

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1612
Eliel BAYEVER et al.	
Application No.: 15/809,815	Examiner: Gollamudi S. Kishore
Filed: November 10, 2017	Confirmation No.: 5137
For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Via EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Kishore:

Applicant responds to the Non-Final Office Action mailed August 26, 2021. The period for response has been extended to February 26, 2022, by request for extension of three months and payment of extension fees herewith. Please amend the above-identified application as follows:

Listing of the Claims begin at page 2.

Remarks begin at page 6.

LISTING OF THE CLAIMS:

The pending claims are listed below. No amendments are included.

1. (Previously Presented) 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 (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.
2. (Canceled)
3. (Canceled)
4. (Original) The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.
5. (Original) The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.
6. (Original) The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.
7. (Original) 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.
8. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over about 90 minutes.

9. (Original) 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.
10. (Original) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.
11. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
12. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
13. (Previously Presented) The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.
14. (Previously Presented) The method of claim 19, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).
15. (Previously Presented) The method of claim 14, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered

prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

16. (Canceled)
17. (Canceled)
18. (Previously Presented) The method of claim 19, 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.
19. (Previously Presented) 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 (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.
20. (Canceled)
21. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

22. (Previously Presented) The method of claim 19, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.
23. (Previously Presented) 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.

REMARKS

I. Status of Claims

Claims 1, 4-15, 18-19, and 21-23 are pending in the application. Applicant includes a listing of the pending claims here for the Examiner's convenience. No amendments are made herein.

II. Rejections Under 35 U.S.C. § 103

Claims 1, 5-8, 10 and 19

The Examiner maintains the rejection of claims 1, 5-8, 10 and 19 under 35 U.S.C. 103 as allegedly being unpatentable over WO 2013/188586 ("Bayever"), in view of Conroy et al., N Engl J Med., 364(19):1816-25, 2011 ("Conroy"), and further in view of Melis et al., The Society for Surgery of the Alimentary Tract, 2011; <http://meetings.ssat.com/abstracts/11ddw/P57.cgi> ("Melis"). Action at page 2. The Examiner alleges that "it would have been prima facie obvious to one of ordinary skill in the art to include oxaliplatin within Bayever's methods of treatment" and that "[a]n ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy..." *Id.* at page 3. The Examiner also alleges that "result effective variables can be optimized by routine experimentation, and it would have been prima facie obvious to optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis." *Id.* at pages 2-3.

Applicant incorporates by reference the arguments presented in the January 7, 2020, Non-Final Office Action Response and February 25, 2021, Final Office Action Response. The combination of references fails to teach the specific antineoplastic therapy *consisting of* the claimed dosages of liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU for "treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent." As previously set forth, Bayever, Conroy, and Melis disclose treatment of pancreatic cancer with a *different* combination of therapeutic agents in *different* doses from that of the claimed invention. The Examiner acknowledges that the references teach different combinations of agents in different dosages, but nonetheless asserts that their teachings can be

combined. Applicant respectfully traverses for the reasons previously presented and described in detail below.

No motivation to combine the references

The Examiner acknowledges “Bayever does not disclose oxaliplatin,” but maintains that Bayever discloses treatment of “metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10)” comprising “co-administering to the patient active agents, at a dose of 60 mg/m² (e.g., liposomal irinotecan),” a dose of 2400 mg/m² 5-fluorouracil, and a dose of 200 mg/m² 1 form or 400 mg/m² 1+d form leucovorin for at least one cycle of two weeks. *See* Action at page 2. The Examiner asserts that it would have been obvious to include oxaliplatin within the methods of Bayever based on the teachings of Conroy and Melis. *See* Action at page 3. The Examiner acknowledges that Conroy does *not* disclose liposomal irinotecan and does not specifically teach 60 mg/m² of oxaliplatin pursuant to the claims. Action at page 3.

Applicant respectfully submits that a person of ordinary skill in the art would *not* have modified the regimen in Conroy and/or combined the teachings of Conroy with Bayever (or Melis) to reach the claimed methods based on the teachings of the references when viewed as a whole. In contrast to the claims, Conroy discloses administering 180 mg/m² non-liposomal irinotecan, 85 mg/m² oxaliplatin, 400 mg/m² leucovorin, and a higher dose of 2,800 mg/m² total 5-fluoruracil (400 mg/m² bolus of 5-fluorouracil before a 2,400 mg/m² administration).

Conroy	Claim 1 regimen
180 mg/m ² <u>non-liposomal</u> irinotecan	60 mg/m ² liposomal irinotecan
85 mg/m ² oxaliplatin	60 mg/m ² oxaliplatin
400 mg/m ² LV	400 mg/m ² LV
<u>2800</u> mg/m ² 5-FU	2400 mg/m ² 5-FU

There is no mention of any liposomal irinotecan in Conroy or adjusting any of the dosages in Conroy towards those required by the claims. Conroy describes the FOLFIRINOX regimen that has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic pancreatic cancer since 2011. *See* the present Specification at page 2, lines 9-11. Despite acknowledging the existence of the FOLFIRINOX regimen as a combination chemotherapy regimen for pancreatic cancer, nowhere does Bayever teach or suggest incorporating oxaliplatin into its therapeutic regimen. *See* Bayever at 1.

Additionally, there is no basis for combining Conroy and Bayever because there is no basis for combining teachings regarding second-line therapy with teachings regarding first-line therapy. Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® (irinotecan liposome injection), which is indicated for the treatment of patients with metastatic adenocarcinoma of the pancreas *after* disease progression following gemcitabine-based therapy—i.e., as a *second-line therapy* for metastatic pancreatic cancer. *See* www.accessdata.fda.gov/drugsatfda_docs/label/2015/2077931bl.pdf and the present Specification at page 2, lines 19-22; *see* Response to Final Office Action filed February 25, 2021, at page 9. By contrast, Conroy describes assessing FOLFIRINOX “as compared with gemcitabine as first-line therapy.” *See* Conroy at abstract. As set forth in more detail below, a person of ordinary skill in the art would not combine teachings regarding first-line cancer treatments and second-line cancer treatments.

The Examiner acknowledges that neither Bayever nor Conroy teach the claimed dosage of 60 mg/m² of oxaliplatin, and cites Melis for allegedly teaching that a dosage of 60 mg/m² oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients. *See* Action at page 3-4. The Examiner states, “Melis was relied upon to show that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation.” Action at page 5. The teachings of Melis, however, fail to establish that the dosage of oxaliplatin in the claimed regimen would be a “result effective variable” in view of the knowledge of the art. The MPEP states that a “result effective variable” as used in an “obvious to try” line of reasoning is one which is known in the art to “achieve[] a recognized result.” *See* MPEP at § 2144.05(II)(B)-(C). In other words, a “result effective variable” is one that can be varied to have a predictable effect on the final outcome. *See* MPEP at § 2143. Melis is a one-paragraph abstract summarizing a chemo-radiation study in regionally advanced pancreatic cancer patients using a combination therapy that does *not* contain irinotecan *or* leucovorin. Melis fails to recognize *any* predictable outcome that may be achieved by varying the dose of oxaliplatin when administered in combination with irinotecan and/or leucovorin, much less any predictable tolerability *or* efficacy when co-administered at any particular doses, in the claimed metastatic patient population. As the Examiner acknowledges, a person of ordinary skill in the art would have known the activity of oxaliplatin to be affected by co-administration of other drugs. *See* Action at page 3.

However, the cited references, including Melis, fail to address the effects of co-administration of the other drugs in the claimed regimen on the efficacy and tolerability of oxaliplatin. As such, the dosage of oxaliplatin cannot be considered a “result-effective variable” that would achieve a recognized result when administered in the claimed therapy.

Additionally, there is no basis for combining the teachings of Melis with Bayever and/or Conroy.¹ Melis assesses the administration of “continuous infusion 5FU (200 mg/m²) and oxaliplatin weekly for 5 weeks” with “concurrent radiation in patients presenting with regionally advanced disease.” *See* Melis at abstract. As set forth above, there is nothing in Melis suggesting its teachings can apply beyond the combination 5FU (200 mg/m²) and oxaliplatin. *Id.* While Melis may teach that administering, “up to 60 mg/m² oxaliplatin” was “well tolerated” in a small number of patients, Melis *must be viewed as a whole*. “It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *See In re Wesslau*, 353 F.2d 238 (CCPA 1965); MPEP § 2141.02(VI). When viewed as a whole, Melis would *not* be combined with Bayever and/or Conroy to reach the claimed regimen. *See* Response to Final Office Action filed February 25, 2021, at page 7-8. As reiterated below, there is no motivation to combine the references or otherwise modify Melis to reach the claimed methods:

First, the Melis Study involved patients with locally advanced pancreatic cancer and thus necessarily *excluded* patients with metastatic disease; as such it would not be combined with Conroy and/or Bayever to achieve the claimed method. *See also* Amodeo et al, “Can we downstage locally advanced pancreatic cancer to resectable? A phase I/II study of induction oxaliplatin and 5-FU chemoradiation,” *J Gastrointest Oncol*, 9(5):922-935, 2018 (“Amodeo”) (cited in the January 7, 2020 IDS) at p. 924. Second, the Melis Study involved *weekly* administration of 60 mg/m² oxaliplatin in contrast to the “every two weeks” co-administration

¹ The Office Action at pages 5-6 cites *In re Keller*, 642 F.2d, 208 USPQ 871 (CCPA 1981) and seems to allege Applicant was “attacking references individually.” However, “[w]here an applicant’s reply establishes that each of the applied references fails to teach a limitation and addresses the combined teachings and/or suggestions of the applied prior art, the reply as a whole does not attack the references individually as the phrase is used in *Keller* and reliance on *Keller* would not be appropriate.” *See* MPEP at § 2145.

schedule recited in the claims, Conroy, and Bayever (*see* claim 3). It would have been well known that adjusting the administration frequency of a dosage regimen could have implications on the efficacy and tolerability of the treatment. Third, not only does Melis fail to disclose any irinotecan and leucovorin (and therefore would not be combined with Conroy and/or Bayever on that basis), but even the method of dosing 5-fluorouracil and oxaliplatin differs from the other cited references and the claims, which could also have implications on the efficacy and tolerability of the treatment. The Melis Study included continuous infusion of 200 mg/m² 5-fluorouracil daily and oxaliplatin weekly for 5 weeks in dose escalation cohorts, which differs from the claimed coadministration of 2,400 mg/m² 5-fluorouracil once every two weeks and the 400 mg/m² bolus of 5-fluorouracil before a 2,400 mg/m² administration disclosed in Conroy. Fourth, there would have been no reason to combine the teachings of Melis with that of Bayever and/or Conroy because the Melis treatment regime did not result in improved outcomes compared to other combination therapies for locally advanced pancreatic cancer. *See* Amodeo at p. 933. Fifth, patients who remained unresectable for cure but did not progress continued on a modified FOLFOX6 regime involving a higher 85 mg/m² dose of oxaliplatin every two weeks. *See* Melis abstract and Amodeo at p. 924. If anything, the teachings of Melis would have *discouraged* treatments using 60 mg/m² of oxaliplatin once every two weeks.

No reasonable expectation of success

Even if there was motivation to combine the cited reference, there can be no *prima facie* case of obviousness as the combination of references fail to establish a reasonable expectation of success in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent. The rejection simply fails to account for the many factors, such as patient population, disease severity, drug combination, dose, dosing schedule, drug-drug interactions, and overlapping toxicities, that each affect tolerability and efficacy of a particular cancer treatment method.

Initially, in contrast to the assertions of the Examiner, there would have been no reasonable expectation that including oxaliplatin from a first-line treatment regimen (e.g., as disclosed in Conroy) into a second-line treatment regimen (e.g., as disclosed in Bayever) would yield an effective and tolerable first-line treatment pursuant to the claims. In general, results

from second-line treatments cannot establish a reasonable expectation of similar results in treating patients who have not previously received an antineoplastic agent (and vice versa). Expectations of efficacy and safety of treatments are entirely different at these two separate stages: in second-line therapy, the tumor may have become more malignant and difficult to treat; patients receiving second-line therapy are also likely significantly more sick and less able to tolerate therapy than those receiving a first-line therapy. As an example of the general unpredictability of moving from one line to another, Conroy teaches that when used as a first-line therapy, FOLFIRINOX yielded prolonged median overall survival compared to gemcitabine, whereas the same results were not observed when used as second-line therapy. *See, e.g.*, Conroy at 1821 (smaller cohort received second-line therapy).

If a person of ordinary skill in the art were to combine the teachings of Bayever and Conroy, the skilled person would only have been led to use the 85 mg/m² dose of oxaliplatin disclosed in Conroy's FOLFIRINOX regimen, which was found to be safe and effective. *See* Conroy at 1824. The Examiner, however, has not established that a person of ordinary skill in the art would have combined the 85 mg/m² oxaliplatin of Conroy with the 60 mg/m² liposomal irinotecan regimen of Bayever, with an expectation of success. Conroy does not provide any comparison of liposomal vs. non-liposomal irinotecan with oxaliplatin or provide any data on how reducing the overall dosage of 5-FU, oxaliplatin, or irinotecan would affect treatment. Bayever similarly does not provide any teachings regarding how adding oxaliplatin to its combination regimen may affect efficacy, tolerability, or even the PK parameters of the liposomal irinotecan. *Cf.* Bayever at page 20. In actuality, the combination of 85 mg/m² oxaliplatin with 60 mg/m² liposomal irinotecan, 5-FU, and LV was ***not tolerable*** as a first-line treatment in patients with metastatic pancreatic cancer. *See* Wainberg Cohort C (described below and in the Wainberg article at 17); *see also* Specification at Tables 2 and 17 (level -2B).

A skilled person, when provided the doses in Conroy that were found to be safe and effective, would not instead have chosen a *different* dose of oxaliplatin that had not been shown to be safe and efficacious in combination with irinotecan, leucovorin, and 5-FU. None of the cited references suggest lowering the dose of oxaliplatin of Conroy with any expectation that reducing the dose would yield a safe and effective treatment. Indeed, none of the references teach or suggest tolerability *and* efficacy of 60 mg/m² oxaliplatin in combination with the

claimed liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU dosages. The Examiner cites to Melis for teaching a 60 mg/m² oxaliplatin dose, but Melis does not remedy the deficiencies of Conroy or Bayever with respect to establishing an expectation of success using the claimed regimen. In actuality, combining the 60 mg/m² oxaliplatin dose cited by the Examiner in Melis with 80 mg/m² liposomal irinotecan, 5 FU, and LV was similarly not tolerable as a first-line treatment. *See* Wainberg Cohort A (described below and in the Wainberg article at 17); *see also* Specification at page 3, lines 23-26 and Example 4 (e.g., Table 15, page 62, lines 16-19, and page 64, lines 4-7).

Indeed, rather than pointing to specific teachings establishing a reasonable expectation of success of the alleged combination, the Examiner relies on asserting that the dosage of oxaliplatin is a “result effective variable” that can be optimized by routine experimentation and doses are “routinely manipulatable parameters practiced by an artisan to obtain the best possible results.” *See* Action at pages 3 and 5. As set forth above, Melis does not provide motivation to combine with Bayever and/or Conroy and otherwise fails to establish that the dosage of oxaliplatin is a “result effective variable.” Importantly, Melis fails to teach how different dosages of oxaliplatin when co-administered with irinotecan and/or leucovorin effects tolerability *and* efficacy—both of which must be assessed to determine the success of cancer treatment in the claimed metastatic patient population.

The Federal Circuit has indicated that “to have a reasonable expectation of success, one must be motivated to do more than merely to ‘vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.’” *See Medichem v. Rolabo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). The Federal Circuit has also recently stated that only with the benefit of hindsight could a person of ordinary skill in the art have had a reasonable expectation of success in view of the asserted references in a case involving cancer treatment. *See OSI Pharmaceuticals, LLC v. Apotex Inc.*, 939 F.3d 1375, 1378, 1381 (Fed. Cir. 2019) (stating that “[c]ancer treatment is highly unpredictable” and reversing the PTAB’s finding of obviousness in a case involving non-small cell lung cancer treatments). The Conroy reference at page 1823 exemplifies the general difficulties in predicting efficacy and

tolerability of cancer treatments, describing the addition of known cytotoxic and targeted agents to gemcitabine treatment as having “almost invariably provided no significant survival improvement, despite an improvement in response rates in some trials.” The Specification also suggests difficulties in successfully predicting the clinical effects of modifying known treatment regimens, indicating modified regimens often have “unknown effects on the efficacy and safety.” *See* Specification at page 2, lines 15-16. Accordingly, without more, the cited references are simply insufficient to establish the requisite degree of predictability for obviousness. *See* MPEP § 2143.02.

Unexpected Results

Respectfully, the Examiner has not specifically commented on and thus has not seemed to consider the unexpected results that were previously presented. The Office Action states “the examiner sees no unexpected and surprising results using the art known pancreatic cancer treatment agents. With regard to the doses, if different, are routinely manipulatable parameters practiced by an artisan to obtain the best possible results.” *See* Action at page 5. To the extent the Examiner did not consider the data presented, the MPEP indicates evidence of unexpected results *must* be considered when properly presented. *See* MPEP § 2145.

The technical results in the instant specification and described herein show that the combination regimens suggested by the Examiner based on the cited references are *not* tolerable, but that the claimed regimen are. Surprisingly, the claimed lower dose combinations and compositions of 60 mg/m² liposomal irinotecan, 60 mg/m² oxaliplatin, 5-FU, and LV are tolerable and, despite the lower combined dose, achieved unexpected therapeutic effects over that of the standard first-line FOLFIRINOX regimen of Conroy. *See* Wainberg Cohort B (described below).

The 2020 Wainberg abstract, poster, presentation, and article (cited in the May 26, 2021 IDS)² report data resulting from the clinical protocol described in Example 3 of the instant

² Wainberg Z, et al., “First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study,” *Ann Oncol.* 31(Suppl 3):S241 doi.org/10.1016/j.annonc.2020.04.076 (2020) (“Wainberg abstract”), and corresponding poster (“Wainberg poster”) and presentation (“Wainberg (continued...)”).

application and builds on the trial results from Example 4 in the specification. 87.5% of patients receiving the claimed dosage regimen (Cohort B) had metastatic disease at diagnosis. *See* Wainberg article at page 17. Four cohorts of patients with unresectable, locally advanced or metastatic pancreatic ductal adenocarcinoma were treated on days 1 and 15 of each 28-day cycle with 5-FU 2400 mg/m² and LV 400 mg/m² in combination with the following doses of liposomal irinotecan and oxaliplatin³:

- Cohort A: 80 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin (“80/60”);
- **Cohort B: 60 mg/m² liposomal irinotecan and 60 mg/m² oxaliplatin (“60/60”);**
- Cohort C: 60 mg/m² liposomal irinotecan and 85 mg/m² oxaliplatin (“60/85”); and
- Cohort D: 65 mg/m² liposomal irinotecan and 70 mg/m² oxaliplatin (“65/70”).

See Wainberg article at page 16. Each of the therapies of Cohorts A (80/60), C (60/85), and D (65/70) were not tolerable, whereas Cohort B (60/60)—which reads upon the claimed regimen—was tolerable. *See* Table 2 of the Wainberg poster and slide 8 of the Wainberg presentation; Wainberg article at page 17.

Wainberg Cohort A	Wainberg Cohort B (Claim 1)	Wainberg Cohort C	Wainberg Cohort D
70 mg/m ² free base dose equivalent to 80 mg/m ² liposomal irinotecan	50 mg/m ² free base dose equivalent to 60 mg/m² liposomal irinotecan	50 mg/m ² free base dose equivalent to 60 mg/m ² liposomal irinotecan	55 mg/m ² free base dose equivalent to 65 mg/m ² liposomal irinotecan
60 mg/m ² oxaliplatin	60 mg/m² oxaliplatin	85 mg/m ² oxaliplatin	70 mg/m ² oxaliplatin
400 mg/m ² LV	400 mg/m² LV	400 mg/m ² LV	400 mg/m ² LV
2400 mg/m ² 5-FU	2400 mg/m² 5-FU	2400 mg/m ² 5-FU	2400 mg/m ² 5-FU

(...continued)

presentation”) presented at the European Society for Medical Oncology (ESMO) World; and Wainberg et al., “First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study,” *European Journal of Cancer* 151 at page 20 (2021) 14e24, <https://doi.org/10.1016/j.ejca.2021.03.028> (“Wainberg article”). The Wainberg article was not discussed in the Response filed February 25, 2021.

³ The 50, 55, and 70 mg/m² free base doses of liposomal irinotecan referenced in the Wainberg abstract, poster, and presentation are equivalent to 60, 65, and 80 mg/m² doses, respectively, of liposomal irinotecan based on the molecular weight of irinotecan hydrochloride trihydrate. *See* Specification at page 8, lines 12-19 and page 67, lines 10-14.

The cohort of patients treated with the only tolerable dose of oxaliplatin and liposomal irinotecan tested (60/60) unexpectedly resulted in primary efficacy outcomes higher than that of the currently preferred FOLFIRINOX regimen as reported in Conroy. Specifically, the median overall survival (OS) was 12.6 months, the median progression free survival (PFS) was 9.2 months, and the objective response rate (ORR) was 34.4 % for the 32 patients⁴ from both the Cohort B and dose-expansion study. *See* Results section of the Wainberg abstract and poster and slides 9 and 10 of the Wainberg presentation; Wainberg article at page 21. These primary efficacy outcomes are each higher than those reported in Conroy for FOLFIRINOX (OS of 11.1 months, PFS of 6.4 months, and ORR of 31.6%). *See* Conroy at page 1817. An increase of nearly 3 months in progression free survival (with no overlap at all in the 95% confidence interval) is a significant efficacy improvement to the treatment of patients with pancreatic adenocarcinoma, with an increase in mean overall survival of 1.5 months. Additionally, where 9% of patients receiving FOLFIRINOX in the Conroy regimen experienced grade 3-4 sensory neuropathy—a “particular concern with oxaliplatin-containing regimens”—no cases were reported by the patients receiving the claimed regimen. *See* Wainberg article at 21 (indicating that for “persistent grade 2 sensory neuropathy, an oxaliplatin dose reduction from 85 to 65 mg/m² was permitted”). These improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen.

The data demonstrate that liposomal irinotecan, when administered with oxaliplatin, 5-FU, and leucovorin according to claim 1, is able to treat metastatic adenocarcinoma of the pancreas in a first-line setting and provides more efficacious treatment than the current standard treatment described in Conroy, with acceptable tolerability and side effects.

Accordingly, as set forth above, there is no motivation to have combined the teachings of Bayever, Conroy, and Melis, and there would have been no reasonable expectation of success. While the right to present additional objective evidence of nonobviousness is reserved, Applicant

⁴ Of the 32 patients in the pooled population of patients from Cohort B and the dose-expansion group, 29 had metastatic disease (i.e., stage IV) at initial treatment. *See* Wainberg presentation at slide 7 pooled patient population column and footnote c.

respectfully asserts that the evidence of unexpected results presented above negates any prima facie case of obviousness. Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 of claims 1, 5-8, 10 and 19 over Bayever, in view of Conroy, and in further view of Melis, as there is no prima facie case of obviousness.

Claims 4, 9, 18 and 23

The Examiner maintains the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. 103 as allegedly being unpatentable over Bayever, in view of Conroy, and further in view of Melis and further in view of Fleming et al. found at <http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-inchemotherapy-administration/article/378072/> (“Fleming”). Action at pages 6-7.

The Examiner alleges that Fleming, which is an opinion by one medical doctor, discloses “the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time.” *See* Action at 7. Fleming, however, states “the best or correct order for drug administration is very difficult to answer” and acknowledges exceptions exist to the generalization the Examiner relies upon. Fleming indicates that, for example, in administering a taxane with a platinum (e.g., Taxol with carboplatin), the taxane should *always* be given first because “myelosuppression has been observed in patients who received the platinum before the taxane.” *See* Fleming. Notably, Fleming does *not* mention any of the drugs in the claimed regimen, and does not speak to whether a need exists for well-defined sequence of administration or the interval between any of the claimed agents (including 5-FU and/or leucovorin⁵), or if any “published reports” exist for the claimed chemotherapy. Fleming also only mentions “half-life” as a basis for the generalization and does not discuss the physiological effects of chemotherapy drugs on their targets. Antineoplastic agents can have different mechanisms of action, activity, and vary in their effects on cell cycle and apoptosis, all of which may factor into determining whether an optimal sequence of their administration exists. As such, the relevance of Fleming to the instant

⁵ Bayever at page 11 indicates leucovorin “increase[s] the binding of folate cofactor and active 5-FU with thymidylate synthetase,” and is known to be administered *prior* to 5-FU.

application is limited as best. Applicant also respectfully traverses for the reasons discussed above, in the February 25, 2021 Final Office Action response, and in the January 7, 2020 Non-Final Office Action Response with respect to claims 1 and 19, from which claims 4, 9, 18, and 23 depend.

Accordingly, claims 4, 9, 18, and 23, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m² liposomal irinotecan, 60 mg/m² oxaliplatin, leucovorin (200 mg/m² l-form or 400 mg/m² l+d form), and 2,400 mg/m² 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, and/or Fleming. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. § 103 over Bayever in view of Conroy, and further in view of Melis and Fleming.

Rejection of claims 11-15 and 21-22

The Examiner maintains the rejection of claims 11-15 and 21-22 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy, further in view of Melis, and as evidenced by WO 2016/094402 (“Bayever II”). Action at pages 8-9.

Applicant respectfully traverses for at least the reasons discussed above, in the February 25, 2021, Final Office Action response, and in the January 7, 2020, Non-Final Office Action Response with respect to claims 1 and 19, from which claims 11-15 and 21-22 depend. Accordingly, claims 11-15 and 21-22, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m² liposomal irinotecan, 60 mg/m² oxaliplatin, leucovorin (200 mg/m² l-form or 400 mg/m² l+d form), and 2,400 mg/m² 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, and/or Bayever II. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 11-15 and 21-22 under 35 U.S.C. § 103 over Bayever in view of Conroy, further in view of Melis, and as evidenced by Bayever II.

III. Nonstatutory Double Patenting

U.S. Patent No. 9,492,442

The Examiner maintains the rejection of claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-18 of U.S. Patent No. 9,492,442 (“the ’442 Patent”) in view of Conroy, and further in view of Melis. Action at pages 11-12. The Examiner alleges that “[a]lthough the claims at issue are not identical, they are not patentably distinct from each other.” The Examiner alleges the claims of the ’442 Patent “recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin” and relies on Conroy and Melis for disclosing oxaliplatin. *Id.*

Claim 1 of the ’442 patent recites:

A method of treating an exocrine pancreatic cancer, the method comprising intravenously administering an antineoplastic therapy once every two weeks to a human patient having the exocrine pancreatic cancer, the antineoplastic therapy *consisting of*:

a. administering a 60-80 mg/m² dose of a liposomal irinotecan composition in a diluted irinotecan injection formulation to the human patient in a single infusion over about 90 minutes, the diluted irinotecan injection formulation comprising irinotecan liposomes in 500 mL of an injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition effective to deliver the dose of liposomal irinotecan, in combination with

b. administering a therapeutically effective amount of leucovorin and 5-fluorouracil,

to treat the exocrine pancreatic cancer in the patient, wherein the irinotecan liposome composition comprises phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposomes in the liposomal irinotecan composition have a diameter of approximately 80-140 nm.

Claims 10 and 19 of the ’442 patent similarly recite “the antineoplastic therapy *consisting of*” the “closed set” of the specifically listed regimen, which the Examiner acknowledges to *not* include administration of oxaliplatin. It is well known that “a double patenting rejection must

rely on a comparison with the *claims* in an issued patent or pending application.” *See* MPEP § 804(III) (emphasis added). Here, the plain language of the claims of the ’442 patent necessarily excludes the addition of oxaliplatin, in contravention of the Examiner’s assertion that “it would have been prima facie obvious to use oxaliplatin in the issued method.”

Applicant further submits that one of ordinary skill in the art would not combine the teachings of Conroy and Melis regarding oxaliplatin with the claims of the ’442 Patent for the reasons set forth above regarding why a person of ordinary skill in the art would not combine the teachings of Bayever with Conroy and/or Melis, much less with a reasonable expectation of success, and further for the reasons set forth in the February 25, 2021, Final Office Action Response, and in the January 7, 2020 Non-Final Office Action Response. Claims 10-30 of the ’442 Patent are further directed to second-line treatment, and the discussion above regarding why a person of ordinary skill in the art would not combine teachings regarding second-line therapy with teachings regarding first-line therapy apply here. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy. Accordingly, the pending claims are not obvious variations of issued claims 1-18 of the ’442 Patent.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-18 of the ’442 Patent, in view of Conroy, and further in view of Melis.

U.S. Patent No. 10,980,795

The Examiner rejects claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-15 of U.S. Patent No. 10,980,795 (“the ’795 Patent”). *See* Action at page 12 (not citing any other references). The Examiner alleges that the claims “the claims in both said patent and instant claims are drawn to treating metastatic adenocarcinoma of the pancreas using the same composition.”

Claim 1 of the ’795 Patent recites:

A method of treating metastatic adenocarcinoma of the pancreas in a human patient *who has previously been treated with gemcitabine*, comprising

intravenously administering an antineoplastic therapy to the patient once every two weeks, the therapy *consisting of*

- i) irinotecan sucrose octasulfate salt liposome injection in a dose providing the equivalent of 70 mg/m² of irinotecan free base,
- ii) 200 mg/m² of the (l) form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- iii) 2400 mg/m² of 5-fluorouracil.

Claim 1 of the '795 Patent and its dependent claims also recite that the therapy "consists of" the specifically listed regimen, which does not include, and in fact necessarily excludes, the addition of oxaliplatin. The pending claims are not obvious variations of the claims of the '795 Patent for at least this reason.

Additionally, the claims of the '795 Patent recite "treating metastatic adenocarcinoma of the pancreas in a human patient *who has previously been treated with gemcitabine*," i.e., second line treatment. *See* '795 Patent at claim 1 (emphasis added). The claims of the '795 Patent would therefore not render the instant claims obvious for the reasons discussed above regarding second-line therapy versus the first-line treatment of the claims. To the extent the Examiner otherwise asserts the '795 claims would render the instant claims obvious in combination with Conroy and Melis, Applicant traverses for the reasons set forth above, and further for the reasons set forth in the February 25, 2021, Final Office Action Response, and in the January 7, 2020 Non-Final Office Action Response. Further, any *prima facie* case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy. Accordingly, the pending claims are not obvious variations of issued claims 1-15 of the '795 Patent.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-15 of the '795 Patent, in view of Conroy, and further in view of Melis.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

MCNEILL BAUR PLLC.

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