 at 26-32

The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

FOLFIRINOX Is Defined As Including 85 mg/m² Oxaliplatin

- The art recognized that Conroy taught FOLFIRINOX as 85 mg/m² oxaliplatin

(head versus body/tail). The FOLFIRINOX regimen included oxaliplatin (85 mg/m²) over 2 h, then irinotecan (180 mg/m²) over 90 min concurrently with leucovorin (400 mg/m²) over 2 h immediately following oxaliplatin, bolus 5-FU (400 mg/m²) and continuous intravenous infusion of 5-FU over 46 h (1,200 mg/m² per day for 2 days). Each cycle of therapy was repeated

Ex. 1041 (Conroy 2013) at 2-3

FOLFIRINOX

Promising phase II results with FOLFIRINOX (FFX) [5] (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², bolus 5-fluorouracil 5FU) (400 mg/m², infusional 5FU 2400 mg/m² over 46 h, every 14 days) were confirmed in a sentinel phase III study (PRODIGE 4/ ACCORD 11) [6], which randomized patients ≤75 years of age with metastatic pancreatic cancer and an ECOG PS of 0 or 1, to receive either gemcitabine or FFX. With a

Ex. 2004 (Marsh 2015) at 1-2

- Dr. Ratain agrees (Ex. 2073 at 85:8-13, 97:21-98:4)
- Petitioner's arguments are rooted in hindsight

Paper 21 at 27-28

The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

FOLFIRINOX Is Defined As Including 85 mg/m² Oxaliplatin

- There was a studied, known rationale for the selection of 85 mg/m² oxaliplatin as the starting dose
 - Ychou et al. (Ex. 2038 at 7-8): Safety and Efficacy data supported recommendation of a starting dose of 85 mg/m² oxaliplatin
- Dr. Oberstein opines (unrebutted) that a POSA would not be motivated to preemptively reduce that starting dose:

tolerable dose of the therapeutic agents to the patient. A POSA would understand that a starting, or “defined,” dose is the dose that has been associated with the best clinical outcomes and would not depart from that preemptively, if possible.

Ex. 2076 at ¶¶ 245; 243-245

Paper 21 at 28-29; Paper 38 at 15

The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

The Conroy Protocol & Appendix teach that *all patients in the FOLFIRINOX arm are treated with a starting dose of 85 mg/m² oxaliplatin*

6.1 Description of trial treatments

After random selection, subjects receive either treatment A (Folfirinox) or treatment B (gemcitabine):

Treatment A: Folfirinox

- Oxaliplatin (Eloxatine®) 85 mg/m² D1 in 2h, subsequently
- Irinotecan (Campto®) 180 mg/m² D1 in 90 min.
- Folinic acid 400 mg/m², D1 in 2h (during irinotecan infusion)
- 5-FU bolus 400 mg/m² D1 followed by continuous 5-FU 2.4 g/m² in total over 46 hours, i.e. 1.2 g/m² on D1 and 1.2 g/m² on D2.

Treatment should be continued until progression, and a maximum of 12 cycles is recommended.

Ex. 1004 at 14; Ex. 2076 at ¶¶ 154-159

Paper 21 at 26-27

The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

TREATMENT A: Folfirinox				
CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU
PNN $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$	No cycle delay	No dose reduction		
PNN $< 1.5 \times 10^9/L$	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, discontinuation of treatment*	1 st episode: dose reduction to 150 mg/m ² 2 nd episode: dose maintained at 150 mg/m ² 3 rd episode: discontinuation of treatment	1 st episode: no dose reduction 2 nd episode: reduce dose to 60 mg/m ² 3 rd episode: discontinuation of treatment	1 st episode: eliminate bolus on D1
Platelets $< 75 \times 10^9/L$	Delay treatment until recovery (platelets $\geq 75 \times 10^9/L$) If no recovery at D29, discontinuation of treatment	1 st episode: no dose reduction 2 nd episode: reduce dose to 150 mg/m ² 3 rd episode: discontinuation of treatment	1 st episode: reduce dose to 60 mg/m ² 2 nd episode: maintenance of reduced dose 3 rd episode: discontinuation of treatment	1 st episode: reduce bolus and continuous infusion dose by 25%

- Conroy's dose reduction guidelines do not motivate a preemptive 60 mg/m² starting dose
- *Instruct reduction only after certain toxicity events*
- Include reductions for all components – not just oxaliplatin

Ex. 1004 at 16-19; Ex. 1017 at 4-7; Ex. 2076 at ¶¶ 154-159; 245-251

Paper 21 at 29-32

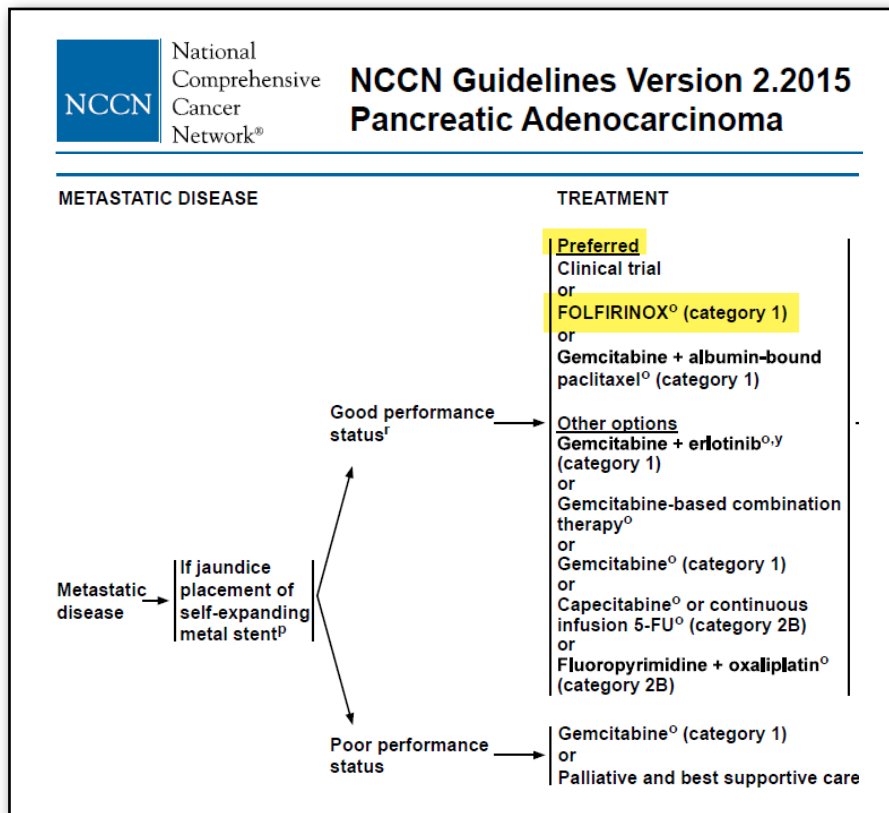
The Conroy References Do Not Provide Motivation to Preemptively Reduce Oxaliplatin Dose

Median Dose Intensity Is Not Related to Starting Dose

- Dr. Ratain/CSPC places undue reliance on Conroy's 78% "median dose intensity" for oxaliplatin
- Does not inform a POSA as to
 - how many patients received dose reductions
 - how many dose reductions occurred over the course of the study, including along with other modifications
- Does not connect dose reduction to the conclusions of safety and efficacy in the study, which are based on a starting dose of 85 mg/m² oxaliplatin dose

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

Despite toxicity, FOLFIRINOX was still a preferred treatment



Dr. Ratain's Declaration

232. In my opinion, claim 1 would have been obvious over the prior art at least because the claimed method of treatment involves administering an antineoplastic therapy consisting of liposomal irinotecan, oxaliplatin, and 5-fluorouracil – the same four-drug combination as in the established gold-standard FOLFIRINOX regimen for first-line treatment of metastatic pancreatic cancer.

233. The FOLFIRINOX regimen as first described by Conroy et al. consists of 85 mg/m² oxaliplatin, 180 mg/m² irinotecan, 400 mg/m² leucovorin, and 5-FU, first administered as a 400 mg/m² bolus and then 2400 mg/m² 5-FU infusion, administered every two weeks in first-line therapy in patients with metastatic pancreatic cancer. (Ex. 1003 at 1.)

Paper 21 at 32-33; Ex. 2036 at 16, 56-57; Ex. 2076 at ¶¶ 232-233

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

- Prior art offered many different approaches, none pointing to the claimed combination
- Dr. Ratain's relied-upon references describe approaches for reducing toxicity other than oxaliplatin reduction:

Post-Conroy Reference	Address FOLFIRINOX toxicity by
Mahaseth (Ex. 1015)	Removal of 5-FU bolus dose and addition of growth factor
Ginocchi (Ex. 1016)	Removal of 5-FU bolus dose and reduction in irinotecan
Hatachi (Ex. 1021)	Removal of 5-FU bolus dose

- Other references teach that **deletion of 5-FU bolus and reduction of irinotecan** were the **most common** modification to address toxicity

(See e.g., Ex. 2076 at 257-258, 261; Ex. 1041 (Conroy 2013) at 4; Ex. 2043 (Gunturu) at 3).

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

- Dose reduction in metastatic pancreatic cancer requires a strong rationale — because patients are at an **advanced stage of disease** and dose reduction **may compromise efficacy**
- Dr. Ratain fails to explain why a POSA would make all four modifications simultaneously
 - Mahaseth purports to be “well tolerated” with “maintained efficacy” by removal of 5-FU bolus alone
 - No rationale as to why further modifications are required
- At best, a POSA would have made one modification at a time, not all four at once

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

Reference Name and Year Published	Regimen Administered	Modifications From Standard FOLFIRINOX	Treatment Administered In First- / Second-Line Patients	Conclusion
Prospective Studies				
Vasile 2012	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,800 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan 400 mg increased 5-FU(iv) Removed 5-FU(bolus)	No prior treatment information	"Chemotherapy with mFOLFOXIRI seems active in locally advanced pancreatic cancer patients and may allow to obtain a downstaging of disease leading some patient to achieve a curative surgical resection."
James 2014	Oxaliplatin: 85 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 300 mg/m ²	25% reduced irinotecan 25% reduced 5-FU(bolus)	First-line	"mFOLFIRINOX, given along with prophylactic pegfilgrastim is associated with a similar RR and improved tolerability compared to full dose FOLFIRINOX in advanced PC."
Stein 2016	Oxaliplatin: 85 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 300 mg/m ²	25% reduced irinotecan 25% reduced 5-FU(bolus)	First-line	"In this first prospective study of modified FOLFIRINOX in MPC and LAPC, we observed decreased AEs compared with historical control patients. In MPC, the efficacy appears comparable with FOLFIRINOX."
Yoshida 2017	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	"Compared to FX, mFX may result in fewer Grade 3 or 4 nonhematological AEs, with a comparable response rate. However, further efforts might be required to reduce hematological AEs."
Li 2017	Oxaliplatin: 68 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	20% reduced oxaliplatin 25% reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	"In summary, we showed that our modified-FOLFIRINOX was well tolerated in MPC patients, with an ORR of 32.5%, median OS of 10.3 month, and PFS of 7.0 months. . . . To our knowledge, this is the first prospective study aiming to evaluate the efficacy of FOLFIRINOX in Chinese MPC patients, and they did benefit from dose reduction with improved safety and similar tumor response."
Ozaka 2018	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	"In conclusion, this is the first prospective study of modified FOLFIRINOX in Asia. The modified FOLFIRINOX regimen in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim."

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

Wang 2019	Oxaliplatin: 65 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	20 mg reduced oxaliplatin 30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	"The efficacy of this modified FOLFIRINOX was comparable to that of the original regimen but with a notably lower rate of adverse events."
Ramanathan 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 180 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	Removed 5-FU(bolus) Added PEGPH20 (recombinant hyaluronidase)	First line	"The control arm of mFOLFIRINOX was remarkably well tolerated and resulted in a median OS of 14.4 months, which is—to our knowledge—the highest reported for this regimen."
Wei 2019	Oxaliplatin: 72.25 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	15% reduced oxaliplatin 25% reduced irinotecan Removed 5-FU(bolus)	First-line	"[W]e provide evidence that pretreatment ctDNA level correlates with tumor burden in PDAC, and serial ctDNA analysis is a robust tool for monitoring cancer response to chemotherapy."
Vivaldi 2021	Oxaliplatin: 85 mg/m ² Irinotecan: 165 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 3,200 mg/m ² 5-FU(bolus): 0 mg/m ²	15 mg reduced irinotecan 800 mg increased 5-FU(iv) Removed 5-FU(bolus)	First-line	"For patients with at least one mutated allele of UGT1A1, careful management of hematological and gastrointestinal toxicity is recommended, and a modified FOLFIRINOX with a dose reduction of 30% of irinotecan in homozygous patients might be appropriate."
Retrospective Studies				
Gunturu 2012	Variable	Median Relative Dose Intensity Compared to FOLFIRINOX: Oxaliplatin: 90% Irinotecan: 64% Leucovorin: undisclosed 5-FU(iv): 100% 5-FU(bolus): 66%	First-line and second-line patients	"In this single institution retrospective study, the routine 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."
Peddi 2012	Variable	Median Dose Intensities for First Cycle for Each Component: 100% Average Dose Intensities for First Cycle:	First-line and second-line patients	"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

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

		<p>Oxaliplatin: 98% Irinotecan: 90% Leucovorin: undisclosed 5-FU(iv): 99% 5-FU(bolus): 59%</p> <p>Overall Average Dose Intensities: Oxaliplatin: 96% Irinotecan: 88% Leucovorin: undisclosed 5-FU(iv): 96% 5-FU(bolus): 57%</p>		<p>patients were able to undergo resection after FOLFIRINOX therapy. This is notable given the extensive desmoplastic stroma reaction in localized disease and concern for reduced efficacy of chemotherapy in this setting. Progression-free and overall survivals were longer than the results published in the ACCORD trial (7.5 months and 13.5 months, respectively) likely reflecting inclusion of patients with non-metastatic disease. One-year survival rate for patients with metastatic disease was 41.8%, similar to the 48.4% reported in the ACCORD trial.”</p>
Lowrey 2012	Variable	<p>Median Starting Dose 80% of that used in PRODIGE/ACCORD trial</p>	First-line	<p>“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.”</p>
Hosein 2012	Variable	<p>Dose Intensity Oxaliplatin: 98% Irinotecan: 95% Leucovorin: undisclosed “5-fluorouracil”: 98%</p>	First-line	<p>“Neoadjuvant therapy with FOLFIRINOX in patients with unresectable or borderline resectable locally advanced pancreatic cancer appears to be feasible in selected patients.”</p>
Alessandretti 2013	Variable	<p>Median Reductions in Dose Compared to FOLFIRINOX:</p> <p><u>First Cycle:</u> Oxaliplatin: 23.3% Irinotecan: 24.6% Leucovorin: undisclosed “Fluorouracil”: 20.6%</p> <p><u>Fourth Cycle:</u> Oxaliplatin: 20.8% Irinotecan: 24.9% Leucovorin: undisclosed “Fluorouracil”: 17.6%</p>	No prior treatment information	<p>“Modified dose-attenuated FOLFIRINOX is a therapeutic option to elderly with advanced pancreatic adenocarcinoma. Although grade 3 and 4 toxicities were reported, they were manageable.”</p>

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

Mahaseth 2013 (Ex. 1005)	Oxaliplatin: 85 mg/m2 Irinotecan: 180 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	Removed 5-FU(bolus)	No prior treatment information	"Overall our modified regimen was well tolerated. . . . The modified FOLFIRINOX regimen appears to have an improved safety profile especially with respect to neutropenia, fatigue, and vomiting."
Blazer 2014	Oxaliplatin: 85 mg/m2 Irinotecan: 165 mg/m2 Leucovorin: 0 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	15 mg reduced irinotecan Removed leucovorin Removed 5-FU(bolus)	No prior treatment information	"Neoadjuvant mFOLFIRINOX is an effective, well-tolerated regimen for patients with advanced nonmetastatic pancreatic cancer. When mFOLFIRINOX is coupled with aggressive surgery, high resection rates are possible even when the initial imaging shows locally advanced disease."
Ghorani 2015	Oxaliplatin: 85 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 400 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	25% reduced irinotecan Removed 5-FU(bolus)	No prior treatment history information	"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."
Kaga 2016	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	"We therefore clinically utilized irinotecan dosage of 150 mg/m2 for patients enrolled in this study. The survival time (median PFS, 5.3 months; median OS, 10.3 months) in our cohort was similar to that of the Japanese phase II trial of FOLFIRINOX (median PFS, 5.6 months; median OS 10.7 months) as well as the FOLFIRINOX phase III trial (median PFS, 6.4 months; median OS, 11.1 months)."
de Jesus 2018	Oxaliplatin: 50-85 mg/m2 Irinotecan: 60-180 mg/m2 Leucovorin: 0-400 mg/m2 5-FU(iv): 1,800-2,400 mg/m2 5-FU(bolus): 0-400 mg/m2	Variably reduced all components	First-line	"To conclude, modified FOLFIRINOX demonstrated similar activity to that of standard FOLFIRINOX in patients with MPA. No major differences in toxicity were observed, mainly due to selection bias, uneven dose reductions and unrestricted use of prophylactic G-CSF."
Kang 2018	Oxaliplatin: 63.75 mg/m2 Irinotecan: 135 mg/m2 Leucovorin: 150 mg/m2 5-FU(iv): 1,800 mg/m2 5-FU(bolus): 300 mg/m2	25% reduced oxaliplatin 25% reduced irinotecan 25% reduced leucovorin 25% reduced 5-FU(bolus) 25% reduced 5-FU(iv)	First-line	"mFOLFIRINOX showed comparable efficacy but better safety compared to sFOLFIRINOX. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy."
Yamada 2018	Oxaliplatin: 85 mg/m2 Irinotecan: 150 mg/m2 Leucovorin: 200 mg/m2 5-FU(iv): 2,400 mg/m2 5-FU(bolus): 0 mg/m2	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	"Modification of the FOLFIRINOX regimen (oxaliplatin 85 mg/m2, irinotecan 150 mg/m2, 5-FU infusion 2400 mg/m2 over 46 h, no bolus 5-FU) reduces the incidence of grade 3-4 neutropenia to 47.8%. More importantly, a meta-analysis showed that the modified

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

				FOLFIRINOX regimen is as effective as the original, with a similar tumor response rate (32% versus 33%, $p = 0.879$), rate of 12-month survival (47% versus 50%, $p = 0.38$), rate of 6-month PFS rate (47% versus 53%, $p = 0.38$) and reduced frequency of grade 3–4 adverse events."
Eraslan 2019	Oxaliplatin: 65 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 0 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	20 mg reduced oxaliplatin 25% reduced irinotecan Removed leucovorin Removed 5-FU(bolus)	First-line and second-line patients	"In advanced pancreatic cancer patients with good ECOG PS, mFOLFIRINOX treatment provided OS and PFS benefit with manageable toxicity profile. Sustainability of treatment due to side effects is a major problem for both the patient and the physician."
Sasaki 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line and second-line patients	"In conclusion, overall treatment outcomes of chemotherapy for metastatic pancreatic cancer were significantly improved after introduction of FOLFIRINOX and GEM+nab-PTX in the daily practice. However, about 25% of the metastatic pancreatic cancer patients could not be treated with these two effective regimens as first-line chemotherapy. Furthermore, only less than 40% of the patients were treated with these two regimens as second-line chemotherapy. More effective second-line and third-line chemotherapy regimens with less toxicity are required to prolong the overall survival of metastatic pancreatic cancer patients."
Vivaldi 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 165 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 3,200 mg/m ² 5-FU(bolus): 0 mg/m ²	15 mg reduced irinotecan 800 mg increased 5-FU(iv) Removed 5-FU(bolus)	First-line	"Our results obtained in a large retrospective cohort of metastatic PC patients treated with standard regimens such as modified FOLFIRINOX and GemNab suggest that an earlier and deeper tumor shrinkage is able to predict long-term outcome of PC patients."
Cavanna 2019	Oxaliplatin: 85 mg/m ² Irinotecan: 135 mg/m ² Leucovorin: 200 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 320 mg/m ²	25% reduced irinotecan 20% reduced 5-FU(bolus)	First-line	"In conclusion, with the limitations of a retrospective study our results demonstrate that attenuated dose of FOLFIRINOX is feasible in outpatients with metastatic/advanced pancreatic cancer in a general hospital, in the real-world clinical practice, the dose reduction as performed in our patients did not compromise efficacy, but reduced the number of AE."
Cui 2020	Oxaliplatin: 85 mg/m ² Irinotecan: 140 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ²	40 mg reduced irinotecan	First-line	"In the majority of the patients, the AEs associated with chemotherapy were manageable and tolerable."

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

	5-FU(bolus): 400 mg/m ²			
Pacheco-Barcia 2020	Oxaliplatin: 85 mg/m ² Irinotecan: 180 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	Removed 5-FU(bolus)	First-line and second-line patients	<p>"In the subgroup analysis defined by treatment, we observed differences between them. The most interesting finding is that when SIRI values were $<2.3 \times 10^9/L$ there were no differences between treatment received; however, in the group of patients with SIRI $\geq 2.3 \times 10^9/L$ we observed a longer OS with mFOLFIRINOX therapy."</p> <p>"The results of this study suggest that SIRI may be useful in appropriately selecting patients who would benefit of mFOLFIRINOX therapy as a more intensive first-line chemotherapy regimen."</p>
Takeda 2021	Oxaliplatin: 85 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	<p>"In conclusion, we demonstrated that the prognosis of PC with peritoneal metastasis has significantly improved over time with the advent of the novel combination chemotherapy regimens (GnP and mFFX). These two regimens showed a satisfactory radiologic tumor response, PFS, and OS, and was identified as an independent prognostic factor for OS."</p>
Zhou 2021	Oxaliplatin: 65 mg/m ² Irinotecan: 150 mg/m ² Leucovorin: 400 mg/m ² 5-FU(iv): 2,400 mg/m ² 5-FU(bolus): 0 mg/m ²	20 mg reduced oxaliplatin 30 mg reduced irinotecan Removed 5-FU(bolus)	First-line	<p>"In summary, we demonstrated the prognostic value of delta HU for both locally advanced PDAC and advanced PDAC. Delta HU was as a potential marker of predicting chemotherapy response. Patients with higher delta HU will benefit from mFOLFIRINOX treatment. The delta HU was positively correlated with stroma MVD, probably explaining the reason of lower ΔHU associated with worse prognosis."</p>

E.g., Paper 21 at 33-34
Ex. 2076 at p. 193-198 (App. B)

Prior Art As a Whole Does Not Direct a POSA to Dr. Ratain's Four Modifications, Let Alone Simultaneously

- Post-priority date conduct confirms the lack of direction in the art
 - Researchers continued to pursue different modifications to FOLFIRINOX (see *Ex. 2076 at Appx. B*), e.g.
 - *Removal or reduction of 5-FU bolus dose*
 - *Removal of 5-FU bolus dose and reduction to irinotecan*
 - *Reduction of several components*
 - *Reduction of a single component*
- None replaced a component with a new drug

Experts Agree: Liposomal Irinotecan Is a Different Drug With Different Properties



Dr. Mark Ratain

CSPC's Expert

Q. Right. And liposomal irinotecan has its own distinct FDA labeling, correct?

A. Yes, and **it's a distinct product, and it has similar but different properties from free irinotecan.** But they're certainly siblings or father-child relationship.

Ex. 2073 at 49:7-12



Dr. Paul Oberstein

Ipsen's Expert

“As of August 21, 2015, a POSA would not have known how liposomal irinotecan would have performed in comparison with free irinotecan in a clinical study for the treatment of metastatic pancreatic cancer. Therefore, **a POSA would not have been motivated to make replace liposomal irinotecan along with the other three proposed modifications.**”

Ex. 2076 at ¶ 276

Known Properties of Liposomal Irinotecan Did Not Motivate the Claimed Methods

- Dr. Ratain explained that the “different properties” of liposomal irinotecan do not translate to a superior approach:



Q. When you say “highly dependent on schedule,” what does that mean?

A. In other words, there have been studies in the past of giving irinotecan by prolonged infusion, and you can only -- if you give a very small amount every day, it's toxic, just because you've got the drug around continuously, and, therefore, it has a greater effect.

So liposomal irinotecan has properties similar to prolonged infusion of irinotecan. And what's unclear is whether liposomal irinotecan can increase the efficacy of irinotecan. It's just not entirely clear.

There's some preclinical studies that certainly suggest that. There was certainly enthusiasm for that possibility, just like there was enthusiasm for encapsulating paclitaxel, and that led to the development of ABRAXANE.

But, you know, it's not yet been proven that this formulation or this schedule of giving irinotecan, so to speak, is superior than the more conventional, historical approach.

Q. Is that true as of today?

A. Yes.

Q. Okay. And so that would have been true as of August 21st, 2015, as well?

A. Yes.

Ex. 2073 (Ratain) at 50:23-51:24

Paper 21 at 36

Known Properties of Liposomal Irinotecan Did Not Motivate the Claimed Methods

- Ko, Saif, and Bayever do not suggest replacing irinotecan in FOLFIRINOX with liposomal irinotecan
 - **Ko** points toward liposomal irinotecan with gemcitabine, not oxaliplatin;
 - **Saif** expressly questions whether the replacement is worthwhile given countervailing toxicity concerns; and
 - **Bayever** is entirely silent on any combination therapy that includes oxaliplatin

Known Properties of Liposomal Irinotecan Did Not Motivate the Claimed Methods

- A POSA would have been aware of the heightened risk of neutropenia, a serious, dose-limiting side effect
 - Irinotecan and oxaliplatin independently carry known risks of neutropenia
 - FOLFIRINOX itself produced neutropenia as the most common grade 3–4 adverse
- Prior art taught dose reduction — not drug substitution — as the solution

No Motivation to Select 60 mg/m² Dose of Liposomal Irinotecan

Arm A (experimental arm): MM-398	MM 398 120 mg/m ² IV over 90 minutes, every 3 weeks. Patients who are homozygous for UGT1A1*28 allele will receive the first cycle of therapy at a reduced dose of 80 mg/m ² . If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased in increments of 20 mg/m ² up to a maximum of 120 mg/m ² .
Arm B (control arm): 5-FU and leucovorin	5-FU 2000 mg/m ² IV over 24-hours (+/- 30 minutes), administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle. Levoleucovorin dosed at 200 mg/m ² or the leucovorin / + d racemic mixture dosed at 400 mg/m ² , given IV over 30 minutes, administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle.
Arm C (experimental arm): MM-398, 5-FU and leucovorin	MM-398 80 mg/m ² IV over 90 minutes, every 2 weeks. Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m ² . If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m ² . 5-FU 2400 mg/m ² IV over 46-hours, every 2 weeks. Levoleucovorin dosed at 200 mg/m ² or the l + d racemic mixture dosed at 400 mg/m ² , IV over 30 minutes, every 2 weeks. MM-398 should be administered prior to 5-FU and leucovorin; leucovorin should always be administered prior to 5-FU. If the dosing of either MM-398 or 5-FU/leucovorin needs to be withheld, then the other drug in the combination should not be administered either.

Ex. 1006 at 26-27

- Bayever does not teach 60 mg/m² as the dose for a combination with oxaliplatin
 - Silent as to combining with oxaliplatin
 - Starting doses are 120 mg/m² or 80 mg/m²
 - 60 mg/m² appears only as a reduced dose for a specific genetic subpopulation, and then *directs dose escalation* if no toxicity occurs
 - Teaches further dose reduction in case of toxicities to 50 mg/m² or lower

Paper 21 at 36-38
Ex. 2076 at ¶¶ 282-283

No Motivation to Select 60 mg/m² Dose of Liposomal Irinotecan

- No prior art correlates the irinotecan dose in FOLFIRINOX to a liposomal irinotecan dose
- Pharmacokinetic differences between liposomal and free irinotecan do not permit straightforward quantitative comparison
- Other art point to higher doses
 - Chen recommends 120 mg/m² every three weeks for future Phase II studies
 - Roy used doses up to 150 mg/m² and concluded higher doses showed better antitumor activity

Paper 21 at 38, 49-50;
Ex. 1057 (Chen);
Ex. 2076 at ¶ 285 (discussing Chen);
Ex. 1055 (Roy);
Ex. 2076 at ¶¶ 95-97 (discussing Roy);
Ex. 2076 at ¶¶ 282-283

No Reasonable Expectation of Success

CSPC's Reasonable Expectation Argument Fails For Several Reasons

- 1) CSPC's Alleged "Reasonable Expectation of Success" Relies on an Erroneous Claim Construction
- 2) CSPC Improperly Relies on the Outcomes Reported for Prior-Art Regimens
- 3) Lowering dose of oxaliplatin was not routine experimentation
- 4) CSPC's "Result-Effective Variable" Argument Fails, Again
- 5) CSPC's Cited Data Would Not Have Inspired a Reasonable Expectation of Success in the Claimed Treatment
- 6) CSPC Ignores Unpredictability of Clinical Effects at Different Doses in Combination Therapy

CSPC's Argument Rests on an Erroneous Claim Construction

- CSPC argues “treating” requires only administration — not actual efficacy
- CSPC's construction would “improperly seek[] to obviate proof of ‘reasonable expectation of success’” altogether
- The PTAB **rejected** this construction

any resulting therapeutic benefit. Rather, on this record, we agree with Patent Owner that the ordinary understanding of a claim reciting a “method of treating metastatic adenocarcinoma of the pancreas” that comprises “administering an antineoplastic therapy to the patient” in order “to treat the metastatic adenocarcinoma of the pancreas” is that the “treatment” would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.

CSPC Improperly Relies on the Outcomes Reported for Prior-Art Regimens

The Board seemed to believe that the “reasonable expectation of success” inquiry looked to whether one would reasonably expect the prior art references to operate as those references intended once combined. That is not the correct inquiry—one must have a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue. The Board's reliance on the absence of a

Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.,
821 F.3d 1359, 1367 (Fed. Cir. 2016)

- CSPC contends that “it has been universally accepted now and in the prior art that providing lower doses of [the chemotherapy drugs used in the claimed invention] results in fewer side effects”
- CSPC, however, relies on portions of Dr. Ratain’s declaration that simply restates the outcomes of the same prior art references he relies on for motivation to combine – ***none of which address the claimed invention as a whole***

Paper 1 at 50-51; Paper 21 at 42-44

CSPC's "Result-Effective Variable" Argument Fails, Again

Lowering the dose of Oxaliplatin (or any component) was not Routine Optimization

- Dr. Oberstein opined that dose adjustment in the context of a multiple-component drug regimen would not be routine experimentation or optimization
 - Compromise efficacy with lower doses
 - Each component has different PK properties
 - Multiple changes can cause variable responses
- Dr. Ratain **does not rebut this opinion**, and his own publications confirm the unpredictable clinical effects of anticancer drugs

FOLFIRINOX without a rational basis for doing so. For example, a POSA would have known that preemptive dose reduction, or dose reduction of the starting dose that has already demonstrated efficacy may negatively compromise treatment outcomes. Ex. 1052 at 2 (“Dose reductions used as a means of reducing toxicity may undermine outcomes when $\leq 85\%$ of the standard dose intensity is delivered.”).

Exhibit 2076 at ¶ 291

Undevia, co-authored by Dr. Ratain, states that: “[a]nticancer drugs can have considerable interindividual pharmacokinetic variability, which, given the narrow therapeutic index of the drugs, results in *unpredictable clinical effects*.” Ex. 2023 at 2 (emphasis added); *see also* Ex. 2026 at 1 (“[C]ombination therapy in oncology

Exhibit 2076 at ¶ 292

Ex. 2076 at ¶¶ 288-293; Paper 21 at 46-48

CSPC's “Result-Effective Variable” Argument Fails, Again

- The Patent Office addressed CSPC's “result-effective variable” argument and Ipsen overcame it
- The Federal Circuit recognizes that where “variables interacted in an unpredictable or unexpected way,” the combination is non-obvious — *ModernaTx v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376 (Fed. Cir. 2021)

CSPC's Cited Data Does Not Support a Reasonable Expectation of Success

- Pre-clinical data regarding liposomal irinotecan alone in Bayever does not support reasonable expectation of success in the claimed four-drug combination
- Dr. Ratain's **own publications** acknowledge that “preclinical studies do not generally predict success of clinical trials” and that Phase II trials “have a high negative predictive value but a low positive predictive value”
- Pancreatic cancer drug development has a particularly low success rate — solid tumor drugs for pancreatic cancer “seemed to have the toughest challenges in Phase III studies (13.1%)”

Ex. 2076 at ¶¶ 294-302; Paper 21 at 48-49

CSPC Ignores the Unpredictability of Clinical Effects in Combination Therapy

- CSPC ignores the unpredictability of clinical effects of the drugs at issue
 - Oncology drugs have a narrow therapeutic window
 - Inter-individual variability
 - Pharmacokinetic variability, including non-linear pharmacokinetics in some drugs
 - More than one oncology drug in combination
- Dr. Ratain opines that Ko and Saif offer at most “hope[] of improving overall survival”
 - Federal Circuit law is clear: “hope that a potentially promising drug will treat a particular cancer is **not enough** to create a reasonable expectation of success in a **highly unpredictable** art” — *OSI Pharms. v. Apotex, Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019).

Unexpected Results

Unexpected Results Support Non-Obviousness

- A POSA would have **expected** an **oxaliplatin dose reduction from 85 mg/m² to 60 mg/m²** — combined with removing the 5-FU bolus and substituting liposomal irinotecan — **would compromise efficacy**

Ex. 2076 at ¶¶ 263, 288-291, 306-08

- NALIRIFOX **surprisingly** delivered **comparable efficacy** to FOLFIRINOX while delivering **substantially improved tolerability**

Ex. 2076 at ¶ 305; Ex. 1011 at Table 1; Ex. 2032 at Table 2

E.g., Paper 21 at 50-53

Unexpected Results Support Non-Obviousness

NAPOLI-3 Trial – Phase III Clinical Trial for
NALIRIFOX (EX 2032 at 6 (Table 2))

Efficacy	NALIRIFOX	Gem + nab-PAC	FOLFIRINOX
OS	11.1 months	9.2 months	11.1 months
PFS	7.4 months	5.6 months	6.4 months
ORR	41.8%	36.2%	31.6%

Ex. 1011 at Table 1

Safety	NALIRIFOX	FOLFIRINOX
Grade $\geq$ 3 peripheral neuropathy	6.5%	9%
Grade $\geq$ 3 Neutropenia/Febrile Neutropenia	24.2%	46.5%
Grade $\geq$ 3 diarrhea	20%	13%

Ex. 1011 at Table 1

Prolonged survival with an improved toxicity profile is a difference in kind

E.g., Paper 21 at 50-53

Unexpected Results Support Non-Obviousness

- Post-priority date studies suggest NALIRIFOX has **better efficacy and tolerability than gemcitabine/nab-paclitaxel (GnP)**, while modified FOLFIRINOX (mFFX) did not demonstrate the same advantage

Efficacy	mFFX (Ex. 2034)	Gem + nab-PAC (Ex. 2034)
OS	12.5 months	15.3 months
PFS	5.9 months	6.5 months

Unexpected Results Support Non-Obviousness

Nevala-Plagemann does not rebut unexpected results

- **It is an opinion piece, not an empirical study** — uses argumentative framing ("we argue that...") and "at most, purports to identify issues for future consideration and study" (Ex. 2076 at ¶ 224; Paper 21 at 51)
- **It does not establish that NALIRIFOX and FOLFIRINOX are "identical" in efficacy** — Nevala-Plagemann does not establish that the two regimens are "identical" in efficacy or "in any other respect," nor does it refute evidence that the '552 Patent's claimed methods offer unexpected benefits (Ex. 2076 at ¶ 224; Paper 21 at 51)
- **Dr. Ratain ignores Nevala-Plagemann's own acknowledgment of NALIRIFOX's benefit** — Nevala-Plagemann acknowledges that NALIRIFOX demonstrated a "modest improvement" in OS over gemcitabine/nab-paclitaxel in NAPOLI-3, which was sufficient for FDA approval (Ex. 2076 at ¶ 311)
- **The comparable OS finding does not defeat unexpectedness** — "As of August 21, 2015, a POSA would not have expected achieving comparable efficacy with FOLFIRINOX while delivering a more tolerable regimen" (Ex. 2076 at ¶ 311)

Paper 21 at 50-53;
Paper 38 at 20-22

Unexpected Results Support Non-Obviousness

Nichetti does not rebut unexpected results

- **It is a retrospective review and meta-analysis with inherent limitations** — Nichetti "reflects a review and meta-analysis, 'with all the inevitable limitations' inherent to such a study, of data from a number of different clinical trials involving different regimens for treatment of pancreatic cancer" (Ex. 2076 at ¶ 221)
- **It does not establish that NALIRIFOX and FOLFIRINOX are "identical" in efficacy** — Nevala-Plagemann does not establish that the two regimens are "identical" in efficacy or "in any other respect," nor does it refute evidence that the '552 Patent's claimed methods offer unexpected benefits (Ex. 2076 at ¶ 221; Paper 21 at 51)
- **Nichetti itself acknowledges NALIRIFOX's superior toxicity profile** — Nichetti indicates that "NALIRIFOX was associated with the most favorable toxicity profile, with a lower incidence of hematological toxic effects and peripheral neuropathy, which often represent the limiting adverse events for the other 2 regimens" (Ex. 2076 at ¶ 221, quoting Nichetti at 9)
- **To the extent Nichetti suggests comparable efficacy, it also indicates differences in toxicity** — those toxicity differences themselves support, rather than undermine, the unexpected results argument (Ex. 2076 at ¶¶ 311-12; Paper 21 at 51)

Paper 21 at 50-53;
Paper 38 at 20-22

Ground 2

Grounds and Challenged Claims

- CSPC challenges all claims of the '552 Patent on three grounds as follows:

Ground	Claims	Basis	Asserted Prior Art
1	1, 3-6, 8-14	103	Conroy, Conroy Protocol, Conroy Appendix, and Mahaseth in combination with Bayever, Saif, Ko, and Cantore
2	2, 7, and 15	103	Ground 1 in addition to Masi and Ginocchi
3	1-15	103	Grounds 1 and 2 in addition to Carnevale and Dean

Pet. at 6.

Claims 2, 7 and 15 Are Not Obvious

2. The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

* * *

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.

* * *

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.

'552 Patent at Claims 2, 7, 15

- Ground 2 fails at least for the same reasons as Ground 1
- Dr. Oberstein's opinions with respect to Ground 2 are not rebutted by Dr. Ratain
- **Claim 2:** No supporting expert opinions at all
- **Claims 2, 7 and 15:** No supporting expert opinions regarding Masi and Ginocchi

Paper 21 at 53-57;
Ex. 2076 at ¶¶ 315, 318

Claim 2 Is Not Obvious

Dr. Ratain admits that he has offered no opinions with respect to claim 2 of the '552 Patent



Q. Okay. So I just want to confirm that you were not asked to consider whether claim 2 of the '552 patent is obvious in view of the prior art, correct?

A. That's correct.

Q. And so you're not offering any opinions with respect to whether claim 2 of the '552 patent is obvious?

A. I am not.

Ratain Dep. at 22:12-20

Paper 21 at 53

Claim 2 Is Not Obvious

2. The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

'552 Patent at Claim 2

in subsequent 4-week courses. FOLFIRINOX consisted of **oxaliplatin** at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, **immediately followed by leucovorin** at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, **with the addition, after 30 minutes, of irinotecan** at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector. This treatment was im-

Conroy (EX1003) at 3

- Claim 2 requires administration of oxaliplatin **2 hours after** administration of liposomal irinotecan
- No asserted reference teaches this limitation
- Conroy & Mahaseth teach administration of oxaliplatin **before** the administration of irinotecan

Paper 21 at 54-55;
Ex. 2076 at ¶¶ 317-322

Claim 2 Is Not Obvious

1. A method of treating pancreatic cancer in a human patient, the method comprising: administering to the patient an effective amount of liposomal irinotecan, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2 , except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2 .

4. The method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

Bayever (EX1006) at 54

- Bayever does not teach the administration of oxaliplatin after liposomal irinotecan
- Bayever is silent as to the use of oxaliplatin in combination with liposomal irinotecan
- Only teaches use of liposomal irinotecan prior to administration of leucovorin and 5-FU

Paper 21 at 54-55;
Ex. 2076 at ¶¶ 315-323; 169-180

Claim 2 Is Not Obvious

MASI

- Masi directed to metastatic colorectal cancer – not pancreatic
- Irinotecan, not liposomal irinotecan
- Based on *in vitro* studies in colon cancer cell lines – do not necessarily predict clinical outcomes
- Published in 2004 – six years before Conroy and FOLFIRINOX

GINOCCHI

- Ginocchi directed to mFFX but is silent as to order of administration
- Irinotecan, not liposomal irinotecan
- Modified regimen was well-tolerated and addressed alleged toxicity concerns
- No motivation to further modify

Paper 21 at 55-56;
Ex. 2076 at ¶¶ 324-331; 201-213

Claim 7 Is Not Obvious

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.

'552 Patent at Claim 7

- Claim 7, like claim 2, requires administration of oxaliplatin after liposomal irinotecan;
- Fails for the same reasons as Claim 2

Paper 21 at 56-57;
Ex. 2076 at ¶¶ 332-346

Claim 15 Is Not Obvious

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.

'552 Patent at Claim 15

first-line treatment of metastatic pancreatic cancer. The determination of whether to use premedication, and which specific agents to use, depends on multiple factors including the expected toxicity profile of the specific chemotherapy regimen, the patient population, and clinical experience with similar regimens. Dr. Ratain's

Ex. 2076 at ¶ 349

- Claim 15 requires:
 - Administration of oxaliplatin after liposomal irinotecan
 - Administration of a corticosteroid and an anti-emetic prior to treatment of the 4-drug regiment
- Fails for at least the same reasons as Claim 2 regarding sequence of administration
- Dr. Oberstein's opinions are not rebutted by Dr. Ratain

Paper 21 at 57;
Ex. 2076 at ¶¶ 347-352

Ground 3

Grounds and Challenged Claims

- CSPC challenges all claims of the '552 Patent on three grounds as follows:

Ground	Claims	Basis	Asserted Prior Art
1	1, 3-6, 8-14	103	Conroy, Conroy Protocol, Conroy Appendix, and Mahaseth in combination with Bayever, Saif, Ko, and Cantore
2	2, 7, and 15	103	Ground 1 in addition to Masi and Ginocchi
3	1-15	103	Grounds 1 and 2 in addition to Carnevale and Dean

Pet. at 6.

- Alternate theory of obviousness *only if* priority date is November 10, 2017

PTAB Determined Priority Date of the '552 Patent

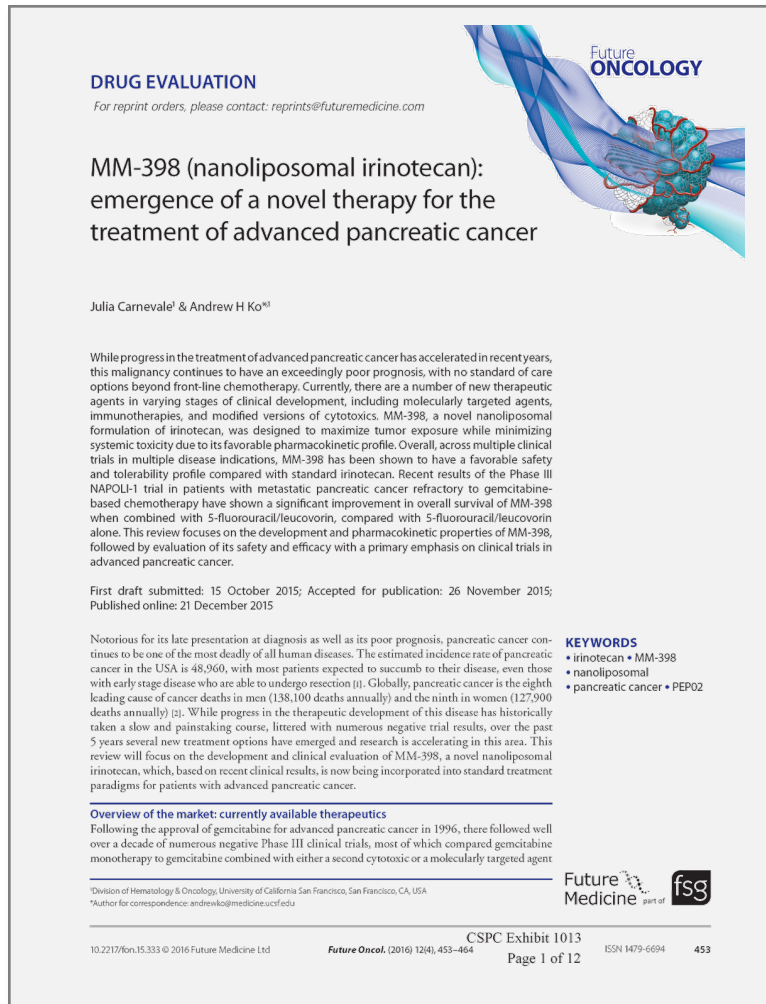
- The Board determined in the Institution Decision that the '552 Patent properly claims priority to August 21, 2015

On the current record, the evidence better supports Patent Owner's position. As discussed above, we agree with Patent Owner that the claims do not require clinical efficacy. Therefore, we also agree with Patent Owner that claims 1–15 have an effective filing date of August 21, 2015, and Carnevale and Dean are not prior art. Consequently, we find that this ground of rejection relies upon references that are not prior art and therefore fails to support a finding of obviousness on the current record.

Paper 13 at 45

- CSPC has not offered any rebuttal, including expert opinions, regarding the Board's finding regarding claim construction and the effective filing date of the '552 Patent

Carnevale Does Not Support Obviousness



- Review article that does not add anything further beyond Ko and/or Saif
- Does not provide any guidance as to dosing for liposomal irinotecan or whether other modifications (e.g., reducing oxaliplatin dose or removing 5-FU bolus) would be necessary
- Dr. Ratain's reliance on Carnevale rests on a single sentence using **conditional, speculative language** — “would make” and “might represent” — appearing in a forward-looking section discussing potential future developments
- Acknowledges the **low likelihood of success in developing new treatments for pancreatic cancer**

Paper 21 at 59-60;
Ex. 2076 at ¶¶ 214-216, 353-368

Carnevale Does Not Support Obviousness

- Dr. Oberstein opines that progress in the field of metastatic pancreatic cancer has been slow and littered with failures:

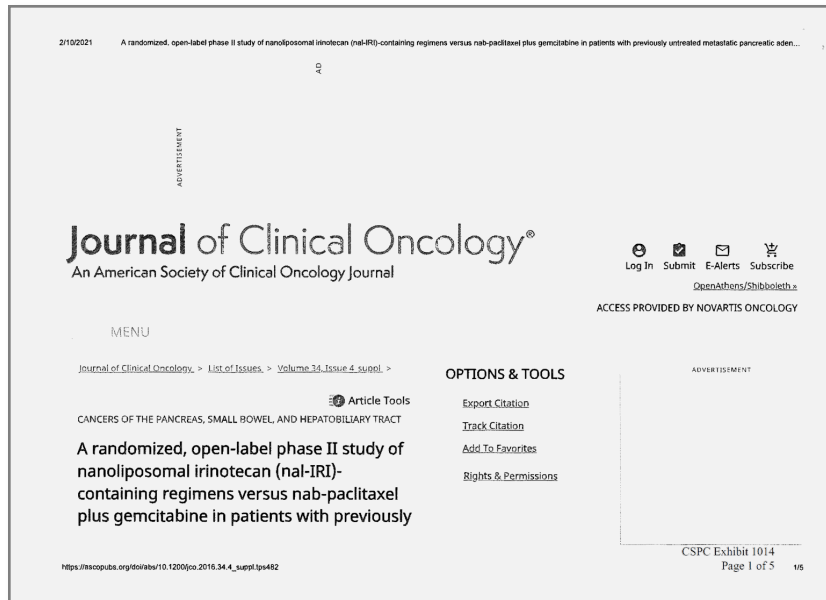
inconsequential trials.” *Id.* at 2. In my clinical experience, this characterization accurately reflects the particularly low likelihood of success in developing new treatments for metastatic pancreatic cancer. This context of high failure rates undermines any suggestion that a POSA would have had a reasonable expectation of success in achieving an effective and tolerable modification of FOLFIRINOX through multiple simultaneous changes.

Ex. 2076 at ¶ 361

- This opinion is unrebutted.

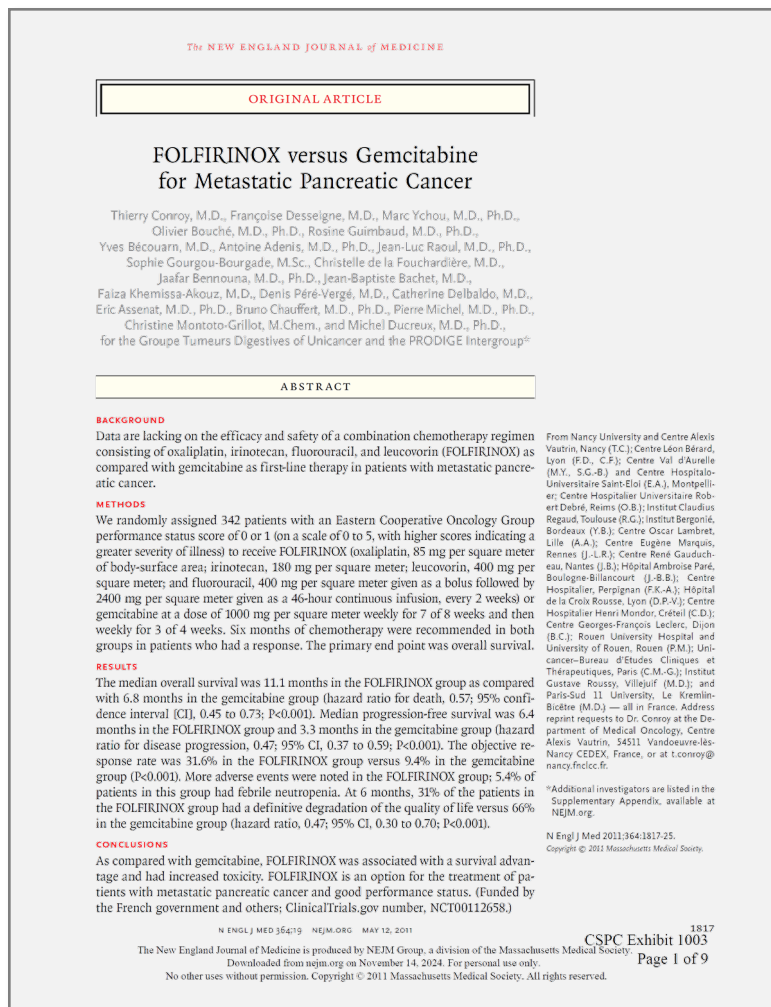
E.g., Paper 21 at 48-49

Dean Does Not Support Obviousness



- Conference abstract for a planned Phase II study
- Does not disclose safety or efficacy data
- Does not disclose dosing of components
- Does not disclose order of administration of components
- At best, teaches that a POSA “would know only that researchers thought a trial of this combination was **worth conducting**”
- Dr. Oberstein opines that “many promising trial protocols ultimately yield disappointing results, particularly in the difficult field of pancreatic cancer therapeutics”

The Alleged Prior Art



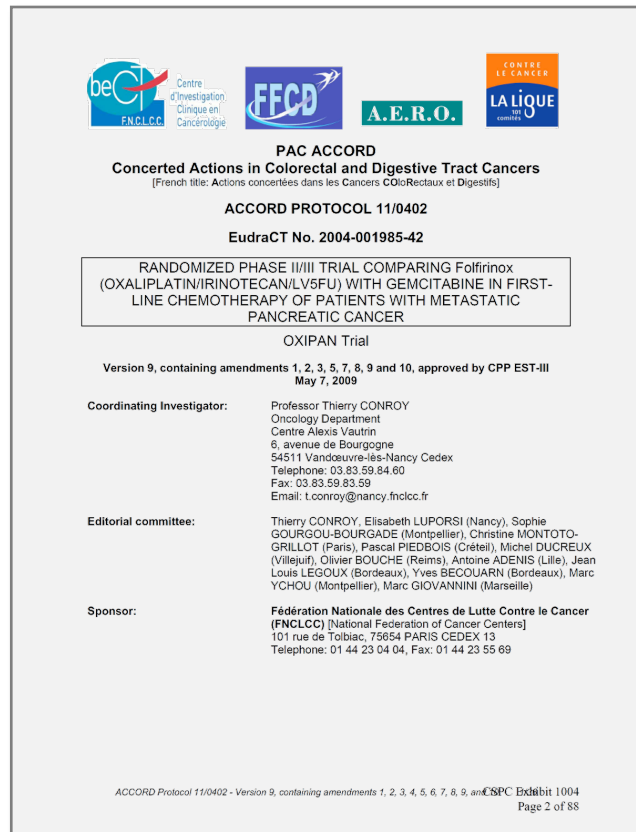
CONROY (Ex. 1003)

- Irinotecan; not liposomal irinotecan
- Starting oxaliplatin dose of 85 mg/m²
- Starting irinotecan dose of 180 mg/m²
- “Median dose intensity” does not teach 60 mg/m² starting dose
- Administers oxaliplatin before irinotecan – opposite of claimed invention

E.g., Paper 21 at 26-32, 56;
Ex. 2076 at ¶¶ 146-161

Conroy Protocol & Appendix

- CSPC has failed to submit any evidence of public availability as of priority date



CONROY (Ex. 1004)



CONROY (Ex. 1017)

E.g., Paper 21 at 13-15;
Ex. 2076 at ¶¶ 154-159

Conroy Protocol & Appendix

- Protocol & Appendix teach that all patients in the FOLFIRINOX arm are treated with a starting dose of 85 mg/m² oxaliplatin
- Reduction only in certain toxicity events

6.1 Description of trial treatments

After random selection, subjects receive either treatment A (Folfirinox) or treatment B (gemcitabine):

Treatment A: Folfirinox

- Oxaliplatin (Eloxatine®) 85 mg/m² D1 in 2h, subsequently
- Irinotecan (Campto®) 180 mg/m² D1 in 90 min.
- Folinic acid 400 mg/m², D1 in 2h (during irinotecan infusion)
- 5-FU bolus 400 mg/m² D1 followed by continuous 5-FU 2.4 g/m² in total over 46 hours, i.e. 1.2 g/m² on D1 and 1.2 g/m² on D2.

Treatment should be continued until progression, and a maximum of 12 cycles is recommended.

Ex. 1004 at 14; Ex. 2076 at ¶¶ 154-159

E.g., Paper 21 at 13-15

Conroy Protocol & Appendix

TREATMENT A: Folfirinoux

CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU
PNN $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$	No cycle delay	No dose reduction		
PNN $< 1.5 \times 10^9/L$	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, discontinuation of treatment*	<u>1st episode</u> : dose reduction to 150 mg/m ² <u>2nd episode</u> : dose maintained at 150 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : no dose reduction <u>2nd episode</u> : reduce dose to 60 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : eliminate bolus on D1
Platelets $< 75 \times 10^9/L$	Delay treatment until recovery (platelets $\geq 75 \times 10^9/L$) If no recovery at D29, discontinuation of treatment	<u>1st episode</u> : no dose reduction <u>2nd episode</u> : reduce dose to 150 mg/m ² <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : reduce dose to 60 mg/m ² <u>2nd episode</u> : maintenance of reduced dose <u>3rd episode</u> : discontinuation of treatment	<u>1st episode</u> : reduce bolus and continuous infusion dose by 25%

- Conroy's dose reduction guidelines do not motivate a preemptive 60 mg/m² starting dose
- Instruct reduction only after certain toxicity events
- Include reductions for all components – not just oxaliplatin

Ex. 1004 at 16-18; Ex. 1017 at 4-7; Ex. 2076 at ¶¶ 154-159

E.g., Paper 21 at 13-15

ORIGINAL ARTICLE

Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma

Hemchandra Mahaseth, MD,* Edith Brucher, NP,* John Kauh, MD,* Natalyn Hawk, MD, PhD,* Sungjin Kim, MS,† Zhengjia Chen, PhD,‡ David A. Kooby, MD,§ Shishir K. Maithel, MD,§ Jerome Landry, MD,|| and Bassel F. El-Rayes, MD*

Objectives: FOLFIRINOX (5-fluorouracil [5-FU], oxaliplatin, and irinotecan) has a central role in the management of patients presenting with advanced stage disease.¹ Until recently, gem-

FOLFIRINOX (see Ex. 1003 at 3)	Mahaseth modified FOLFIRINOX (see Ex. 1005 at 2)
<ul style="list-style-type: none"> • Oxaliplatin: 85 mg/m² • Leucovorin: 400 mg/m² • Irinotecan: 180 mg/m² • 5-FU Bolus: 400 mg/m² • 5-FU IV: 2,400 mg/m² 	<ul style="list-style-type: none"> • Oxaliplatin: 85 mg/m² w/ 5% dextrose • Leucovorin: 400 mg/m² • Irinotecan: 180 mg/m² • 5-FU Bolus: 0 mg/m² (removed) • 5-FU IV: 2,400 mg/m² • Pegfilgrastim: 6 mg

Pancreatic cancer (PC) is the fourth leading cause of cancer mortality in the United States.¹ Complete surgical resection remains the only treatment with curative potential; however, only 10% to 20% of patients with PC present with resectable disease.² The management of this small subset of patients usually involves resection followed by chemotherapy or chemoradiotherapy. Approximately 30% of patients present with locally advanced unresectable or borderline resectable disease.² Although there is no consensus on the best management approach for this group of patients, chemotherapy and radiation are often used initially in an attempt to enable tumor resection. The majority of patients present with advanced disease where the objective of therapy is palliative. Systemic FOLFIRINOX is administered until best response, and then patients are evaluated for concurrent chemoradiotherapy. The objective of this retrospective study was to evaluate the safety and efficacy of the modified FOLFIRINOX regimen. The second objective was to provide a preliminary evaluation of the efficacy of FOLFIRINOX in patients with borderline or locally advanced unresectable PC.

MATERIALS AND METHODS

Selection Criteria

After approval from the institutional review board, the tumor registry of Emory University was queried to identify patients carrying a diagnosis of PC between June 2010 and June 2012. Patients were considered eligible if they received at least 1 dose of modified FOLFIRINOX for PC. The charts of eligible patients were reviewed for age, sex, race, Eastern Cooperative Oncology Group performance status, pathological diagnosis, tumor stage, tumor location, stent status, CA-19-9, complete blood counts with differentials, treatment regimens, number of cycles and duration of treatment with modified FOLFIRINOX, imaging results, adverse events, and outcome events such as disease response.

From the *Department of Hematology and Medical Oncology, †Biostatistics and Biomarkers Shared Resource at Winship Cancer Institute, ‡Department of Biostatistics, §Division of Surgical Oncology, Department of Surgery, and ||Department of Radiation Oncology, Emory University, Atlanta, GA. Received for publication October 3, 2012; accepted May 21, 2013. Reprints: Bassel F. El-Rayes, MD, 1365 Clifton Rd NE, C2080, Atlanta, GA 30309 (e-mail: belfray@emory.edu). The authors declare no conflict of interest. Copyright © 2013 by Lippincott Williams & Wilkins

Pancreas • Volume 42, Number 8, November 2013

CSPC Exhibit 1005
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- Irinotecan; not liposomal irinotecan
- Modified FOLFIRINOX
 - Removed 5-FU bolus
 - Added growth factor
- Teaches administration of oxaliplatin before irinotecan
- Reports an “improved safety profile with maintained efficacy in” metastatic pancreatic cancer
- No motivation to further modify

Ex. 2076 at ¶¶ 162-168; See MAHASETH (Ex. 1005) generally

E.g., Paper 21 at 18-19

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Published:
 — with international search report (Art. 21(3))
 — with amended claims and statement (Art. 19(1))

(54) Title: TREATMENT OF BREAST CANCER WITH LIPOSOMAL IRINOTECAN

(57) Abstract: Provided are methods for treating breast cancer in a patient by administering effective amounts of liposomal irinotecan succinofate (MM-398). The breast cancer may be triple negative breast cancer (TNBC), estrogen receptor/progesterone receptor (ER/PR) positive breast cancer, ER-positive breast cancer, or PR-positive breast cancer, or metastatic breast cancer.

CSPC Exhibit 1026
 Page 1 of 42

WO 2016/094402 A1

Ex. 1026

- Before the Patent Examiner
- Teaches that use of liposomal irinotecan in combination with 5FU and Leucovorin
- Teaches the complex metabolism and variability with irinotecan and liposomal irinotecan
- Does not disclose a treatment regimen with oxaliplatin

E.g., Paper 21 at 15-16

PANCREAS NEWS

MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastatic Pancreatic Cancer

Muhammad Wasif Saif

Tufts University School of Medicine, Boston, MA, USA

MM-398 (irinotecan liposome injection), also known as "nal-IRI", is a nanoliposomal encapsulation of irinotecan, a topoisomerase-I poison. 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]. The primary log-rank analysis of overall survival was statistically significant (P=0.012) with a corresponding hazard ratio of 0.67. A statistically significant advantage for progression free survival was also observed in the combination arm. These results were based on a randomized large phase III study called the NAPOLI-1 study. This study treated patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy. The most common Grade ≥3 toxicities seen were neutropenia (14.5%), fatigue (13.7%), diarrhea (12.8%) and vomiting (11.1%).

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

Keywords Carcinoma; Drug Therapy; Gemcitabine; Neoplasm Metastasis; Pancreas; Pancreatic Neoplasms; Therapeutics
Abbreviations FOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan, leucovorin
Correspondence Muhammad Wasif Saif
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 E-mail: wsai@tuftsmedicalcenter.org

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.

However, keeping the history of drug testing for pancreatic cancer, it is clearly a groundbreaking study in the gemcitabine-refractory setting. Previously only one study by the Charité Onkologie Clinical (CONKO) tested combination of oxaliplatin, folinic acid and 5-fluorouracil (OFF) regimen versus best supportive care (BSC) [5]. Moreover, this also underlines the proof of concept development of drugs such as MM-398, a nanoliposomal drug. These results also enhance the importance of clinical studies in order to improve the outcome in this deadly disease.

This study has been approved for oral presentation at the European Society for Medical Oncology World Conference on Gastrointestinal Cancer to be held in Barcelona, Spain on June 25-28, 2014.

Conflict of Interest

The author has no potential conflicts of interest

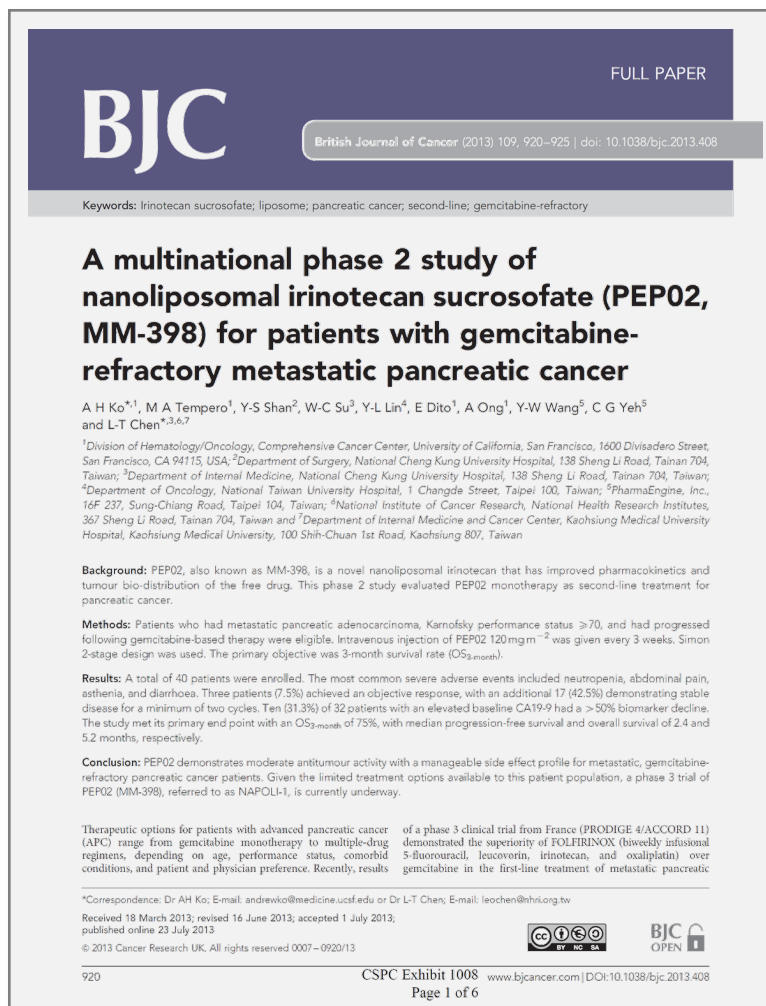
References

1. <http://www.marketwatch.com/story/merrimack-pharmaceuticals-announces-mm-398-achieves-primary-endpoint-of-overall-survival-in-phase-3-trial-in-post>

- Reports minimal results from NAPOLI-1 study
- No dosing information re any components, including liposomal irinotecan
- No disclosure of specific treatment regimen
- Silent as to use of oxaliplatin in combination with liposomal irinotecan
- Points away from claimed invention

Ex. 2076 at ¶¶ 181-185; Ex. 1007

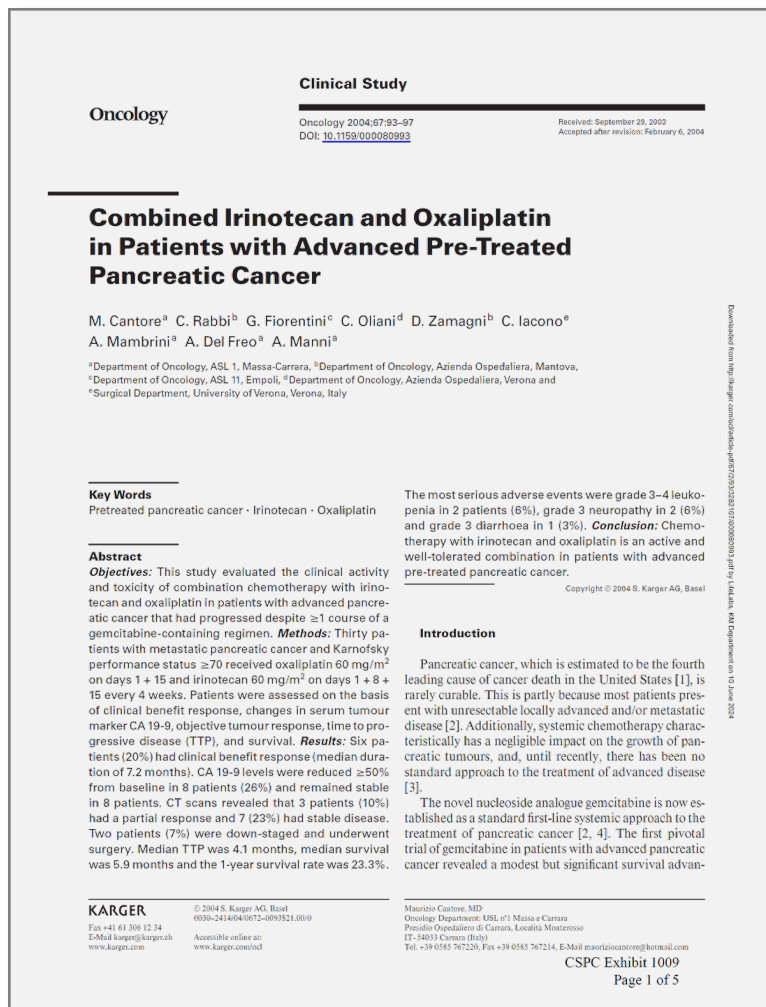
E.g., Paper 21 at 16-17



- Liposomal irinotecan as monotherapy, second-line
- 120 mg/m² of liposomal irinotecan with escalation up to 150 mg/m²
- Silent as to combination with oxaliplatin; rather points to combination with gemcitabine

Ex. 2076 at ¶¶ 186-192; See Ex. 1008

E.g., Paper 21 at 17-18



CANTORE (Ex. 1009)

- Tests only oxaliplatin with irinotecan; not with any other components
- Did not measure tumor regression or survival – instead focused on clinical benefit defined by pain, functional impairment, and weight loss
- Limitations to study: small population, lack of control
- Teaches higher doses of both irinotecan and oxaliplatin
- Outdated and superseded by FOLFIRINOX

E.g., Paper 21 at 19-20