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

(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.

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

RELATED APPLICATIONS

This patent application claims priority to each of the following pending U.S. provisional patent applications, each incorporated herein by reference in their entirety: 62/208,209 (filed August 21, 2015), 62/216,736 (filed September 10, 2015), 62/273,244 (filed December 30, 2015), 62/281,473 (filed January 21, 2016), 62/302,341 (filed March 2, 2016), 62/323,245 (filed April 15, 2016) and 62/343,313 (filed May 31, 2016).

TECHNICAL FIELD

This disclosure relates to novel therapies useful in the treatment of pancreatic cancer, including the use of liposomal irinotecan in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer.

BACKGROUND

Pancreatic cancer is chemotherapy-resistant, with an extremely poor prognosis. It is the fourth leading cause of cancer death in the United States; the 5-year survival rate is 6%. The incidence of pancreatic cancer has increased during the past several decades and in 2014, an estimated 46,420 patients were diagnosed with pancreatic cancer and 39,590 died. Pancreatic cancer is projected to surpass liver, breast, prostate, and colorectal cancers to become the second-leading cause of cancer-related death by 2030. These statistics reflect the dire nature of the disease and lack of effective therapies. The location of the tumor results in few early symptoms and is often diagnosed at a late stage as a result. The absence of effective screening tools, and a limited understanding of risk factors, means that patients have advanced or metastatic disease at the time of diagnosis. Given the poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, new treatment options are still needed.

Tolerability of multi-drug regimens is important in cancer treatment. The longer the duration of manageable treatment should translate into improved outcome due to longer

drug exposure. During the last 5 years, one combination chemotherapy regimen that has emerged as standard of care for first-line treatment of metastatic pancreatic cancer is the combination therapy of 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX). However, FOLFIRINOX is known to have significant toxicity, and use is limited to patients with better performance status (i.e. ECOG performance score of 0 or 1). With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity. Therefore, if equally effective double regimens can be identified, patients may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit. Although the FOLFIRINOX regimen has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic disease since 2011, there are some concerns about the toxicity associated with FOLFIRINOX. One dose regimen of FOLFIRINOX is 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, and fluorouracil at a dose of 400 mg/m^2 administered by IV bolus followed by a continuous infusion of 2400 mg/m^2. Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules.

CPT-11 is irinotecan hydrochloride trihydrate, marketed as Camptosar® in the United States. MM-398 is a liposomal irinotecan and is marketed in the U.S. as the FDA-approved product ONIVYDE® in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

SUMMARY

Improved antineoplastic therapies for the treatment of pancreatic cancer provide the administration of liposomal irinotecan in combination with oxaliplatin and 5-fluorouracil to patients with previously untreated pancreatic cancer (e.g., untreated metastatic pancreatic adenocarcinoma, or mPAC). The 5-fluorouracil can be administered in combination with leucovorin. The improved antineoplastic therapies can provide improved therapeutic index (e.g., improved toxicity profiles) relative to prior FOLFIRINOX regimens.

A method of treating pancreatic cancer can comprise the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient. Optionally, leucovorin can also be administered prior to each administration of the 5-fluorouracil. Each administration of the liposomal irinotecan can be administered in a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein). A total of 2,400 mg/m^2 5-fluorouracil can be administered over 46 hours starting on each day when the liposomal irinotecan is administered. A total of 60, 75 or 85 mg/m^2 oxaliplatin can be administered on each day the liposomal irinotecan is administered. A total of 200 mg/m^2 (l) leucovorin can be administered prior to each administration of the 5-flurouracil (e.g., optionally administered as 400 mg/m^2 of (l+d) leucovorin). The antineoplastic therapy can be administered starting on days 1 and 15 of a 28-day treatment cycle, with the liposomal irinotecan, oxaliplatin, and optionally leucovorin administered on days 1 and 15 and initiating the 46-hour administration of the 5-fluorouracil on days 1 and 15.

The invention is based in part on several pre-clinical discoveries. First, liposomal irinotecan improved anti-tumor activity of the topoisomerase 1 inhibitor SN-38 (an active metabolite of irinotecan) relative to exposure-matched doses of non-liposomal irinotecan. Second, liposomal irinotecan combined with 5-fluorouracil and oxaliplatin consistently improved tumor growth inhibition and survival in mouse xenograft models of pancreatic cancer relative to non-liposomal irinotecan, without exacerbating the baseline toxicities of these agents.

In addition, the invention is based in part on the discovery that the administration of a dose of 80 mg/m^2 liposomal irinotecan was not well tolerated in humans when administered in combination with 60 mg/m^2 oxaliplatin, 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 (l+d) leucovorin. Accordingly, preferred methods of treating (previously untreated) pancreatic cancer provide for the administration of a human-tolerated antineoplastic therapy once every two weeks, where each administration of the antineoplastic therapy is a combination of the antineoplastic agents liposomal irinotecan, oxaliplatin and 5-fluorouracil provided herein. Preferably, the antineoplastic therapy administered once every two weeks consists of: (a) a total dose of 60 mg/m^2 liposomal irinotecan (dose based on the amount of irinotecan hydrochloride trihydrate, as defined herein), (b) a total dose of 60-85 mg/m^2

oxaliplatin (including, e.g., 60 or 85 mg/m^2), and (c) a total of 2,400 mg/m^2 5-fluorouracil optionally administered in combination with leucovorin. Optionally, the combination can include administration of a total of 200 mg/m^2 (l) leucovorin (optionally administered as 400 mg/m^2 of (l+d) leucovorin), prior to initiating the administration of the 5-fluorouracil. Preferably, no other antineoplastic agent is administered during the antineoplastic therapy, other than amounts of SN-38 produced within the patient from the liposomal irinotecan, after administration of the liposomal irinotecan. For example, the antineoplastic therapy can be administered without (non-liposomal) CPT-11 irinotecan. Preferably, the liposomal irinotecan, oxaliplatin, and (optionally) leucovorin are consecutively administered as separate infusions on a single (first) day and the 5-fluorouracil is administered starting on the first day after the administration of the leucovorin (if administered) and continuing into the following day (e.g., over a total of 46 hours).

Brief Description of the Drawings

Figure 1A is a graph showing the simulated levels of the active irinotecan metabolite SN-38 over time based on liposomal irinotecan human clinical biopsy data and human clinical trial data.

Figure 1B is a schematic showing how the tumor exposure of SN-38 over time observed with liposomal irinotecan (MM-398) is prolonged compared to SN-38 tumor exposure from non-liposomal irinotecan (CPT-11).

Figure 1C is a graph showing the percent relative cell growth inhibition of SN-38 based on various times of total SN-38 cell exposure for 5 different cell lines.

Figure 1D is a graph showing the percent relative cell growth inhibition of the cell lines tested in Figure 1C at different exposure times (4 hours or 48 hours) for different combinations of SN-38 with 5-fluorouracil (5-FU) or oxaliplatin (oxali).

Figure 2A is a graph showing the cell viability as a function of SN-38 exposure for BxPC-3 pancreatic cancer cells.

Figure 2B is a graph showing the cell viability as a function of SN-38 exposure for CFPAC-1 pancreatic cancer cells.

Figure 3A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with individual antineoplastic agents: including 5-fluorouracil (5FU), oxaliplatin (Ox), (non-liposomal) irinotecan (IRI) and MM-398 liposomal irinotecan (nal-IRI).

Figure 3B is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with various combinations of antineoplastic agents: (non-liposomal) irinotecan (IRI) and 5FU; (non-liposomal)irinotecan (IRI), oxaliplatin and 5FU; MM-398 liposomal irinotecan (nal-IRI) and 5FU; and 398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU.

Figure 4A is a graph showing the tumor volume over time measured in a BxPC-3 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 4B is a graph showing the tumor volume over time measured in a CFPAC-1 pancreatic cancer xenograft mouse efficacy model after treatment with oxaliplatin monotherapy, MM-398 liposomal irinotecan (nal-IRI) monotherapy, and a combination of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin (Ox).

Figure 5A is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5B is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the MM-398 containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU), MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 5C is a graph showing the tumor volume over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with the oxaliplatin containing combination therapies shown in Figure 5A: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6A is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (nal-IRI) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan).

Figure 6B is a graph showing the percent tumor volume change over time measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6C is a graph of the progression free survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 6D is a graph of the overall survival measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 7 is a graph showing the tumor volume measured in a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal irinotecan (nal-IRI) monotherapy, (non-liposomal) irinotecan monotherapy (irinotecan), and various combination therapies: MM-398 liposomal irinotecan (nal-IRI) and 5-fluorouracil (5FU); (non-liposomal) irinotecan (irinotecan) and 5FU; MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU.

Figure 8 is a table showing the results obtained from a patient-derived xenograft (PDX #19015) pancreatic cancer mouse efficacy model after treatment with MM-398 liposomal

irinotecan alone, non-liposomal irinotecan alone (monotherapy), MM-398 liposomal irinotecan in combination with 5FU (NAPOLI, double therapy), MM-398 liposomal irinotecan in combination with 5FU + oxaliplatin (NAPOX, triple therapy) and non-liposomal irinotecan combined with oxaliplatin and 5-fluorouracil (FOLFIRINOX).

Figure 9 is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of a saline control, liposomal irinotecan (nal-IRI), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin on days 0, 7, 14 and 21.

Figure 10A is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given together on the same day.

Figure 10B is a graph showing the tolerability of various therapies in a mouse model, measured by recording the body weight of the mouse after administration of high doses of MM-398 liposomal irinotecan (nal-IRI), oxaliplatin and a combination of MM-398 liposomal irinotecan and oxaliplatin given sequentially on separate successive days with the MM-398 administered on day 1 and the oxaliplatin administered on day 2.

Figures 11A, 11B and 11C are bar graphs depicting hematological toxicities observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: A. White blood cells; B. Neutrophils; and C. Lymphocytes.

Figures 11D, 11E and 11F is bar graphs depicting liver enzyme levels observed in mice after administration of high doses of MM-398 liposomal irinotecan (nal-IRI) and oxaliplatin administered on the same day or with oxaliplatin administered at least one day after administration of MM-398: D. aspartate aminotransferase (AST); E. alanine transaminase (ALT); F. alkaline phosphatase (ALKP).

Figure 12 is a schematic of methods of treating pancreatic cancer, including methods comprising the administration of liposomal irinotecan, oxalipaltin, 5-fluorouracil and leucovorin.

DETAILED DESCRIPTION

Unless otherwise indicated, the dose of liposomal irinotecan or irinotecan liposome as recited herein refers to the amount of irinotecan hydrochloride trihydrate providing an amount of irinotecan encapsulated in the liposome of the liposomal irinotecan or irinotecan liposome. For example, a dose of 60 mg/m^2 liposomal irinotecan refers to an amount of the liposomal irinotecan providing the same amount of liposome encapsulated irinotecan that is present in 60 mg/m^2 of irinotecan hydrochloride trihydrate, and is equivalent to a dose of about 50 mg/m^2 of liposomal irinotecan based on the amount of the irinotecan free base encapsulated in the liposomal irinotecan.

As used herein, unless otherwise indicated, the term "nal-IRI" (nanoliposomal irinotecan) and "MM-398" refer to a form of liposomal irinotecan. The term "CPT-11" refers to (non-liposomal) irinotecan hydrochloride trihydrate.

As used herein, "5-FU" and "5FU" and used interchangeably and refer to 5-fluorouracil.

All cited documents are incorporated herein by reference.

Using pancreatic cancer cell lines (Example 1), we demonstrated enhanced cell death when liposomal irinotecan treatment is simulated using prolonged exposure of SN-38 (the active metabolite of irinotecan) in combination with 5-FU and oxaliplatin. Figure 1 shows that prolonged exposure of SN-38 simulates MM-398 treatment in vitro. Referring to Figure 1A, MM-398 treatment results in prolonged tumor exposure to the active metabolite, SN-38, compared to non-liposomal irinotecan (CPT-11). Referring to Figure 1B, prolonged low-dose exposure of SN-38 mimics MM-398 tumor delivery in vitro. Referring to Figure 1C, prolonged low-dose exposure resulted in greater cell growth inhibition in multiple pancreatic cancer cell lines. The graph comprises four sections, and for each section the cell line data is presented with AsPC-1 data at the top, followed next by BxPC-3, Capan-2, CFPAC-1, and finally MaPaCa-2 on the bottom. Referring to Figure 1D, the benefit of prolonged exposure to low concentrations of SN-38 was also observed when combined with

5-FU (20.7 mM for 48h) or oxaliplatin (12.3 mM for 4h). Both combinations also increased sensitivity of resistance cell lines to prolonged low-dose SN-38.

Figure 2 is two line graphs that depict cell viability following treatment with SN-38 as a single agent or the combination of SN-38 and oxaliplatin. BxPC-3 (Figure 2A) or CFPAC-1 (Figure 2B) cells were treated for 4h or 72h, washed and then incubated for an additional 24h or 144h with fresh media, following which cell viability was assessed. The data traces are labeled "1" (SN-38 alone for four hours followed by a 24 hour incubation; "2" SN-38 + oxaliplatin for four hours followed by a 24 hour incubation; "3" SN-38 alone for 72 hours followed by a 144 hour incubation; and "4" SN-38 + oxaliplatin for 72 hours followed by a 144 hour incubation. Treatment of the cells with a combination of SN-38 and oxaliplatin decreased the IC-50 when cells were treated for 4h only as compared to treatment with single agents in both cell lines tested.

Testing of cell line-derived and patient-derived xenograft models of pancreatic cancer in Example 2 demonstrated improved anti-tumor activity of liposomal irinotecan relative to exposure-matched doses of non-liposomal irinotecan. In the mouse animal studies in Example 2, a dose of "x" mg/kg liposomal irinotecan provides about the same exposure to the topoisomerase 1 inhibitor (irinotecan and/or SN-38) as a dose of "5x" non-liposomal irinotecan (CPT-11). The liposomal irinotecan consistently improved tumor growth inhibition and survival relative to non-liposomal irinotecan in preclinical models, both as a monotherapy and in combination with 5-FU and oxaliplatin. The addition of MM-398 to 5-FU and/or oxaliplatin did not exacerbate the baseline toxicities of these agents, including weight loss and neutropenia, and tolerability could be further improved by delaying the administration of oxaliplatin to 1 day post-MM-398. These findings illustrate the therapeutic potential of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and support an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2).

An animal model of the FOLFIRINOX regimen was tested against the MM-398 + 5-FU/LV + oxaliplatin regimen in a pancreatic tumor xenograft mouse model. Liposomal irinotecan (MM-398) performed better than conventional (non-liposomal) irinotecan (CPT-11) at equivalent exposure doses (5 mg/kg MM-398 vs. 25 mg/kg free IRI) in the BxPC-3 pancreatic

xenograft cancer models (Example 2) either alone (e.g., Figure 3A), or in combination with oxaliplatin and/or 5-FU (e.g., Figure 3B).

In the mouse model tested in Example 2, efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3) was evaluated. Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with free irinotecan (IRI), MM-398, 5-FU, oxaliplatin (Ox) or control was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. Figure 3A depicts a line graph representing tumor growth after treatment with various individual treatment agents. Figure 3B depicts a line graph representing tumor growth after treatment with various combinations of treatment agents.

Efficacy of MM-398 in a 5-FU insensitive pancreatic cancer model (BxPC-3). Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm^3, IV treatment with doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs. In comparison to Figure 4A (discussed below), doublet or triplet regimens containing either IRI or MM-398 in combination with oxaliplatin and/or 5-FU demonstrate that the MM-398-containing doublet and triplet regimens inhibit tumor growth significantly better than the IRI-containing regimens. The addition of oxaliplatin to the doublet combinations of FOLFIRI or MM-398+5-FU/LV causes a slight increase in tumor growth inhibition (Figure 3B: compare IRI + 5FU to IRI + 5FU +Ox for FOLFIRI vs. FOLFIRINOX; compare nal-IRI + 5FU to nal-IRI + 5FU + Ox for MM-398+5-FU/LV vs. MM-398+5-FU/LV+Ox). However, comparison of FOLFIRI versus the MM-398+5-FU/LV doublet (IRI + 5FU vs. nal-IRI + 5FU), and FOLFIRINOX vs. the MM-398+5-FU/LV+Ox triplet (IRI + 5FU +Ox vs. nal-IRI + 5FU + Ox), demonstrates significantly more tumor growth inhibition with the MM-398-containing regimens. Further, the MM-398-containing doublet regimen performed better than the FOLFIRINOX triplet (nal-IRI + 5FU vs. IRI + 5FU +Ox), owing to the improved efficacy of MM-398 compared to conventional irinotecan.

Single agent results of the individual treatments are shown in Figure 4A, demonstrating that MM-398 significantly inhibits tumor growth compared to free IRI. Figures 4A and 4B are

two line graphs depicting tumor growth in mouse xenograft models following intravenous treatment with saline (control, circles), 5 mg/kg oxaliplatin (triangles), 5 mg/kg MM-398 (light squares), or the combination of BxPC-3 (Figure 4A) or CFPAC-1 (Figure 4B) tumor cells were implanted subcutaneously in mice. Treatment was initiated after tumors were well established, and treatments were given four times (BxPC-3 model) or three times (CFPAC-1 model) at the time points indicated by dashed lines on the graphs.

Figures 5A, 5B, 5C, 6A, 6B, 6C, 6D and 7 are graphs obtained by measuring tumor growth inhibition in mice following various treatments. Tumor cells (PDX model 19015) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone, or in combination with 5-FU or 5-FU + oxaliplatin, was initiated. Treatment doses are indicated in the figure beside each treatment, and were given 4 times.

Figures 5A-5C are three line graphs depicting tumor growth inhibition in mice following various treatments. Tumor cells, PDX 19015 model, were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan as monotherapy, or in combination with 5-FU and Oxaliplatin, was initiated. Treatment doses are indicated in the legend beside each treatment, and were given four times, at time points indicated by dashed lines on the graphs. The addition of 5-FU to MM-398 or non-liposomal irinotecan significantly improved tumor growth inhibition relative to the respective monotherapies. The addition of oxaliplatin to MM-398 + 5-FU further improves response by significantly delaying tumor progression as compared to MM-398 monotherapy. The delay in tumor progression was not significant in the group treated with the double therapy of MM-398 + 5-FU. Figure 5A is a line graph comprising data from all of the combinations (both those with MM-398 and those with irinotecan), and shows that the combination of MM-398, oxaliplatin, and 5-FU resulted in the most inhibition of tumor growth (lowest line trace), although the combination of MM-398 and 5-FU also inhibited tumor growth (next lowest line). Figure 5B is a line graph comprising data from the MM-398 combinations only (no irinotecan combinations or control line) for the purpose of comparison. As can be seen in the graph, the triple combination treatment resulted in the most tumor growth inhibition (lowest line), and the double combination of irinotecan and 5-FU (middle line) was better than MM-398 alone

(highest line) in inhibiting tumor growth. Figure 5C is a subset of the same data that allows comparison of the oxaliplatin combinations to the saline control.

Figure 6A is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with a saline control, MM-398 liposomal irinotecan (MM-398) monotherapy, or (non-liposomal) irinotecan monotherapy (irinotecan). The data in Figure 6A shows a significantly greater reduction in the percent tumor volume change for administration of 10 mg/kg liposomal irinotecan (MM-398) compared to non-liposomal irinotecan (CPT-11) at 50 mg/kg, each administered on days 0, 7, 14 and 21 followed by observation for a total of about 60 days. Figure 6B is a graph showing the percent tumor volume change over time measured in a PDX 19015 pancreatic cancer xenograft mouse efficacy model after treatment with saline control or two oxaliplatin containing combination therapies: MM-398 liposomal irinotecan (MM-398), oxaliplatin and 5FU; and (non-liposomal) irinotecan, oxaliplatin and 5FU. Mice receiving the combination of liposomal irinotecan (MM-398, also called MM-398) with 5FU and oxaliplatin on days 0, 7, 14 and 21 showed significantly reduced tumor volume percent change through the observation period of about 60 days, compared to mice receiving the combination of non-liposomal irinotecan (CPT-11) with oxaliplatin and 5-FU on days 0, 7, 14 and 21. Referring to Figure 6C, the addition of oxaliplatin to MM-398 + 5-FU significantly improves progression free survival of mice bearing PDX 19015 tumors, as compared to the control group and MM-398 monotherapy. The difference between MM-398 + 5FU and MM-398 monotherapy is not statistically significant. Referring to Figure 6D, the addition of 5-FU and oxaliplatin to MM-398 significantly improve overall survival relative to the control group. No benefit of added 5-FU or oxaliplatin was observed with non-liposomal irinotecan. Referring to Figure 7, the addition of oxaliplatin to MM-398 + 5-FU significantly delays tumor progression relative to MM-398 monotherapy, as indicated by significantly reduced tumor volume at day 35.

Figure 8 is a table showing results of tumor growth and survival in mice following various treatments. Tumor cells (PDX 19015 model) were implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~250 mm^3, IV treatment with MM-398 or non-liposomal irinotecan alone (monotherapy), or in combination with 5-FU (NAPOLI, double therapy) or 5-FU + oxaliplatin (NAPOX, triple therapy), was initiated.

Mice treated with the triple therapy, NAPOX (50%) had the best Overall Response Rate (ORR), as compared to double NAPOLI (38%), or monotherapy MM-398 monotherapy (0%). Further, triple therapy treated mice also had a better Disease Control Rate (DCR): NAPOX (75%), NAPOLI (63%), MM-398 monotherapy (38%), and Progression Free Survival (PFS): NAPOX was 47 days, relative to 36.5 days for NAPOLI and 12 days for MM-398 monotherapy. NAPOX PFS was significantly better than the monotherapy, whereas NAPOLI is not significantly better than the monotherapy. Notably, the combination of liposomal irinotecan with 5FU and oxaliplatin was better tolerated than the combination of an SN-38 exposure-matched dose of non-liposomal irinotecan with 5FU and oxaliplatin in a mouse tolerability study over 100 days. Figure 9 is a graph showing the body weight of mice after administration of various regimens: a saline control, liposomal irinotecan (MM-398), a combination of nanoliposomal irinotecan, 5-FU and oxaliplatin or a combination of non-liposomal irinotecan (CPT11), 5FU and oxaliplatin. Liposomal irinotecan improved tolerability in a mouse model following repeated dosing in mice relative to non-liposomal irinotecan when combined with 5-FU and oxaliplatin. Significance was determined by ordinary 2-way analysis of variance (ANOVA). The regimens were administered on days 0, 7, 14 and 21 of the study. The administration of 10 mg/kg liposomal irinotecan and the 50 mg/kg dose of non-liposomal free irinotecan (CPT11) provide a comparable dose of SN-38 to tumor cells in the mouse model.

The tolerability of combinations of MM-398 liposomal irinotecan and oxaliplatin was improved in mouse models when the oxaliplatin was administered one day after the administration of the MM-398. Figures 10A and 10B depict line graphs demonstrating the toxicities associated with MM-398 and oxaliplatin given as monotherapy or combined therapy given concurrently (A) or staggered, with oxaliplatin given 1 day after MM-398 administration (B). Co-administration of MM-398 and oxaliplatin leads to significant toxicities as measured by loss of body weight, whereas delaying oxaliplatin administration by 24h after MM-398 does not lead to significant changes in body weight.

Figure 11A-11F are bar graphs depicting hematological and liver toxicities following treatment with MM-398 with or without oxaliplatin given either concurrently or sequentially with MM-398. Hematological toxicities (A-C) were improved by delayed

administration of oxaliplatin. Liver enzymes (D-F) remained comparable to monotherapies when oxaliplatin administration was delayed.

These preclinical findings support the therapeutic use of liposomal irinotecan in combination with 5-FU/LV and oxaliplatin and an ongoing Phase 2 trial (NCT02551991) of this triplet regimen in first-line PDAC (Example 2). Figure 12 depicts a graphical representation of the study design employing the combination of MM-398 + 5-FU/LV + oxaliplatin in (Arm 1) and MM-398 + 5-FU/LV (Arm 2), and nab-paclitaxel + gemcitabine (Arm 3) as described herein.

For example, use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of: (a) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (b) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient; (c) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (d) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient, wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle; (e) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the

oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; (f) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil; or (g) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2-85mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan. Each of these exemplary uses can be modified to replace the doses of liposomal irinotecan, oxaliplatin, leucovorin and 5-flurouracil disclosed herein in the following passages relating to these specific components. Sometimes the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes. Sometimes, the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

As provided herein, irinotecan can be administered in an irinotecan liposome preparation. Preferably, the liposomal irinotecan is irinotecan sucrose sulfate liposome injection (otherwise termed “irinotecan sucrose octasulfate salt liposome injection” or “irinotecan sucrosofate liposome injection”), the formulation referred to herein as “MM-398” (also known as PEP02, see US 8,147,867) is a form of “nanoliposomal irinotecan” (also called “irinotecan liposome” or “liposomal Irinotecan”). MM-398 is irinotecan as the irinotecan sucrose octasulfate salt encapsulated in a nanoliposome drug delivery system.

The liposomal irinotecan can be a pharmaceutical composition prepared for human intravenous administration. For example, the liposomal irinotecan may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of

liposomal irinotecan may be diluted, e.g., in 500 mL of 5% dextrose injection USP, to provide a variety of concentrations, for example, 5 mg/mL, and may be infused over a 90 minute period.

The active ingredient of the MM-398 injection, irinotecan, is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38. SN-38 is cleared via glucuronidation, (for which major pharmacogenetic differences have been shown), and biliary excretion. These drug properties contribute to the marked differences in efficacy and toxicity observed in clinical studies with irinotecan.

The liposomal irinotecan can be a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space that contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for every 200 phospholipid molecules.

The amount of liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 180 mg/m^2, preferably 60 mg/m^2 when administered in combination with oxaliplatin and 5-fluorouracil for treatment of pancreatic cancer (dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt). The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received MM-398, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m^2 (amount of irinotecan base, equivalent to 60 -180 mg/m^2 dose expressed in terms of the amount of irinotecan hydrochloride trihydrate salt) and 353 patients with cancer using population pharmacokinetic analysis. Over the dose range of 50 to 155 mg/m^2, the C_{max} and AUC of total irinotecan increases with dose. Additionally, the

C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

The combination treatment described herein encompasses administration of MM-398 liposomal irinotecan in combination with multiple additional active agents: oxaliplatin, leucovorin and 5-fluorouracil, in doses and schedules to human patients with metastatic pancreatic cancer not previously treated with a prior chemotherapeutic agent in the metastatic setting as described herein.

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis. An exemplary effective amount of 5-fluorouracil administered to a human patient can range from about 2,000 mg/m^2 to about 3,000 mg/m^2. In some embodiments, the amount of 5-fluorouracil administered to the human patient is 2,400 mg/m^2.

Leucovorin is optionally administered prior to the 5-fluorouracil. Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase. Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levo-leucovorin") has also been approved by the FDA for treatment of cancer. The dosage of leucovorin is that of the racemic mixture containing both dextro (d) and levo (l) isomers, or optionally the (l) form of leucovorin at half the dosage of the (l + d) racemic form. An exemplary effective amount of leucovorin administered to the human patient can include an amount of (l)-form leucovorin ranging from about 100 mg/m^2 to about 300 mg/m^2. In some embodiments, the amount of (l)-form leucovorin administered to the human patient is 200 mg/m^2. In other embodiments, the leucovorin administered is the

(l + d)-form of leucovorin, in an amount ranging from about 200 mg/m^2 to about 600 mg/m^2. In some embodiments, the amount of (l + d)-form of leucovorin administered is 400 mg/m^2.

Oxaliplatin is a platinum-based drug that acts as a DNA cross-linking agent to effectively inhibit DNA replication and transcription, resulting in cytotoxicity which is cell-cycle non-specific. Oxaliplatin is typically used in combination with infusional 5-FU/LV, and is approved for use in advanced colorectal cancer (refer to package insert for more details). The effective amount of oxaliplatin administered to the human patient can range from about 30 mg/m^2 to about 150 mg/m^2, for example, from about 40 mg/m^2 to about 100 mg/m^2, or an amount of oxaliplatin of 50 mg/m^2, 55 mg/m^2, 60 mg/m^2, 65 mg/m^2, 70 mg/m^2, 75 mg/m^2, 80 mg/m^2, 85 mg/m^2, 90 mg/m^2, or 95 mg/m^2.

Dose modifications may be made to methods of administering the combination treatment described herein as a result of adverse events, include hematological and non-hematological adverse events.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of MM-398 administered according to the embodiments herein. In some embodiments, the dose of MM-398 is modified according to Table 1.

Table 1A: Examples of Dose Modifications for MM-398 (salt)

Toxicity **NCI CTCAE v4.0**	**Occurrence**	**MM-398 adjustment in patients receiving** **60 mg/m^{2‡} (salt)**	**Patients homozygous for UGT1A1*28 without previous increase to** **60 mg/m^2 (salt)**
Grade 3 or 4 adverse reactions	Withhold MM-398. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1 or baseline grade resume MM-398 at:		
	First	45 mg/m^2	35 mg/m^2
	Second	35 mg/m^2	30 mg/m^2
	Third	Discontinue MM-398	Discontinue MM-398
Interstitial Lung Disease	First	Discontinue MM-398	Discontinue MM-398
Anaphylactic Reaction	First	Discontinue MM-398	Discontinue MM-398

In some embodiments, the first, second or any subsequent dose of MM-398 can be reduced by 20-30% (including dose reductions of 20%, 25% and/or 30%) in response to patient tolerability considerations such as an adverse reaction to a first or subsequent dose of MM-398 and/or other antineoplastic agent, and/or identifying a patient as being homozygous for the UGT1A1*28 allele. In some embodiments, the second or subsequent dose of MM-398 is reduced by about 20%, 25% or 30% (e.g., a dose reduction from 60 mg/m2 to . In some embodiments, the dose of MM-398 is reduced by 25%. In some embodiments, the dose of

MM-398 is reduced by 30%. In some embodiments, the reduced dose of MM-398 is in a range starting from 30 mg/m^2 to (and including) 55 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 60 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 45 mg/m^2. In some embodiments, the dose of MM-398 is reduced to 35 mg/m^2.

Other dose reduction schedules are provided Tables 1B-1E below. When the starting (initial) dose of MM-398 is 60 mg/m^2, 5FU 2400mg/m^2, LV(l+d) 400mg/m^2 and Oxaliplatin is either 85mg/m2 OR 60mg/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 despite the first dose reduction, an additional 25% dose reduction in each of the antineoplastic agents of MM-398, 5-fluorouracil and oxaliplatin is preferred. Further toxicity will then lead to discontinuation of treatment in some instances. For non-hematologic toxicities, the same dose reduction schema can be followed as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which can be selected based on the medically appropriate dose for the patient.

Table 1B Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	1800
Second Reduction	35	35	1350

Table 1C Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	1800
Second Reduction	35	45	1350

Table 1D Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	60	2400
First Reduction	45	45	2400
Second Reduction	35	35	1800

Table 1E Examples of Reduced Doses of MM-398 and oxaliplatin

Dose	MM-398 (mg/m2) (salt)	Oxaliplatin (mg/m2)	5-fluorouracil (5FU) (mg/m2)
Initial	60	80	2400
First Reduction	45	60	2400
Second Reduction	35	45	1800

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of Oxaliplatin administered according to the embodiments herein. In some embodiments, the dose of Oxaliplatin is reduced by 20-30%. In some embodiments, the, the dose of Oxaliplatin is reduced by 20%. In some embodiments, the, the dose of Oxaliplatin is reduced by 25%. In some embodiments, the, the dose of Oxaliplatin is reduced by 30%. In some embodiments, the reduced dose of Oxaliplatin is in a range from 30 mg/m^2 to 75 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 75 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 65 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 60 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 45 mg/m^2. In some embodiments, the dose of Oxaliplatin is reduced to 34 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of 5-fluorouracil administered according to the embodiments herein. In some embodiments, the dose of 5-fluorouracil is reduced by 20-30%. In some embodiments,

the, the dose of 5-fluorouracil is reduced by 20%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 25%. In some embodiments, the, the dose of 5-fluorouracil is reduced by 30%. In some embodiments, the reduced dose of 5-fluorouracil is in a range from 1000 mg/m^2 to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1800 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1350 mg/m^2. In some embodiments, the dose of 5-fluorouracil is reduced to 1200 mg/m^2.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include further reducing or otherwise modifying the dose of MM-398, Oxaliplatin and/or 5-fluorouracil administered according to the embodiments herein.

In some embodiments, methods of administering the combination treatment described herein to patients having one or more characteristics can include reducing or otherwise modifying the dose of more than one of MM-398, Oxaliplatin and 5-fluorouracil administered according to the embodiments herein.

Additional dose modifications for MM-398, Oxaliplatin and/or 5-fluorouracil can be found in the respective Package Inserts, which are incorporated herein by reference.

In one embodiment, the method of administering the combination treatment comprises 34, 45, or 60 mg/m^2 of liposomal irinotecan, 34, 42, 45, 60 or 85 mg/m^2 oxaliplatin, 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 1,200, 1,350, 1,800 or 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Thus, in some embodiments, the method of administering the combination treatment to treat the metastatic adenocarcinoma of the pancreas in the human patient comprises:

(A) (i) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 35 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and

2,400mg/m^2 5-FU; (v) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 35 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 35 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 35 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (B) (i) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 45 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2

oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 45 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 45 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or (xx) 45 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; or (C) (i) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (ii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (iii) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (iv) 60 mg/m^2 of liposomal irinotecan, 35 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (v) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (vi)

60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (vii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (viii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (ix) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (x) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xi) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xii) 60 mg/m^2 of liposomal irinotecan, 45 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xiii) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xiv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xv) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; (xvi) 60 mg/m^2 of liposomal irinotecan, 60 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU; (xvii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,200mg/m^2 5-FU; (xviii) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,350mg/m^2 5-FU; (xix) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 1,800mg/m^2 5-FU; or(xx) 60 mg/m^2 of liposomal irinotecan, 85 mg/m^2 oxaliplatin, 200 mg/m^2 (l)-form or 400 mg/m^2 racemic leucovorin, and 2,400mg/m^2 5-FU.

Liposomal irinotecan is preferably administered intravenously, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin. In one embodiment, liposomal irinotecan is administered prior to oxaliplatin, 5-FU and leucovorin. In another embodiment, leucovorin is administered prior to 5-FU. In another embodiment, the MM-398 liposomal irinotecan is administered followed by administration of the oxaliplatin, followed by administration of the leucovorin, and followed by the administration of the 5-fluorouracil. In certain embodiments, the liposomal irinotecan is administered to the patient intravenously over 90

minutes. In another embodiment, the oxaliplatin is administered to the patient intravenously over 120 minutes. In another embodiment, 5-FU is administered intravenously over 46 hours. In one embodiment, the oxaliplatin is administered from about 6 to about 72 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered for example, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, or 72 hours, after administration of the liposomal irinotecan. In another embodiment, leucovorin is administered intravenously over 30 minutes. In various embodiments the liposomal irinotecan is MM-398. In various embodiments, the human patient with metastatic pancreatic cancer is pre-medicated with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan, and other active agents.

Further embodiments of the invention

The following methods and embodiments can be considered alone, in combination other embodiments in this section, or in combination with the methods disclosed above. The invention provides methods for treating pancreatic cancer in a human patient, such as in a patient not previously treated with a chemotherapeutic agent in the metastatic setting, the method comprising administering to the patient liposomal irinotecan, also referred to as MM-398 (e.g., irinotecan sucrose octasulfate salt liposome injection) in combination with oxaliplatin, leucovorin and 5-FU.

1. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

2. The method of embodiment 1, wherein the amount of MM-398 liposomal irinotecan administered is administered is 60 mg/m^2 or 80 mg/m^2.

3. A method for treating pancreatic cancer in a human subject who has not previously received chemotherapy to treat the pancreatic cancer, the method comprising: administering to

the subject 60 mg/m^2 of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-FU to treat the pancreatic cancer in the human subject.

4. The method of any one of embodiments 1-3, wherein the amount of oxaliplatin administered is from about 50 mg/m^2 to about 100 mg/m^2, such as about 60 mg/m^2 to about 85 mg/m^2, for example 60 mg/m^2, 75 mg/m^2, or 85 mg/m^2.

5. The method of any one of embodiments 1-4, wherein the leucovorin administered at a dosage of 400 mg/m^2 of the (l + d) racemic form, or 200 mg/m^2 of the (l) form.

6. The method of any one of embodiments 1-5, wherein the amount of 5-FU administered is 2,400 mg/m^2.

7. The method of any one of embodiments 1-6, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU are administered at least once, such as wherein the MM-398, oxaliplatin, leucovorin, and 5-FU are administered on days 1 and 15 of a 28-day cycle.

8. The method of any one of embodiments 1-7, wherein multiple cycles are administered.

9. The method of any one of embodiments 1-8, wherein the pancreatic cancer is adenocarcinoma of the pancreas, such as unresectable, locally advanced or metastatic adenocarcinoma of the pancreas, for example, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas; or wherein the metastatic pancreatic cancer is an exocrine metastatic pancreatic cancer selected from the group consisting of Duct cell carcinoma, Acinar cell carcinoma, Adenosquamous carcinoma, Cyst adenocarcinoma (serous and mucinous types), Giant cell carcinoma, Invasive adenocarcinoma associated with cystic mucinous neoplasm or intraductal papillary mucinous neoplasm, Mixed type (ductal-endocrine or acinar-endocrine), Mucinous carcinoma, Pancreatoblastoma, Papillary-cystic neoplasm (Frantz tumor), Papillary mucinous carcinoma, Signet ring carcinoma, Small cell carcinoma, Unclassified, Undifferentiated carcinoma, serous cystadenocarcinoma, and Solid and Pseudopapillary tumors.

11. The method of any one of embodiments 1-10, wherein the oxaliplatin is administered to the patient prior to the leucovorin, such as wherein the leucovorin is administered to the patient prior to the 5-FU, optionally wherein the MM-398 liposomal irinotecan is administered to the patient prior to the oxaliplatin, leucovorin, and 5-FU.

12. The method of embodiment 11, wherein the MM-398 is administered over 90 minutes, followed by administration of the oxaliplatin over 120 minutes, followed by administration of the leucovorin over 30 minutes, followed by the administration of the 5-FU over 46 hours.

In a particular embodiment, a human patient with metastatic adenocarcinoma of the pancreas who has not previously been treated with any chemotherapeutic agent in the metastatic setting, is treated with a combination regimen of the present disclosure, the method comprising, intravenously administering to the patient, beginning on day 1 of a 2-week cycle, 80 mg/m^2 of MM-398 liposomal irinotecan over 90 minutes, followed by 60-85 mg/m^2 oxaliplatin, followed by 200 mg/m^2 of the (*l*) form of leucovorin, or 400 mg/m^2 of the (*l+d*) racemic form of leucovorin, followed by 2,400 mg/m^2 5-FU, wherein the human patient is treated with one or multiple cycles. In the embodiments disclosed herein, the effective amount of MM-398 liposomal irinotecan administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 80 mg/m^2. In various embodiments, the amount of MM-398 liposomal irinotecan administered to the human patient is 60 mg/m^2 or 80 mg/m^2. In the embodiments disclosed herein, the effective amount of Oxalyplatin administered to the human patient can range from about 40 mg/m^2 to about 100 mg/m^2, for example, from about 60 mg/m^2 to about 85 mg/m^2. In various embodiments, the amount Oxalyplatin administered to the human patient is 60 mg/m^2 or 85 mg/m^2. In one variant of this embodiment, oxaliplatin is administered over 120 minutes, leucovorin is administered over 30 minutes, and 5-FU is administered over 46 hours.

Examples

Example 1: *In vitro* pancreatic cancer cell exposure to topoisomerase 1 inhibitor

Simulated tumor exposure of SN-38 in patients administered with free irinotecan or MM-398 were shown in Figure 1A. MM-398 is shown to result in prolonged SN-38 duration in tumors compared to free irinotecan (CPT-11). The effect of various SN-38 durations on cell growth inhibition was studied in a panel of pancreatic cell lines (AsPC-1, BxPC-3, Capan-2, CFPAC-1, and MiaPaCa-2). Figure 1B illustrates the in vitro conditions for mimicking this clinically comparable SN-38 exposure of the 2 drugs, where cells exposed to SN-38 at high concentrations for a short period of time approximates for free irinotecan, and at low concentrations for a long period of time for MM-398. The results and experimental conditions are summarized in Figure 1C. For example, cells incubated with 139 nM of SN-38 for 144h vs. 417 nM for 24h have similar SN-38 tumor exposure ratios of MM-398 vs. free

irinotecan in patient tumors. Under these clinically relevant conditions, prolonged exposure (i.e. MM-398) primarily resulted in more pancreatic cancer cell growth inhibition compared to short exposure at high concentrations (i.e. free irinotecan). Similar results were also obtained when SN-38 were combined with 5-FU or oxaliplatin, demonstrating that prolonged exposure also led to increased cell growth inhibition when combined with these other chemotherapeutics agents that are used in the FOLFIRINOX regimen.

Example 2: Evaluation of *in vivo* tolerability and efficacy of combination therapies in an animal model

BxPC-3 and CFPAC-1 mouse xenograft studies (efficacy):

Tissue culture: BxPC-3 cells were cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin. CFPAC-1 cells were also cultured in RPMI growth media supplemented with 10% FBS and 1% penicillin/streptomycin.

Animals: Experiments were performed according to approved guidelines. Female NOD.scid mice were obtained from Charles River Laboratories (Wilmington, MA). BxPC-3 or CFPAC-1 cells were inoculated into the right hind flank at 5e6 cells in a total volume of 50 uL per mouse. Eight animals were treated per group, unless otherwise indicated. Animals were randomized and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 2 weeks post post-final dose.

PDX19015 mouse xenograft study (efficacy and tolerability):

Animals: Experiments were performed according to approved guidelines. Female CB.17 SCID mice were obtained from Roswell Park Cancer Institute (Buffalo, NY), initially at 6-8 weeks of age. Per treatment group, 8 animals were treated, unless otherwise indicated. Tumor pieces were derived from donor mice and engrafted subcutaneously. Animals were randomized

and dosing initiated when tumors reached an average volume of 200-250 mm^3 (range 100-400 mm^3), unless otherwise indicated.

Treatment efficacy: MM-398, irinotecan and oxaliplatin were administered intravenously. 5-FU was administered intraperitoneally. Administration of the indicated doses of each agent was initiated when tumors reached an average volume of 200-250 mm^3 and continued for a total of 4 weekly doses. Tumor volumes were measured twice weekly during the dosing cycle, then once weekly until tumors reached 1000-2000 mm^3, as indicated, animals were in poor general health, or 100 days post-first dose. Tolerability: Mouse weights were measured once weekly to monitor treatment tolerability. Mice were euthanized when body weight declined to ≥20% below baseline, or they exhibited overt signs of poor general health.

Delayed dosing of oxaliplatin:

Animals: Experiments were performed according to approved guidelines. Female CD-1 mice were obtained from Charles River Laboratories (Wilmington, MA). Tolerability studies were performed in naïve (non-tumor-bearing) mice. Three animals were treated per group.

Treatment tolerability: Agents were administered intravenously at their pre-defined maximum tolerated doses (MM-398, 50mg/kg; oxaliplatin, 17mg/kg). Each drug was administered individually, or in combination. Combinations were given in one of 3 independent dosing schedules: coinjection (drugs administered simultaneously), MM-398 given on day 1 and oxaliplatin given on day 2 (24h delay), or MM-398 given on day 1 and oxaliplatin given on day 4 (72h delay). A single administration of each drug was given. Mouse body weights were measured daily for up to 2 weeks post-treatment. Mice were euthanized when body weight declined to ≥20% below baseline, they exhibited overt signs of poor general health, or at 2 weeks post-treatment (end of study).

Measurement of hematologic and liver toxicities: At the end of study, terminal bleeds were performed for each mouse via cardiac puncture. Hematologic function (blood cell count) was measured by Hemavet (Drew Scientific, Miami Lakes, FL), according to manufacturer's protocol. Liver function (enzyme levels) was measured by CatalystDx (Idexx Laboratories, Westbrook, ME) according to the manufacturer's protocol.

Example 3: Treatment of Pancreatic Cancer

As schematically shown in Figure 12, the present study is an open-label, phase 2 comparative study to assess the safety, tolerability, and efficacy of MM-398 in combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with metastatic pancreatic adenocarcinoma who have not received prior chemotherapy. This study assesses the following regimens: (1) MM-398 + 5-FU/LV + oxaliplatin (Arm 1), (2) MM-398 + 5-FU/LV (Arm 2) and (3) nab-paclitaxel + gemcitabine (Arm 3).

This phase 2 study evaluates the preliminary safety and efficacy of MM-398 + 5-FU/LV with or without oxaliplatin versus nab-paclitaxel + gemcitabine in patients with previously untreated mPAC. The study may also provide important information on the impact of MM-398 combination treatment on patient HRQL and identify potential biomarkers of response.

In the study, MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen. The addition of oxaliplatin to the NAPOLI-1 regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398 prolonged PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the efficacy of FOLFIRINOX.

A modified triplet combination regimen of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU)/leucovorin is provided herein, whereby no bolus of 5-FU will be administered. The target dose of oxaliplatin (60-85 mg/m^2) is evaluated in the Arm 1 combination regimen with the continuous infusion dose of 5-FU (excluding the bolus), and the every 2 week dose of MM-398 previously shown to be tolerable and efficacious in combination with 5-FU. Note that with MM-398 dosing, the C_{max} of SN-38 is expected to be lower than would be expected for standard dosing with free irinotecan.

The study is conducted in two parts, as illustrated in the schematic of Figure 12: 1) a safety run-in of the MM-398 + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the MM-398 + 5-FU/LV + oxaliplatin regimen, the MM-398 + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), and a nab-paclitaxel + gemcitabine control arm.

Part 1:

Part 1 consists of an open-label safety run-in of the combination regimen in Arm 1: MM-398 + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and MM-398 + 5-FU/LV has been demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore was not included in this part of the study. The safety run-in enrolls small cohorts of patients following a traditional 3 + 3 dose escalation design in order to confirm the target dose of oxaliplatin. Dose limiting toxicities (DLTs) are evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2^{nd} dose of study treatment if there is a treatment delay in cohorts of patients to determine if the target combination dose is tolerable (note: the target combination dose is based on the established dose of the FOLFIRINOX regimen)). If there are no DLTs within the safety evaluation period, then the subsequent cohort is initiated following agreement between the Investigators, Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort is expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose is considered to exceed the safety and tolerability criteria of the combination, and the dose is not be escalated further; however, lower doses can be explored. The Part 2 dose is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Additionally, UGT1A1*28 allele status is considered when evaluating DLTs. Based on previous experience with irinotecan, individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan, in a study of 66 patients who received single-agent irinotecan (350 mg/m^2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. Importantly, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of accompanying life threatening neutropenia is described (for details refer to the prescribing information for irinotecan). Population PK studies of MM-398 have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study, no differences in toxicity were seen in

cohorts of heterozygous or WT patients, and DLTs of diarrhea with or without accompanying dehydration or fatigue, were seen in both cohorts. For these reasons, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results are not required prior to the first dose of MM-398 on this study and the starting dose for all patients will be 80 mg/m^2. However, if patients are known to be homozygous for UGT1A1*28, the dose of MM-398 may be reduced as described herein.

Part 2:

Part 2 consists of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either MM-398 + 5-FU/LV + oxaliplatin, MM-398 + 5-FU/LV, or nab-paclitaxel + gemcitabine. The randomization is stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1).

The following adverse events are common (≥ 40%) with past oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the MM-398-containing combination regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. Additional adverse events may be anticipated, as described in the package insert for oxaliplatin, including allergic and anaphylactic reactions. In a Phase 3 study of the FOLFIRINOX combination, the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia. Considering these expected toxicities, Arm 1 is evaluated for safety and tolerability in Part 1 of the study as described below.

A dose of oxaliplatin of 85 mg/m^2 is the target dose for Part 2 of this study. The purpose of Part 1 is to confirm whether this dose is compatible when MM-398 is used instead of conventional irinotecan. In case there are any unexpected toxicities, 3 to 6 patients are initially treated at a lower dose of oxaliplatin (60 mg/m^2, see Table 1) prior to administration of oxaliplatin at the highest proposed dose of 85 mg/m^2. The dose of the triplet combination to be administered in Part 2 of the study is defined as the highest dose level at which a DLT is experienced by fewer than 2 patients in a cohort of 3 to 6 patients. If one patient experiences a treatment-related toxicity that qualifies as a DLT, up to 3 additional

patients are enrolled at that dose level, for no more than 6 total patients per cohort. If no additional DLTs are observed, the dose escalation resumes. If a second patient experiences a treatment-related toxicity that qualifies as a DLT at that dose, that dose is considered to exceed the optimal safety and tolerability criteria of the combination. The dose to be used in Part 2 is then defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

Dosing of patient cohorts begins at dose level -1 with planned escalation to dose level -2B (target dose), in which the dose for one of the three drugs is increased while the other two drugs will maintain a constant dose. If the -1 dose level is evaluated and deemed to be safe, escalation to the -2B dose level may be initiated. Any decisions to de-escalate, as well as enrollment at alternative doses following de-escalation, must be made according to the established decision process for dose escalation, as described herein. Planned dose escalation for the Arm 1 combination regimen is outlined in Table 2 below; additional details on dose administration as described herein in the section "Study Treatment".

Table 2 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Arm 1: MM-398 + 5-FU/LV + Oxaliplatin

The order of the infusions to be administered in the clinic is as follows: MM-398 administered first, followed by oxaliplatin, then LV, followed by 5-FU.

In Part 1, patients receive the oxaliplatin infusion 2 hours after the completion of the MM-398 infusion. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly

after completion of the MM-398 infusion. If any grade 3 or higher infusion reactions are seen in Part 2 patients, the DSMB may elect to revert back to administration of oxaliplatin two hours after the completion of the MM-398 infusion.

Arm 1 Premedication

All patients must be premedicated prior to MM-398 infusion, 5-FU/LV infusion, and oxaliplatin infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan, 5-FU, and oxaliplatin administration, or the Summary of Product Characteristics (SmPC) for sites located in the European Union (EU). Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

Arm 2: MM-398 + 5-FU/LV

The order of the infusions to be administered in the clinic will be as follows: MM-398 will be administered first, followed by LV, followed by 5-FU.

Arm 2 Premedication

All patients must be premedicated prior to MM-398 infusion and 5-FU/LV infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan and 5-FU administration, or the SmPC for sites located in the EU. Atropine may be prescribed prophylactically, according to standard institutional practices, for patients who experienced acute cholinergic symptoms in the previous cycles.

Doses and Administration of MM-398 (Arms 1 and 2)

MM-398 is administered by intravenous (IV) infusion over 90 minutes (±10 minutes) every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) or normal saline to a final volume of 500 mL. Care should be taken not to use in-line filters or any diluents other than D5W or normal saline. MM-398 can be administered at a rate of up to 1 mL/sec (30 mg/sec).

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

Doses and Administration of 5-FU and Leucovorin (Arms 1 and 2)

Leucovorin is administered at a dose of 400 mg/m^2 of the (l + d)- racemic form, or (l) form 200 mg/m^2, as an IV infusion over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle

5-FU is administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle

Leucovorin should be reconstituted per the instructions on the package insert, SmPC or standard institutional guidelines for reconstitution of leucovorin.

Leucovorin should be administered prior to the 5-FU infusion (on Arm 1, leucovorin will be given concurrently with oxaliplatin). Actual dose of 5-FU and leucovorin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

Doses and Administration of Oxaliplatin (Arm 1 only)

In Part 1, oxaliplatin is administered at increasing dose levels as indicated in Table 2 (from 60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle

In Part 2, oxaliplatin is administered at a dose of 85 mg/m^2, IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle (if target dose is confirmed in accordance with methods described herein).

Oxaliplatin should be prepared according to the instructions on the package insert, SmPC or per standard institutional guidelines for preparation and administration of oxaliplatin.

Oxaliplatin should be administered following MM-398 infusion; in Part 1, the first 3 patients in Dose Level 1 begin the oxaliplatin infusion two hours after the completion of the MM-398 infusion. Actual dose of oxaliplatin to be administered is determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose is allowed for ease of dose administration.

Arm 3: nab-Paclitaxel + Gemcitabine

The order of the infusions to be administered in the clinic is as follows: nab-paclitaxel will be administered first, followed by gemcitabine.

Arm 3 Premedication

All patients receiving nab-paclitaxel and gemcitabine should be pre-medicated per the respective package inserts. If different institutional guidelines exist for premedication of weekly nab-paclitaxel and/or gemcitabine, the investigator should use their standard practice or the SmPC for sites located in the EU.

Doses and Administration of nab-Paclitaxel and Gemcitabine (Arm 3)

The nab-paclitaxel will be administered at 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

The gemcitabine will be administered at 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle.

Dose Limiting Toxicities (DLTs)

For MM-398 administered in combination with 5-FU/LV and oxaliplatin, the following adverse events are considered as dose limiting toxicities (DLTs) if they occur during the first cycle of treatment and are deemed related to the study treatment regimen:

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia);
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection;

- Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity; and
- Any grade 4 non-hematologic toxicity with the specific exclusion of: Fatigue/asthenia < 2 weeks in duration, increases in alkaline phosphatase level, nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen), and diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

Any toxicity that is related to disease progression will not be considered a DLT.

The safety assessment period for purposes of DLT evaluation and dose escalation decisions is one cycle of treatment (i.e. 28 days; or 14 days after the 2nd dose of study treatment if there is a treatment delay according as described herein). The dose can escalate to the next level only after the safety data have been evaluated at the current dose level (once the last patient enrolled in the cohort completes the first cycle of treatment) and the criteria for safety and tolerability of the optimal dose have not been exceeded (see Section Part 2 dose definition). In addition, any drug-related toxicities of Grade 3 or higher that arise after Cycle 1 (if applicable) are assessed for their potential relationship to cumulative MM-398 or combination therapy doses and considered in the decision to escalate the dose. PK data may be available, but is not be required for decisions on dose escalation.

Inclusion Criteria	Exclusion Criteria

In order for inclusion into the study, patients must have/be:
• Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting
  ○ Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment
  ○ Part 2: must have
	Patients must meet all the inclusion criteria and none of the following exclusion criteria:
	• Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed)
	• Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy)
	• Known metastasis to the central nervous system
	• Clinically significant gastrointestinal disorder including hepatic disorders, bleeding,

Inclusion Criteria	Exclusion Criteria
metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed • Measurable or non-measurable disease as defined by RECIST v1.1 • ECOG performance status of 0 or 1 • Adequate biological parameters as evidenced by the following blood counts: ○ ANC > 1,500 cells/µl without the use of hematopoietic growth factors, ○ Platelet count > 100,000 cells/µl, and ○ Hemoglobin > 9 g/dL • Adequate hepatic function as evidenced by: ○ Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and ○ AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) • Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.72 m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean	inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction • History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. • Known hypersensitivity to any of the components of MM-398, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin • Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only) • Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: ○ Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion ○ NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure ○ Known historical or active infection with HIV, hepatitis B, or hepatitis C • Active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome • Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan • Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin • Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only) • Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or

Inclusion Criteria	Exclusion Criteria
body weight should be used instead. • Normal ECG or ECG without any clinically significant findings • Recovered from the effects of any prior surgery or radiotherapy • ≥ 18 years of age • Agreeable to submit unstained archived tumor tissue for analysis, if available • Able to understand and sign an informed consent (or have a legal representative who is able to do so)	interfere with the interpretation of the results • Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 3 months following the last dose of study drug.

Dose Modifications

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03). All dose reductions for all arms should be based on the worst preceding toxicity.

Dosing may be held for up to 2 weeks from when it was due to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than 2 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor regarding risks and benefits of continuation. If oxaliplatin is not well tolerated in patients enrolled in Arm 1, oxaliplatin may be discontinued and patients may continue to receive MM-398 + 5-FU/LV at the discretion of the Investigator.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Dose Modifications

Prior to each dosing, patients must have: ANC ≥ 1500/mm^3, WBC ≥ 3500/ mm^3, Platelet count ≥ 100,000/mm^3 and Diarrhea ≤ Grade 1.

Treatment should be delayed to allow sufficient time for recovery to levels noted above, and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to ≥ 1500/mm^3 and the patient must have recovered from infection. For Grade 3 or 4 non-hematological toxicities, treatment should be delayed until they resolve to Grade 1 or baseline. Guidelines for dose adjustments of each individual treatment within the regimen are found in the tables below for Arm 1 (Table 3), and for Arm 2 (Tables 6 through 14). In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management should be followed.

For all tables below, patient should be withdrawn from study treatment if more than 2 dose reductions are required or if MM-398 reductions lower than 35 mg/m^2 are required. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well.

Treatment discontinuation that is required due to MM-398 or 5-FU toxicity will result in discontinuation from the study. However, for Arm 1, toxicity that requires discontinuation from oxaliplatin only (e.g. neuropathy) will result in the option to continue on study treatment with MM-398 + 5-FU/LV only for all future dosing.

<u>Arm 1 Dose Modifications</u>

The starting dose of ONIVYDE will be 60mg/m^2, 5FU 2400mg/m^2, LV 400mg/m^2 and Oxaliplatin either 85mg/m^2 or 60mg/ m^2. 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.

For non-hematologic toxicities, the dose reduction will be the same dose reduction schema as for hematotoxicity, except for the specific toxicities associated with the drug (ie 5FU hand foot syndrome, and oxaliplatin neuropathy) which will be as shown in Table 3.

Table 3: Arm 1 Dose Modifications

Worst Toxicity by CTCAE Grade	**MM-398**	**5-FU**	**Oxaliplatin**
Hematological Toxicities			
Grade 2 neutropenia (ANC <1500 - 1000 cells/ mm^3)	100 % of previous dose	100 % of previous dose	1st occurrence: 100% of previous dose
Grade 3 or 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia[a]	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/$m^2$2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
≥ Grade 2 thrombocytopenia (Grade 2: platelets ≤ 75,000/mm^3 – 50,000/mm^3 OR Grade 3-4: platelets < 50,000/mm^3)	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2

Other hematologic toxicities not specifically listed above	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[b]			
Grade 1 or 2, including diarrhea[c]	100 % of previous dose	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100 % of previous dose
Grade 3 or 4, including diarrhea[d] (except nausea and vomiting)	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% *except for Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2

Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Optimize anti-emetic therapy AND reduce dose by 25% ; if the patient is already receiving a reduced dose, reduce dose an additional 25%	1st occurrence: Reduce dose from 85 mg/ m^2 to 65 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 2nd occurrence: Reduce dose from 65 mg/ m^2 to 50 mg/m^2 or from 45 mg/m^2 to 35 mg/m^2
Grade 2 hand foot syndrome	100 % of previous dose[d]	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25%	100 % of previous dose
Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose to 45 mg/m^2 2nd occurrence: Reduce dose to 35 mg/m^2	Discontinue therapy	No dose modifications required
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	No dose modifications required[e]	Discontinue therapy	No dose modifications required

Sensory neuropathy	No dose modifications required[e]	No dose modifications required[e]	Grade 2, persistent: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, recovers prior to next cycle: Reduce dose from 85 mg/m^2 to 60 mg/m^2 or from 60 mg/m^2 to 45 mg/m^2 Grade 3, persistent: Discontinue therapy Grade 4: Discontinue therapy

[a]Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia.

[b]Asthenia and Grade 3 Anorexia do not require dose modification

[c]Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment

[d] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment

Arm 2 Dose Modifications

Dosing may be held for up to 3 weeks from when it was due, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any

patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Table 4

Grade 1: Transient flushing or rash, drug fever <38º C (<100.4º F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Table 5

Grade 1 • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2 • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 25-50 mg IV
Grade 3 • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary

• No further treatment with MM-398 will be permitted
Grade 4 • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table 6: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm^3 (Worst CTCAE grade)	**MM-398 Dose for Next Cycle**		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28** **Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
$\geq$ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose

< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 7: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below. Infusion reactions should be handled as described above.

Table 8: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28
Grade 1 or 2 (2-3 stools/day >	100% of previous dose	100% of previous dose	100% of previous dose

pretreatment or 4-6 stools/day > pretreatment)			
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence

Table 9: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia

Worst Toxicity CTCAE Grade	**MM-398 Dose for Next Cycle**		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28 Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28**
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence	Reduce dose to 45 mg/m^2 for the first occurrence and to 35 mg/m^2 for the second occurrence
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m^2 to a minimum dose of 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2	Optimize anti-emetic therapy **AND** reduce dose to 40 mg/m^2

5-FU and Leucovorin Dose Modifications

Guidelines for 5-FU dose modifications are provided below. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for MM-398 infusion reaction management should be used.

5-FU Dose Modifications for Hematological Toxicities

Prior to the next dose in a cycle or prior to initiating a new cycle of therapy, the patients must have:

- ANC ≥ 1500/mm^3
- WBC ≥ 3500/mm^3
- Platelet count ≥ 75,000/mm^3 (according to the European summary of product characteristics for 5-FU, the platelets should have recovered to ≥ 100,000/mm^3 prior to initiating therapy)

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines provided in the table below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 10: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC (cells/mm^3)		**Platelets (cells/mm^3)**	**5-FU Dose for D8, D15, D22[a]**	**5-FU Dose for Next Cycle[a]**
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25%[b]	Reduce dose by 25% [b]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study

5-FU Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until all Grade 3 or 4 non-hematological toxicities resolve to Grade 1 or baseline. Guidelines for dose adjustment of 5-FU related toxicities are provided below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table 11: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[c]

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25%[b]	Reduce dose by 25%[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25%[b], except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25%[b],except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study
[c] Asthenia and Grade 3 Anorexia do not require dose modification

*MM-398 Dose Modifications for UGT1A1*28 Positive Patients (Arms 1 and 2)*

Patients are tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of MM-398. All patients will begin dosing at 80 mg/m^2 (salt), however future doses may be reduced for patients who are positive (i.e. homozygous) for UGT1A1*28 7/7 genotype. For Part 1 patients receiving 80 mg/m^2 (salt) of MM-398: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m^2 (salt) after discussion between the PI, Sponsor and Medical Monitor. Any Part 1 patients who receive a reduced dose during Cycle 1 due to UGT1A1*28 homozygosity will not be evaluable for the cohort and are replaced.

Arm 3 Dose Modifications

Dose level reductions required due to toxicities related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 12.

Table 12: Dose Level Reductions for nab-Paclitaxel and Gemcitabine

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800

2nd dose reduction	75	600
If additional dose reductions required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 13 and adjustments related to other toxicities are provided in Table 14.

Table 13: nab-Paclitaxel and Gemcitabine Dose Modifications at the Start of Each Cycle or Within a Cycle for Neutropenia and/or Thrombocytopenia.

Cycle Day	**ANC (cells/mm^3)**		**Platelet count (cells/mm^3)**	**Nab-paclitaxel / Gemcitabine**
Day 1	<1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: IF day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = absolute neutrophil count

Table 14: nab-Paclitaxel and Gemcitabine Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	**Nab-paclitaxel**	**Gemcitabine**
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves ≤ Grade 1; resume at next dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next dose level	

Disease Evaluation

Tumor responses are evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, to establish disease progression by CT or MRI. In addition, other imaging procedures, as deemed appropriate by the Investigator, are performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Investigators should select target and non-target lesions in

accordance with RECIST v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

Tumor assessments should be completed until it has been determined that the patient has progressive disease (in accordance with RECIST v1.1). For patients who do not have documented disease progression per RECIST v. 1.1 at the time of treatment termination, imaging studies should be continually performed into the follow-up period every 8 weeks until disease progression is documented. Continued imaging follow-up on schedule is recommended to reduce potential bias in the evaluations of the impacts of the experimental treatments on disease.

EORTC-QLQ-C30 and EQ-5D-5L (Part 2 Only)

Health-related quality of life (HRQL) is assessed by the EORTC-QLQ-C30 and EQ-5D-5L instruments. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. EQ-5D is a generic, preference-based measurement of HRQL. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to do.

Patients are required to complete both questionnaires at time points outlined in the Schedule of Assessments. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients for whom validated translations of the questionnaires are available will be required to complete the questionnaire.

Efficacy Analysis

In the assessments of efficacy, each MM-398-containing arm is compared to the control arm. Efficacy comparisons use stratified analyses, incorporating randomization strata. Each comparison uses 0.10 level one-sided testing to evaluate whether the MM-398 -containing

arm improves the efficacy parameter. Confidence intervals are presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals are not adjusted for multiple comparisons. The primary efficacy comparisons are based on the ITT population, which includes all randomized patients.

Tumor evaluation is measured according to RECIST v1.1. For each patient, progression free survival time is determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical Progression of Disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time is censored at the time of the last non-PD tumor assessment.

A primary analysis is conducted when the Week 24 progression-free status for all randomized patients can be determined, anticipated at approximately 24 weeks after the last patient is randomized. A subsequent analysis for PFS and other endpoints is performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients.

Primary Efficacy Analysis

In the intention-to-treat (ITT) analysis, a patient is considered to have achieved progression-free survival at 24 weeks if the patient has data to indicate the patient has not progressed at 24 weeks. That is, a patient is considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.

Patients who do not meet the 24-week progression-free achievement criteria (e.g. patients progressed/died up to Week 24, patients censored prior to Week 24), if progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment.

For each arm, the progression-free survival achievement rate at 24 weeks is estimated by the number of patients meeting the 24 week achievement criteria divided by the number of ITT patients in the arm. The rate estimates are presented with corresponding 95% confidence intervals. Each MM-398 containing arm is assessed for increase in rate relative to

the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at 0.10 level of significance.

Secondary Efficacy Analyses

Progression-Free Survival (PFS) is descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits are presented. For each MM-398-containing arm, PFS is compared to the control arm. Hypothesis tests are conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment are considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI are calculated for each treatment arm. For each MM-398-containing arm, ORR is compared to the control arm. Differences in objective response rate between each MM-398-containing arm and control arm are provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, are used to compare objective response rates.

The maximum reduction (% change from baseline) in CA19-9 is computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses is carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement is considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline are included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response is estimated, along with corresponding 95% confidence intervals, by treatment arm.

Overall Survival (OS) is the time from randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS is descriptively summarized for each arm using Kaplan-Meier

methodology. For each MM-398-containing arm, OS is compared to the control arm. Hypothesis tests are conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS are estimated using stratified Cox models.

Quality of Life Analyses

Quality of life analyses are performed using patients in the analysis populations for each quality of life instrument (EORTC-QLC-C30, EQ-5D-5L). EORTC-QLQ-30 and EQ-5D-5L results will be summarized at each visit by treatment group

For each EORTC QLQ-C30 administered, scores are computed for the following scales: Global Health Status, Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial difficulties.

Scoring is carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations are applied to the raw scores so that the reported score will have range 0-100 for all scales. Summary statistics are presented for each subscale. A summary health state index value is computed for each EQ-5D-5L assessment. Summary statistics are presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses are tabulated.

Safety Analysis

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events are reported by the MedDRA version 17.1 or higher. Toxicity is graded according to the NCI CTCAE version 4.03.

Safety analysis of patients in Part 1 is to include a summary of dose-limiting toxicity events.

The period for treatment-emergent adverse events and safety findings is from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event is then considered as treatment-emergent.

Tabular summaries are to be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events are to be summarized by System Organ Class and preferred term. All adverse event data is to be listed by patient.

Laboratory data is presented by cycle. Abnormal laboratory values are assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data are reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) are assessed. Shift to most severe toxicity grade are summarized.

Vital signs and ECG are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Vital signs are tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Biomarker Subgroup Analysis

Analyses are performed to assess the associations between potential biomarkers (from plasma and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays are performed when appropriate.

Pharmacokinetics Analysis

Plasma concentrations of MM-398 and oxaliplatin can be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients can be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated (MM-398) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), are used to examine any possible interactions between MM-398 and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. NONMEM®, Version 7.3, is used to estimate individual PK parameters and simulate plasma exposures.

Example 4: Tolerability of Antineoplastic Therapies in Human Clinical Trial

The tolerability of antineoplastic therapies combining liposomal irinotecan, 5-FU/leucovorin and oxaliplatin was evaluated in a human clinical trial described in Example 3, using two different doses: 80 mg/m^2 (salt) of liposomal irinotecan (MM-398) and 60 mg/m^2 (salt) of liposomal irinotecan (MM-398). Table 15 summarizes three dosing regimens for the treatment of previously untreated (front-line) pancreatic cancer in humans over a 28 day treatment cycle.

Table 15 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
1	60	1, 15	2400/400	1, 15	80	1, 15
2	85	1, 15	2400/400	1, 15	80	1, 15
-2A[d]	75	1, 15	2400/400	1, 15	80	1, 15

a First dose administration in conjunction with first dose of nal-IRI; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle
Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

Initially, a combination of oxaliplatin, MM-398 liposomal irinotecan, leucovorin and 5-fluorouracil at dose level 1 in Table 15 above. The results are summarized in Table 16 for dose level 1 in Table 15 above (for 80 mg/m^2 (salt) M-398 dose), showing that the 80 mg/m^2 (salt) dose of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin at dose level 1 was not tolerated in humans.

Table 16: Antineoplastic Therapy with 80 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 3 Day 15
1	✓	✓	X	X	X	X
2	✓	R	R	R	X	X
3	✓	X	X	X	X	X

4	✓	✓	X	X	X	X
5	✓	X	X	X	X	X
6	✓	✓	R	R	R	R
7	✓	X	X	X	X	X

Table 16 summarizes the results from treating a total of seven (7) patients as part of Part 1 of Arm 1 shown in Figure 12. All seven patients met the applicable inclusion criteria specified below, including a diagnosis of pancreatic cancer.

A "check mark" (✓) in Table 16 indicates the patient received the antineoplastic therapy of dose level 1 in Table 15 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R" in Table 16 indicates the patient received a reduced dose of antineoplastic therapy of dose level -1 in Table 2 (Example 3 above) on the corresponding cycle and day: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

An "X" in Table 16 indicates the patient did not receive an antineoplastic therapy combining liposomal irinotecan, oxaliplatin, 5-fluorouracil and leucovorin or combining liposomal irinotecan, oxaliplatin, and 5-fluorouracil. After cycle 1, day 1 and prior to cycle 1, day 15, patient 2 was determined to be homozygous for the UGT1A1*28 allele, and subsequent reduced doses of the antineoplastic therapy were administered on days indicated in Table 16, based on the protocol of Example 3. Patients 1 and 3-7 were not homozygous for UGT1A1*28 allele.

The antineoplastic therapy of dose level 1 in Table 15 (Example 4) was only administered to 2 of these 6 patients on day 15 of (28-day) cycle 1, no patients received dose level 1 for more than 2 consecutive doses, and none of the patients received this therapy after cycle 1.

Accordingly, as noted in the Table 16, antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of

5-fluorouracil and (l+d) leucovorin were not well tolerated in a human clinical trial (resulting in dose limiting toxicities). Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 15.

In contrast, as noted in Table 18 below, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m2 of 5-fluorouracil and (l+d) leucovorin were tolerated in a human clinical trial. In particular, dose level -1 in Table 17 (a 60 mg/m^2 (salt) M-398 dose) was administered two or more consecutive times to multiple human patients in the clinical trial described in Example 3. These antineoplastic therapies comprising the reduced 60 mg/m^2 (salt) of liposomal irinotecan (MM-398) in combination with oxaliplatin and 5-fluorouracil/leucovorin were better tolerated in humans than dose level 1 in Table 15. In other embodiments, patients are administered the therapy of dose level -2B in Table 17.

Table 17 Part 1 Dose Escalation Table (MM-398 + 5-FU/LV + oxaliplatin)

Level	**Oxaliplatin**		**5-FU/LV**		**MM-398 (nal-IRI)**	
	Dose (mg/m^2)[a]	**Dose Day[c]**	**Dose (mg/m^2)[b]**	**Dose Day[c]**	**Dose (mg/m^2)**	**Dose Day[c]**
-1	60	1, 15	2400/400	1, 15	60	1, 15
-2B	85	1, 15	2400/400	1, 15	60	1, 15

a First dose administration in conjunction with first dose of MM-398; oxaliplatin to be administered 2 hours after the completion of the nal-IRI infusion in Part 1.
b 46 hour infusion, no bolus is given; leucovorin and 5-FU will be administered last, following the completion of the oxaliplatin infusion
c Day indicated is part of a 28-day cycle

Table 18: Antineoplastic Therapy with 60 mg/m^2 liposomal irinotecan in combination with oxaliplatin/5FU/leucovorin in human clinical trials

Patient	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 15	Cycle 3 Day 1
1	✓	✓	R2	R2	R2
2	✓	✓	✓		
3	✓	✓	✓		
4	✓	✓			

5	✓	✓	✓		

Table 18 summarizes the results from treating a total of five (5) patients as part of Part 1 of Arm 1 shown in Figure 12. All five patients met the applicable inclusion criteria specified in Example 3, including a diagnosis of pancreatic cancer. A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 60 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

In contrast to the antineoplastic therapy of dose level 1 in Table 14, the antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered repeatedly to patients 2 and 6 for at least 3 consecutive administrations (including 4 consecutive administrations for patient 6).

The antineoplastic therapy of dose level -1 in Table 2 (Example 3) was administered to 5 of 5 patients on days 1 and 15 of (28-day) cycle 1, and days 1 and 15 of (28 day) to 3 of 4 patients in the study, with no dose limiting toxicities. The antineoplastic therapy of dose level -1 was administered repeatedly to all 5 patients for at least 2 consecutive administrations.

A "check mark" (✓) in Table 18 indicates the patient received the antineoplastic therapy of dose level -1 in Table 17 above, starting on the indicated days of 3 consecutive 28-day treatment cycles: 80 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 2,400 mg/m^2 5-fluorouracil, as described in the protocol of Example 3.

A "R2" in Table 18 indicates the patient received a reduced dose of antineoplastic therapy of dose on the corresponding cycle and day: 50 mg/m^2 liposomal irinotecan (MM-398, dose based on the corresponding amount of irinotecan hydrochloride trihydrate salt), 60 mg/m^2 oxaliplatin, 400 mg/m^2 (l+d) leucovorin and 1,800 mg/m^2 5-fluorouracil (a 25% reduction compared to dose level -1 dose), as described in the protocol of Example 3. One patient in

Table 18 received this reduced dose in response to Grade II symptoms (non-hematologic), but without a dose limiting toxicity.

Accordingly, as noted in the Table 18, antineoplastic therapies combining a dose of 60 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin were well tolerated in a human clinical trial. Examples of antineoplastic therapies combining a dose of 80 mg/m^2 liposomal irinotecan with 60 mg/m^2 oxaliplatin and doses of 2,400 and 400 mg/m^2 of 5-fluorouracil and (l+d) leucovorin include the therapies in Table 17.

Example 5: ONIVYDE® (irinotecan liposome injection) Liposomal Irinotecan

One preferred example of an irinotecan liposome described herein is the product marketed as ONIVYDE® (irinotecan liposome injection). ONIVYDE® is a topoisomerase inhibitor, formulated with irinotecan in a liposomal dispersion, for intravenous use.

The finished ONIVYDE® product is a white to slightly yellow opaque sterile concentrate for infusion. It consists of an isotonic dispersion of liposomes containing irinotecan hydrochloride trihydrate. The liposomes are small unilamellar lipid bilayer vesicles, approximately 110 nm in diameter, enclosing an aqueous compartment that contains irinotecan in a gelated or precipitated state, as sucrosofate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL. The liposomes are dispersed in an aqueous buffered solution.

The ONIVYDE® product contains irinotecan sucrosofate encapsulated in a liposome, obtained from an irinotecan hydrochloride trihydrate starting material. The chemical name of irinotecan is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. The dosage of ONIVYDE® can be calculated based on the equivalent amount of irinotecan trihydrate hydrochloride starting material used to prepare the irinotecan liposomes, or based on the amount of irinotecan in the liposome. There are about 866 mg of irinotecan per gram of

irinotecan trihydrate hydrochloride. For example, an ONIVYDE® dose of 80 mg based on the amount of irinotecan hydrochloride trihydrate starting material actually contains about 0.866x(80mg) of irinotecan in the final product (i.e., a dose of 80 mg/m^2 of ONIVYDE® based on the weight of irinotecan hydrochloride starting material is clinically equivalent to about 70 mg/m^2 of irinotecan in the final product). Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL.

Claims

1. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.
2. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 85 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.
3. The use of any one of claims 1-2, wherein the 5-fluorouracil is administered as an infusion over 46 hours.
4. The use of any one of claims 1-3, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.
5. The use of any one of claims 1-4, wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle.
6. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not

previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

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

wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle.

7. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,
b. 85 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

8. The use of any one of claims 1-7, wherein the liposomal irinotecan is administered as an infusion over a total of about 90 minutes.
9. The use of any one of claims 1-8, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.
10. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:

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

wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

11. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 85 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

    wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

12. The use of any one of claims 1-9, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

13. A use of a combination of liposomal irinotecan, oxaliplatin, and 5-fluorouracil in treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the metastatic adenocarcinoma of the pancreas, the use comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of:
    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2-85mg/m^2 oxaliplatin,

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

d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient

wherein the liposomal irinotecan, oxaliplatin and leucovorin is administered on days 1 and 15 of a 28-day treatment cycle, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil, wherein the administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

14. The use of any one of claims 1-11, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

15. The use of any one of claims 1-8, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposome vesicles consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

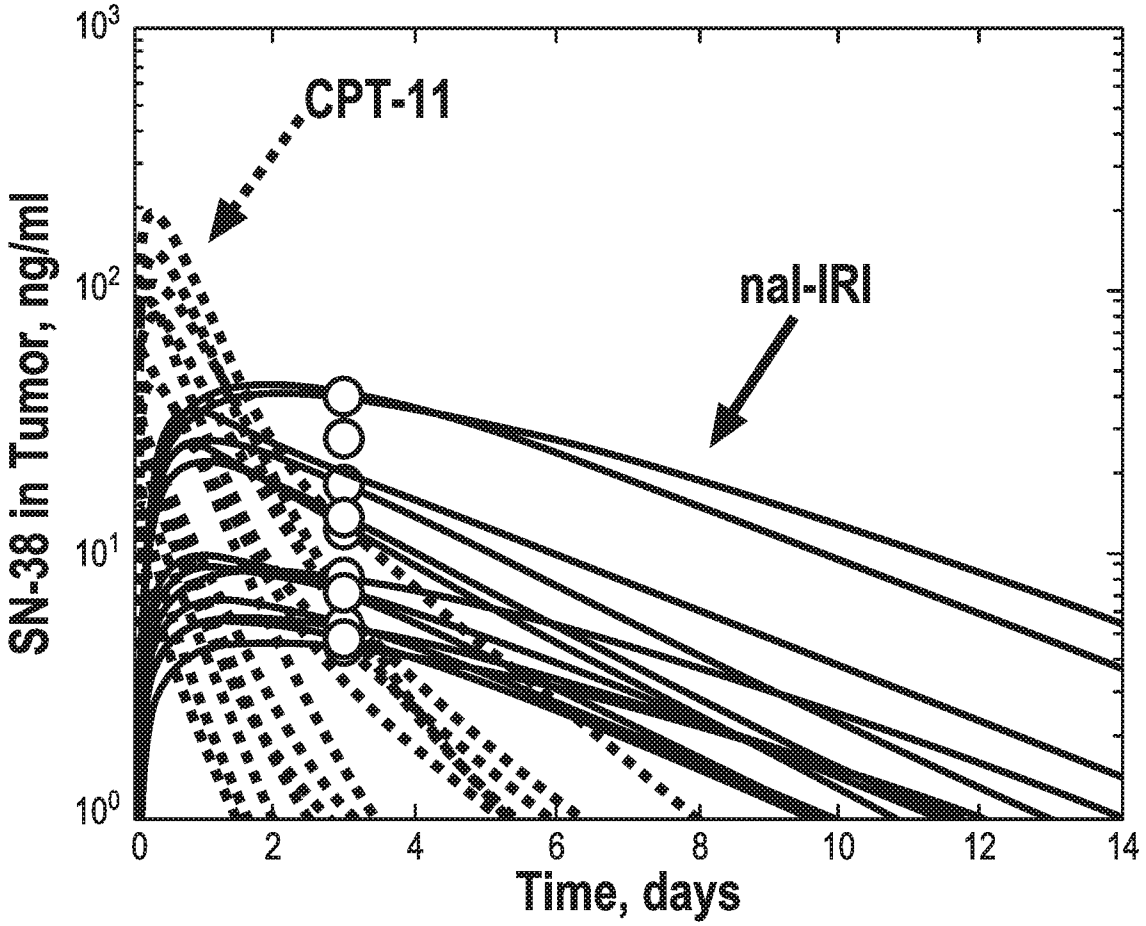

CPT-11
nal-IRI
SN-38 in Tumor, ng/ml
10^3
10^2
10^1
10^0
0
2
4
6
8
10
12
14
Time, days

FIG. 1A

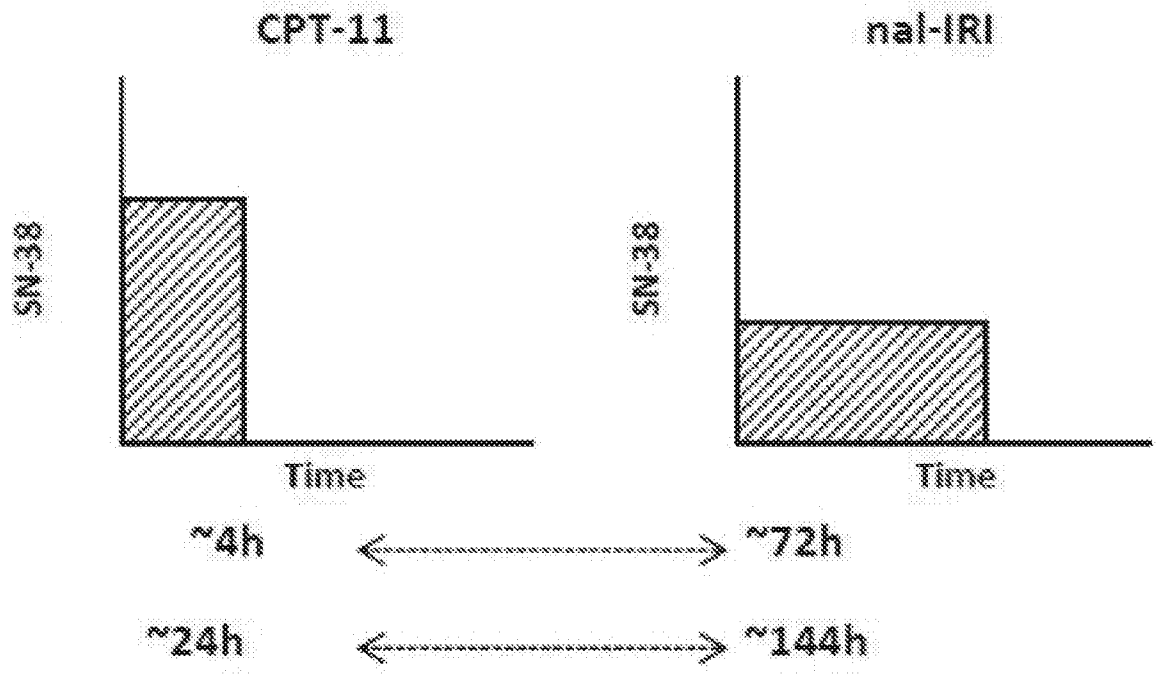

CPT-11
nal-IRI
SN-38
SN-38
Time
Time
~4h
~72h
~24h
~144h

FIG. 1B

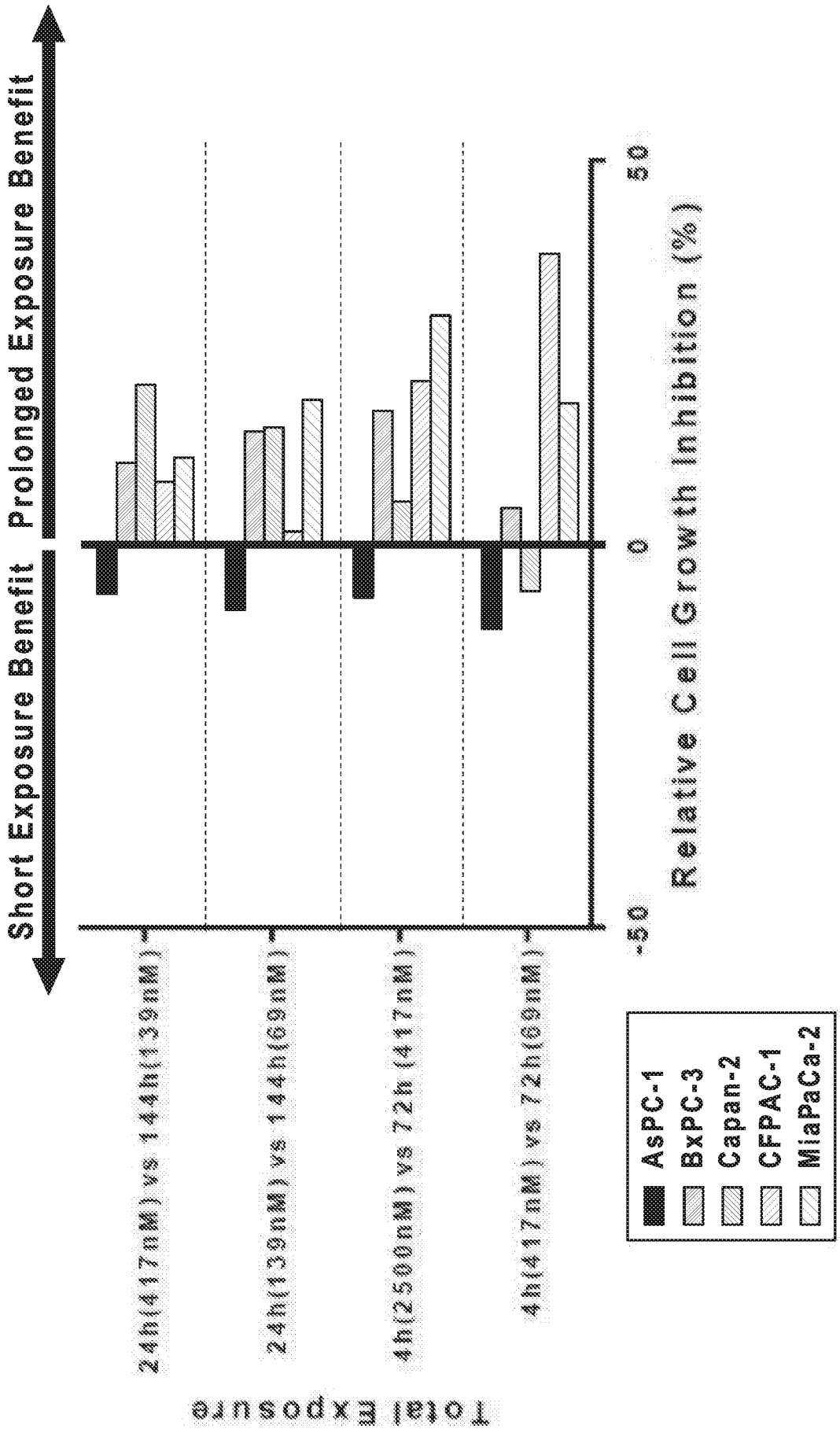

Short Exposure Benefit
Prolonged Exposure Benefit
Relative Cell Growth Inhibition (%)
50
0
-50
Total Exposure
24h(417nM) vs 144h(139nM)
24h(139nM) vs 144h(69nM)
4h(2500nM) vs 72h (417nM)
4h(417nM) vs 72h(69nM)
AsPC-1
BxPC-3
Capan-2
CFPAC-1
MiaPaCa-2

FIG. 1C

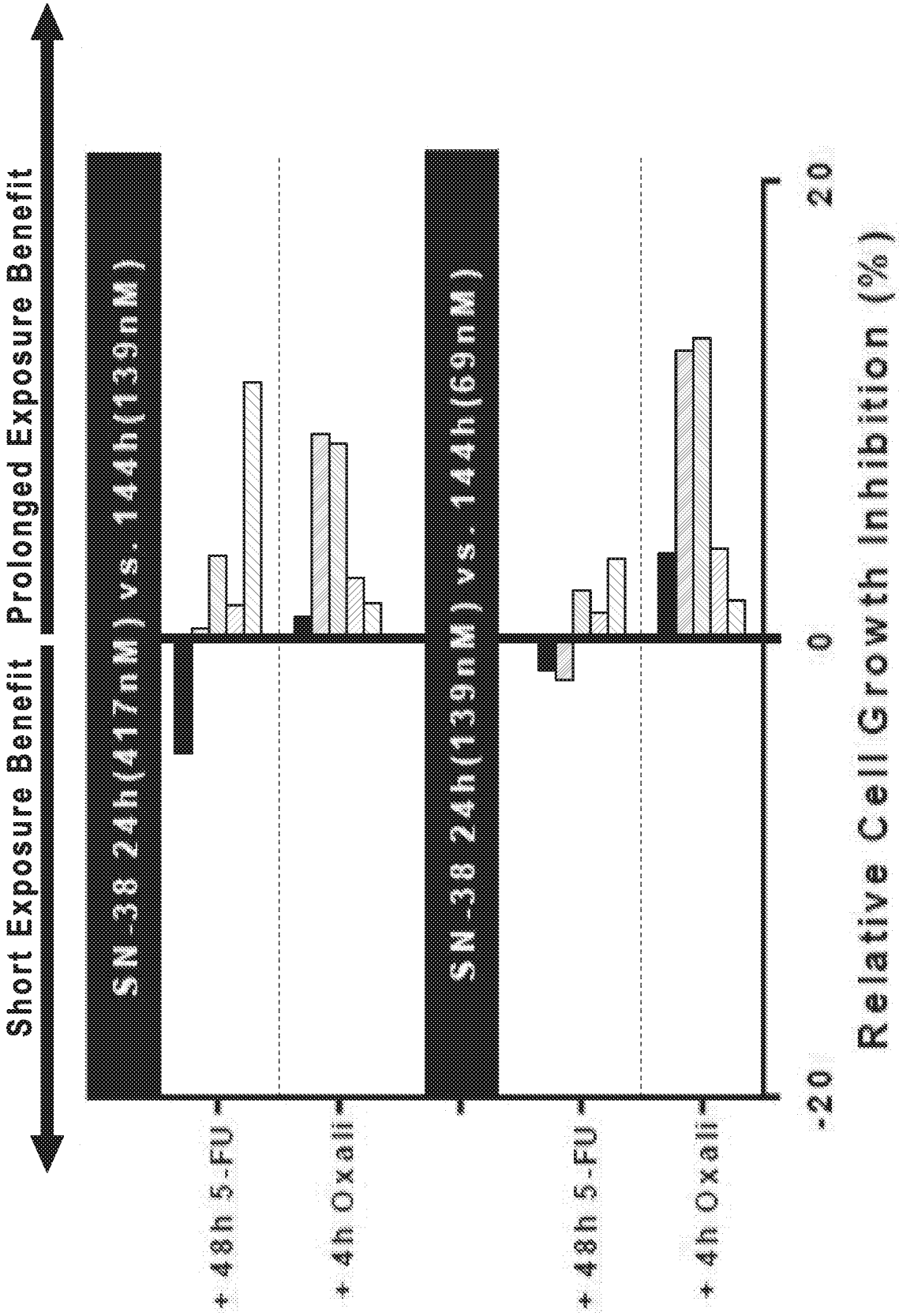

Short Exposure Benefit
Prolonged Exposure Benefit
SN-38 24h(417nM) vs. 144h(139nM)
SN-38 24h(139nM) vs. 144h(69nM)
+ 48h 5-FU
+ 4h Oxali
+ 48h 5-FU
+ 4h Oxali
Combination Partner
-20
0
20
Relative Cell Growth Inhibition (%)

FIG. 1D

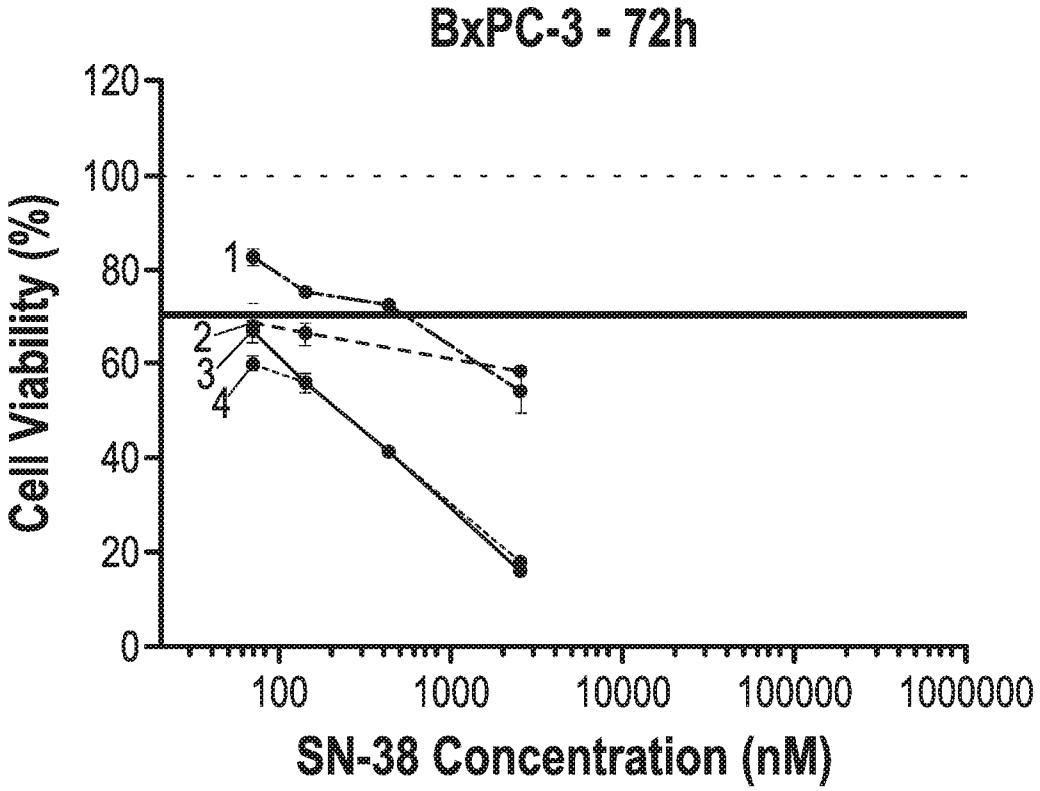

BxPC-3 - 72h
Cell Viability (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 Concentration (nM)

FIG. 2A

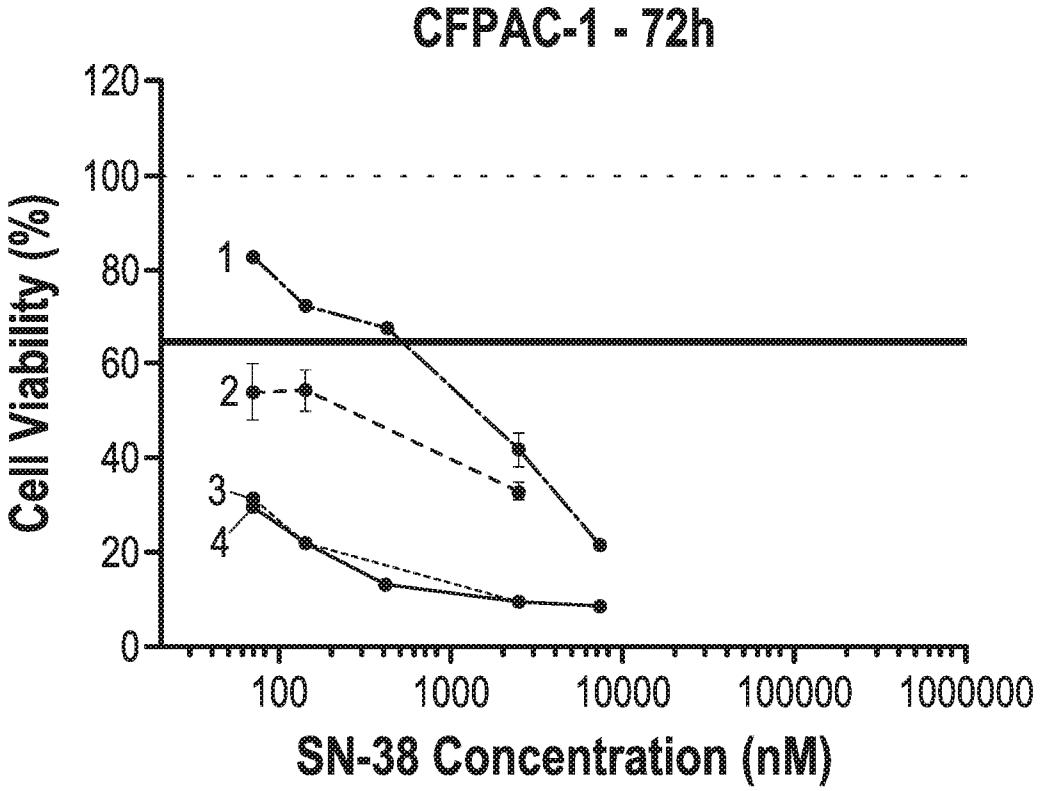

CFPAC-1 - 72h
Cell Viability (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 Concentration (nM)

FIG. 2B

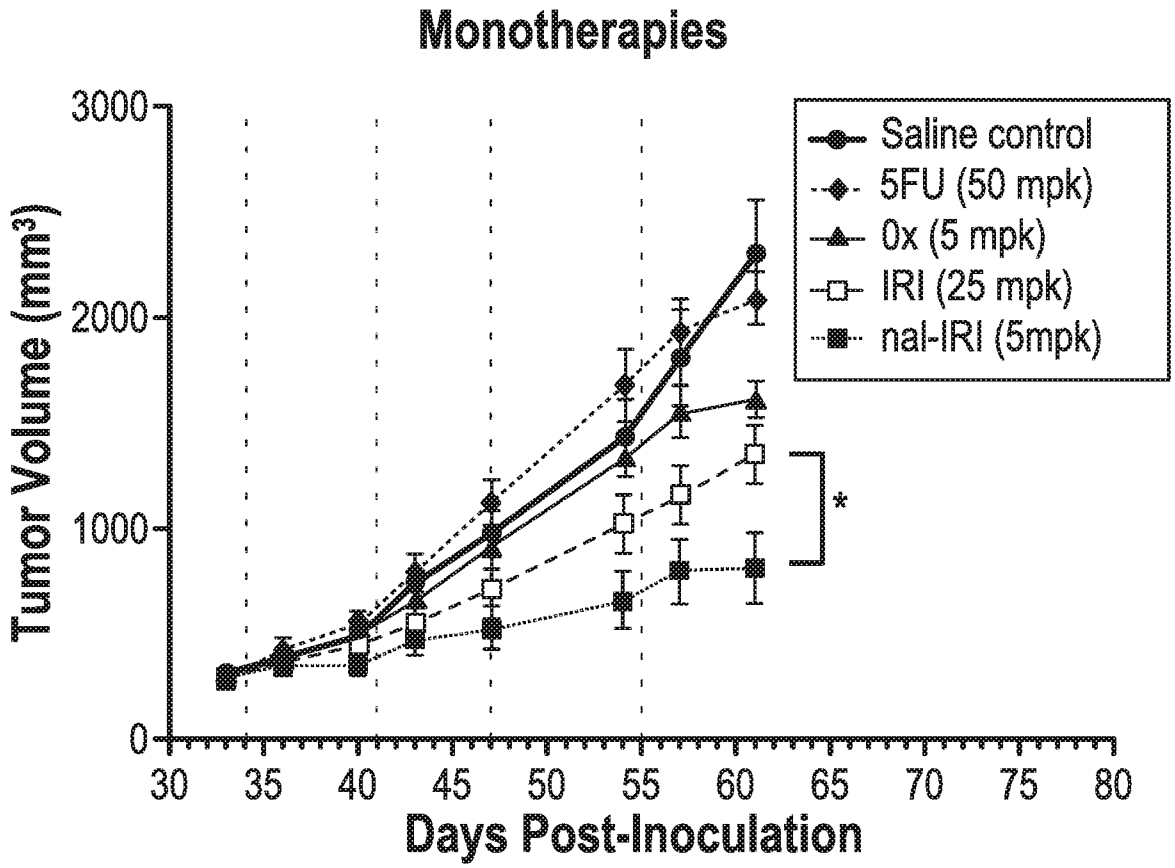

Monotherapies
Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
5FU (50 mpk)
0x (5 mpk)
IRI (25 mpk)
nal-IRI (5mpk)
*

FIG. 3A

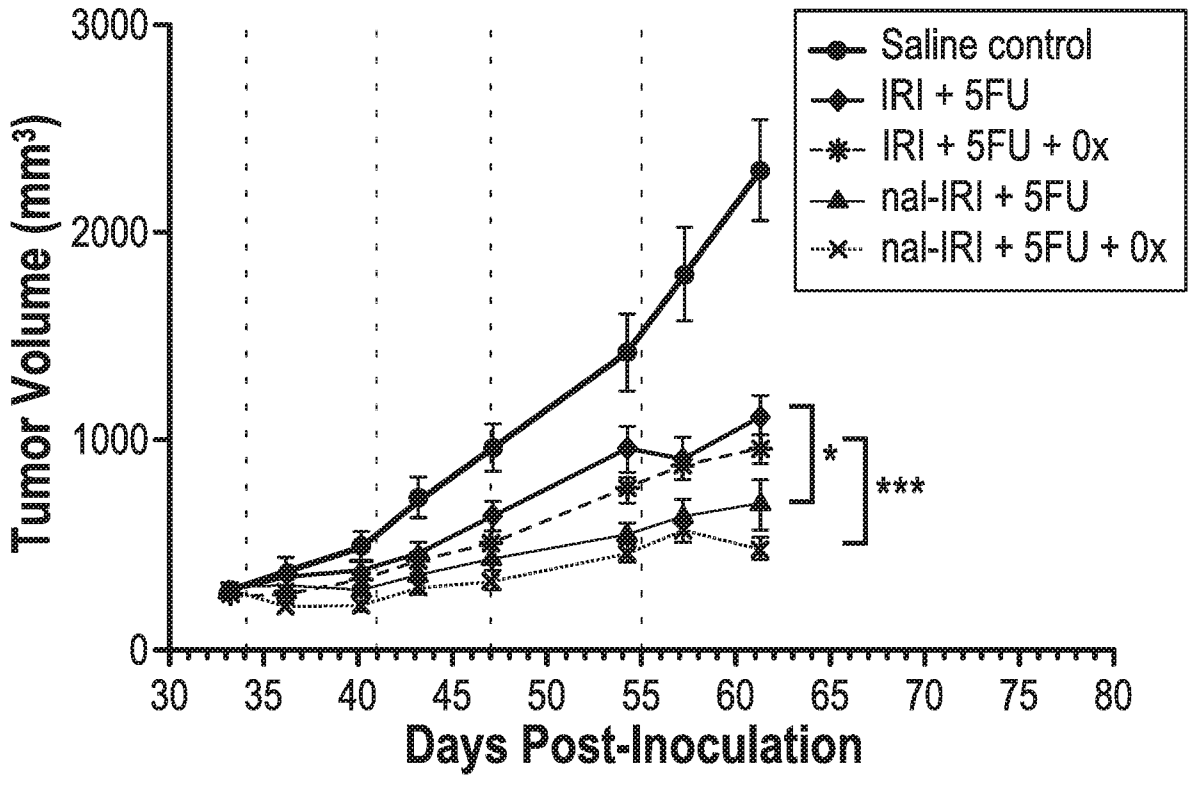

Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
IRI + 5FU
IRI + 5FU + 0x
nal-IRI + 5FU
nal-IRI + 5FU + 0x
*
***

FIG. 3B

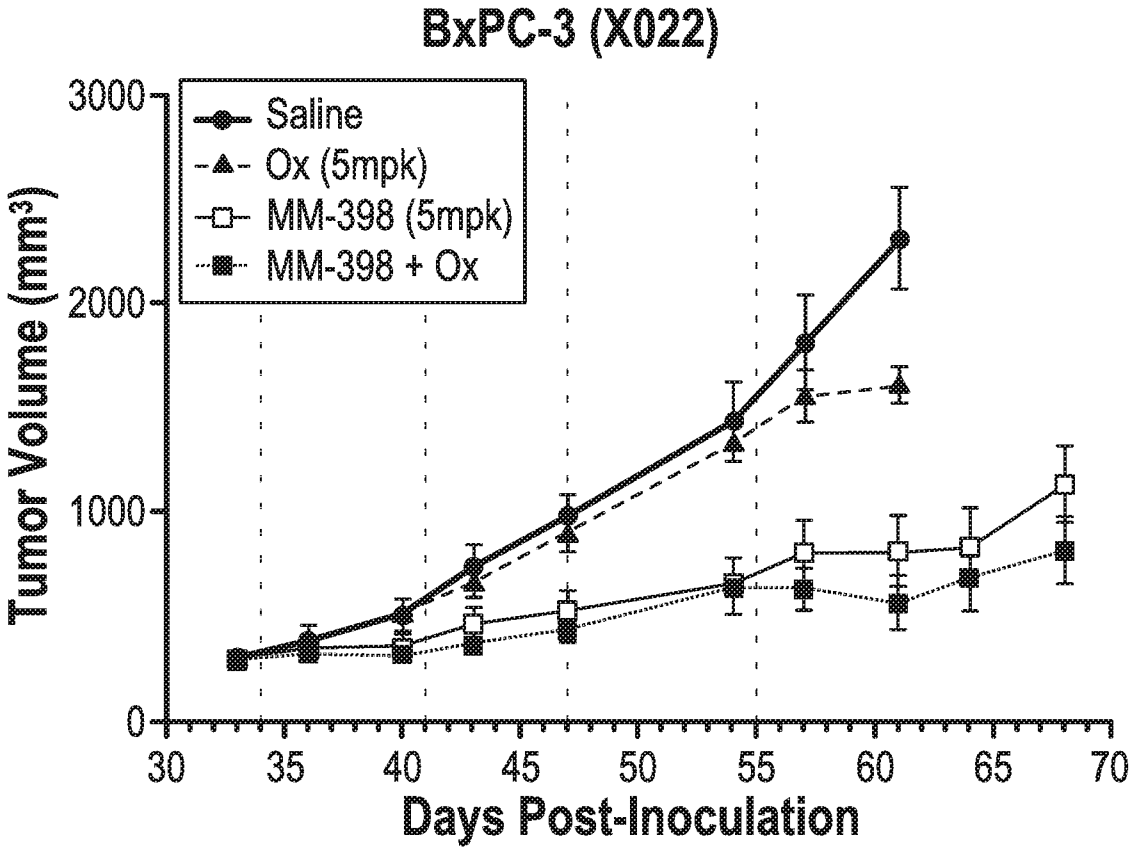

BxPC-3 (X022)
Saline
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
Tumor Volume (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
Days Post-Inoculation

FIG. 4A

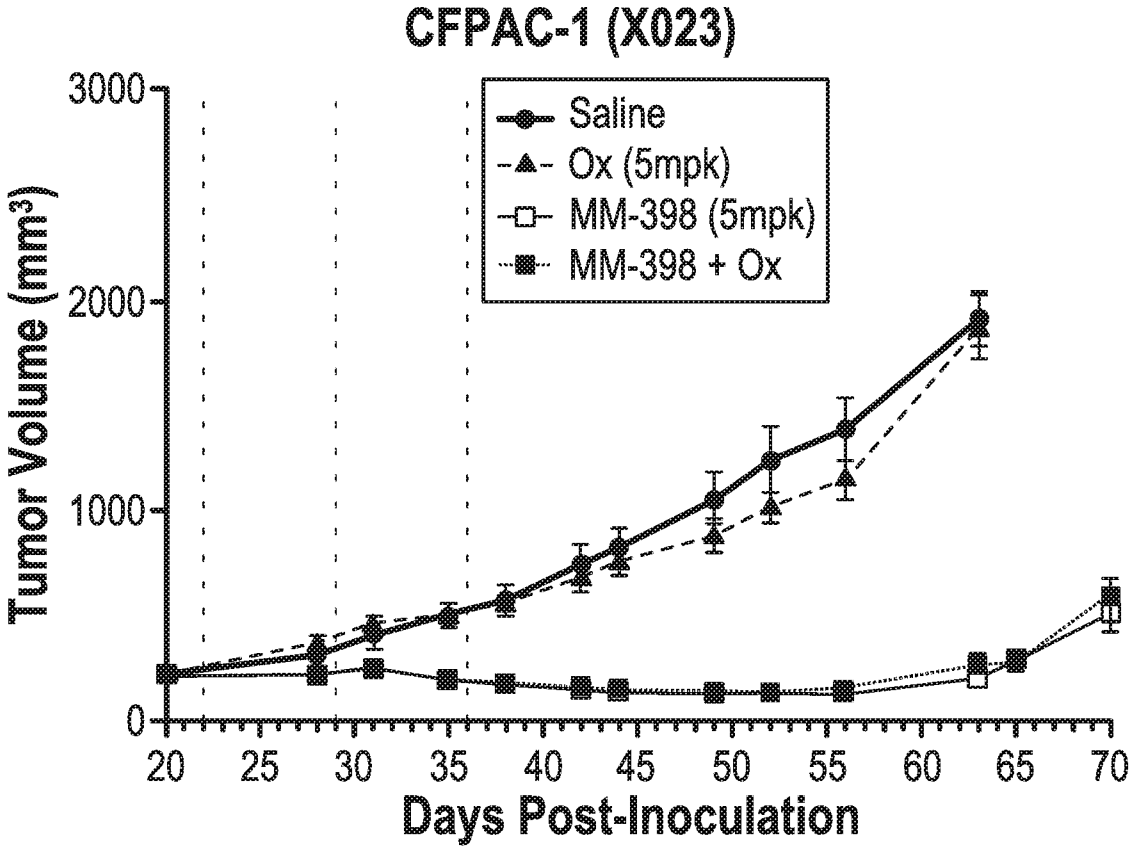

CFPAC-1 (X023)
Saline
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
Tumor Volume (mm³)
3000
2000
1000
0
20
25
30
35
40
45
50
55
60
65
70
Days Post-Inoculation

FIG. 4B

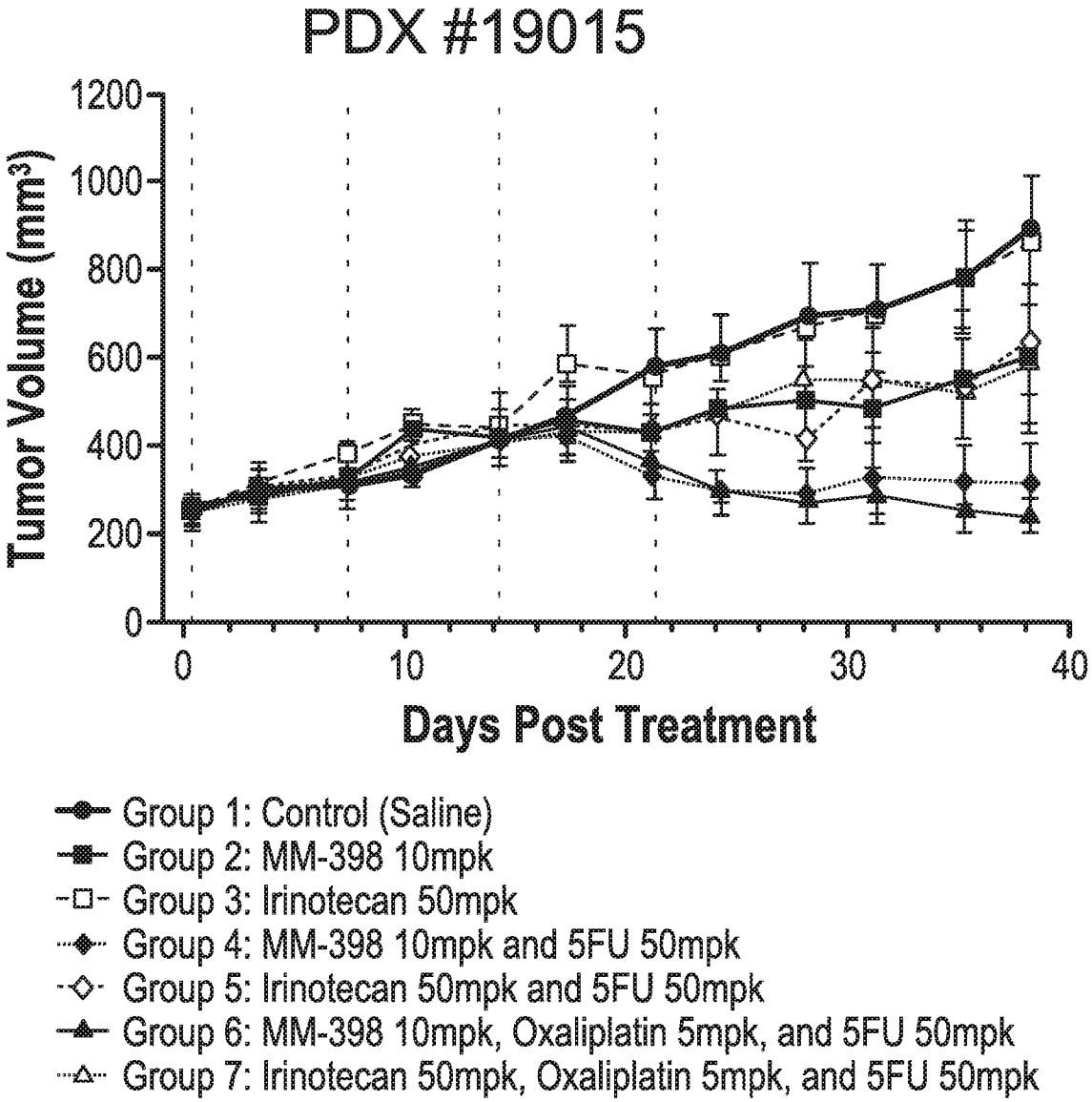

PDX #19015
Tumor Volume (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
Days Post Treatment
Group 1: Control (Saline)
Group 2: MM-398 10mpk
Group 3: Irinotecan 50mpk
Group 4: MM-398 10mpk and 5FU 50mpk
Group 5: Irinotecan 50mpk and 5FU 50mpk
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk
Group 7: Irinotecan 50mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5A

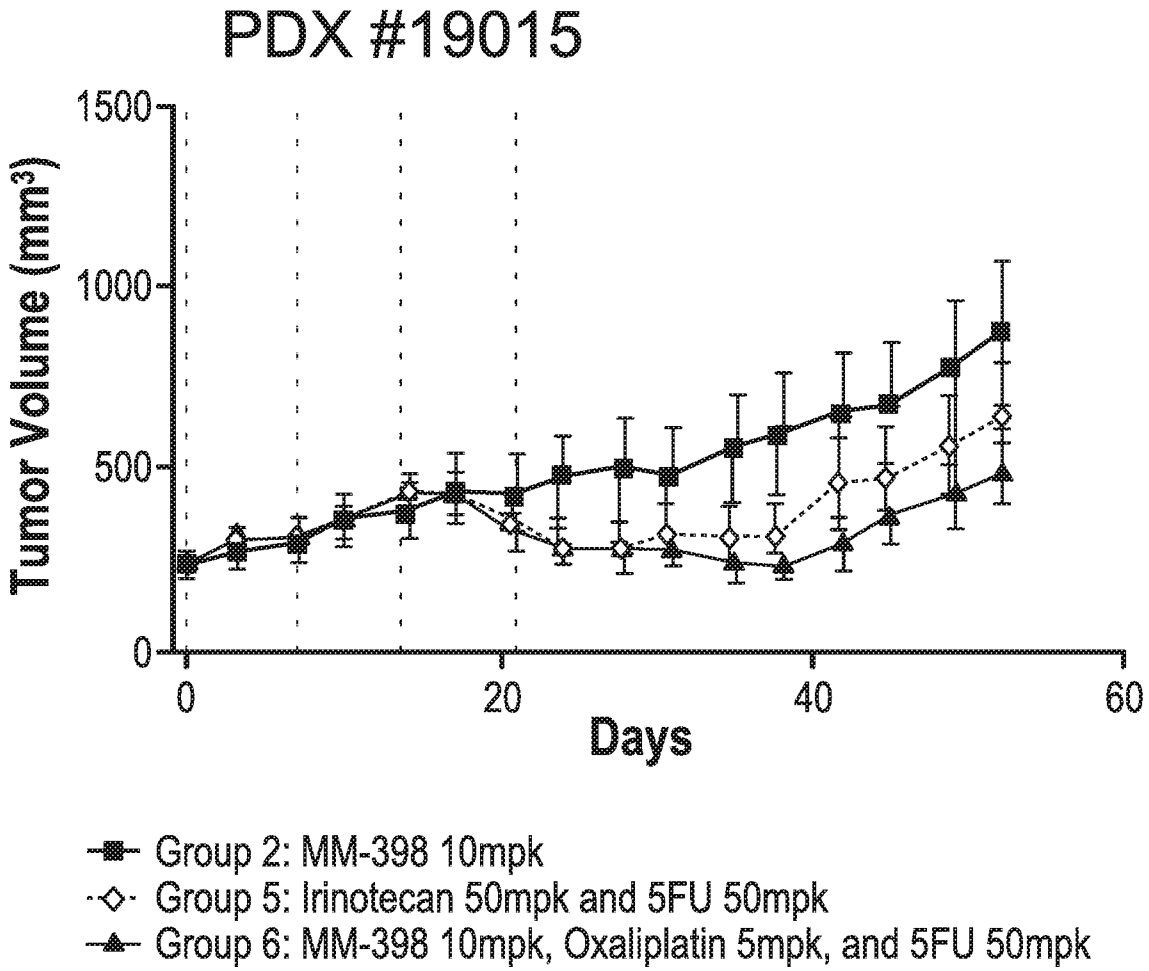

PDX #19015
Tumor Volume (mm3)
1500
1000
500
0
0
20
40
60
Days
Group 2: MM-398 10mpk
Group 5: Irinotecan 50mpk and 5FU 50mpk
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5B

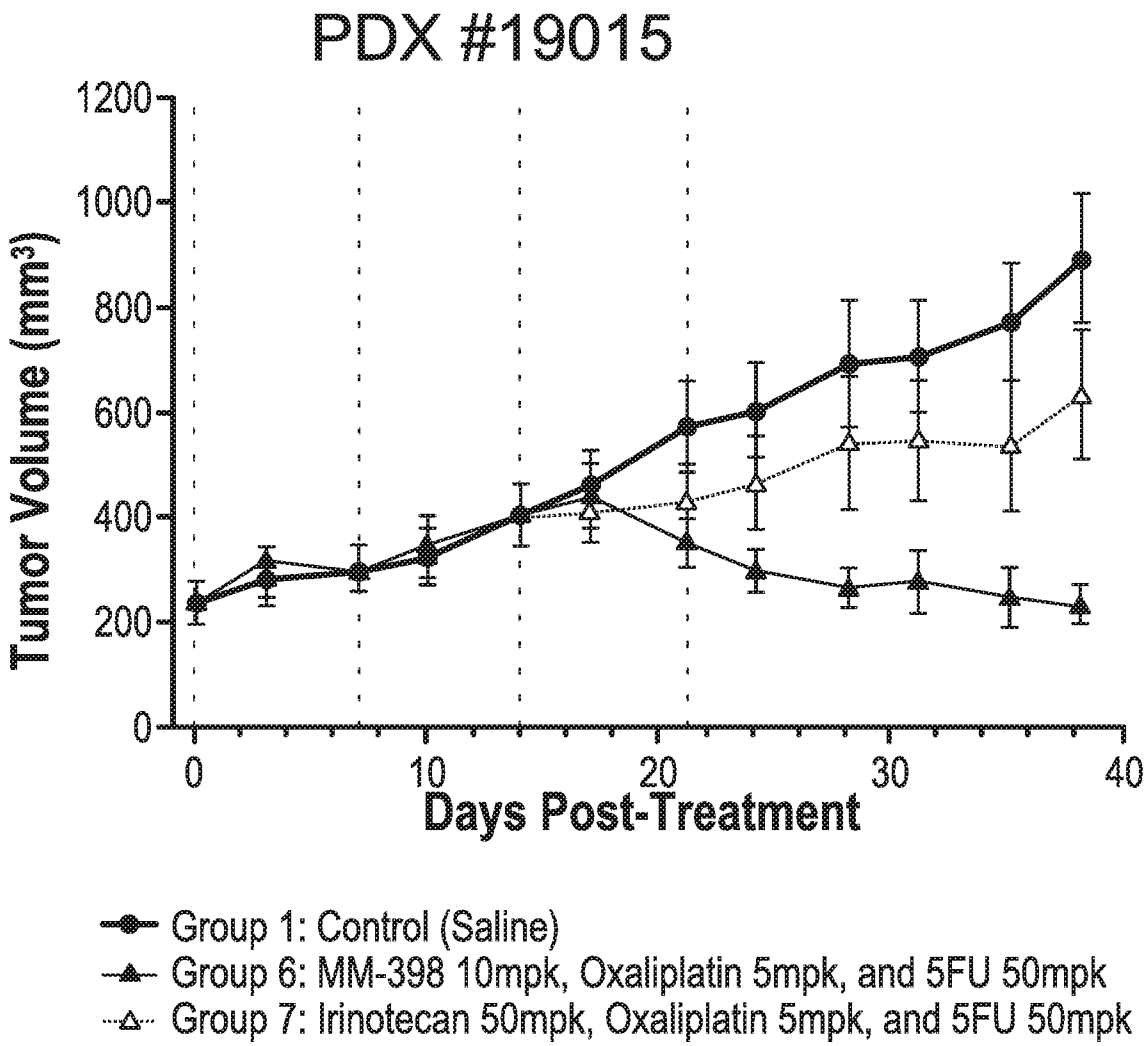

PDX #19015
Tumor Volume (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
Days Post-Treatment
Group 1: Control (Saline)
Group 6: MM-398 10mpk, Oxaliplatin 5mpk, and 5FU 50mpk
Group 7: Irinotecan 50mpk, Oxaliplatin 5mpk, and 5FU 50mpk

FIG. 5C

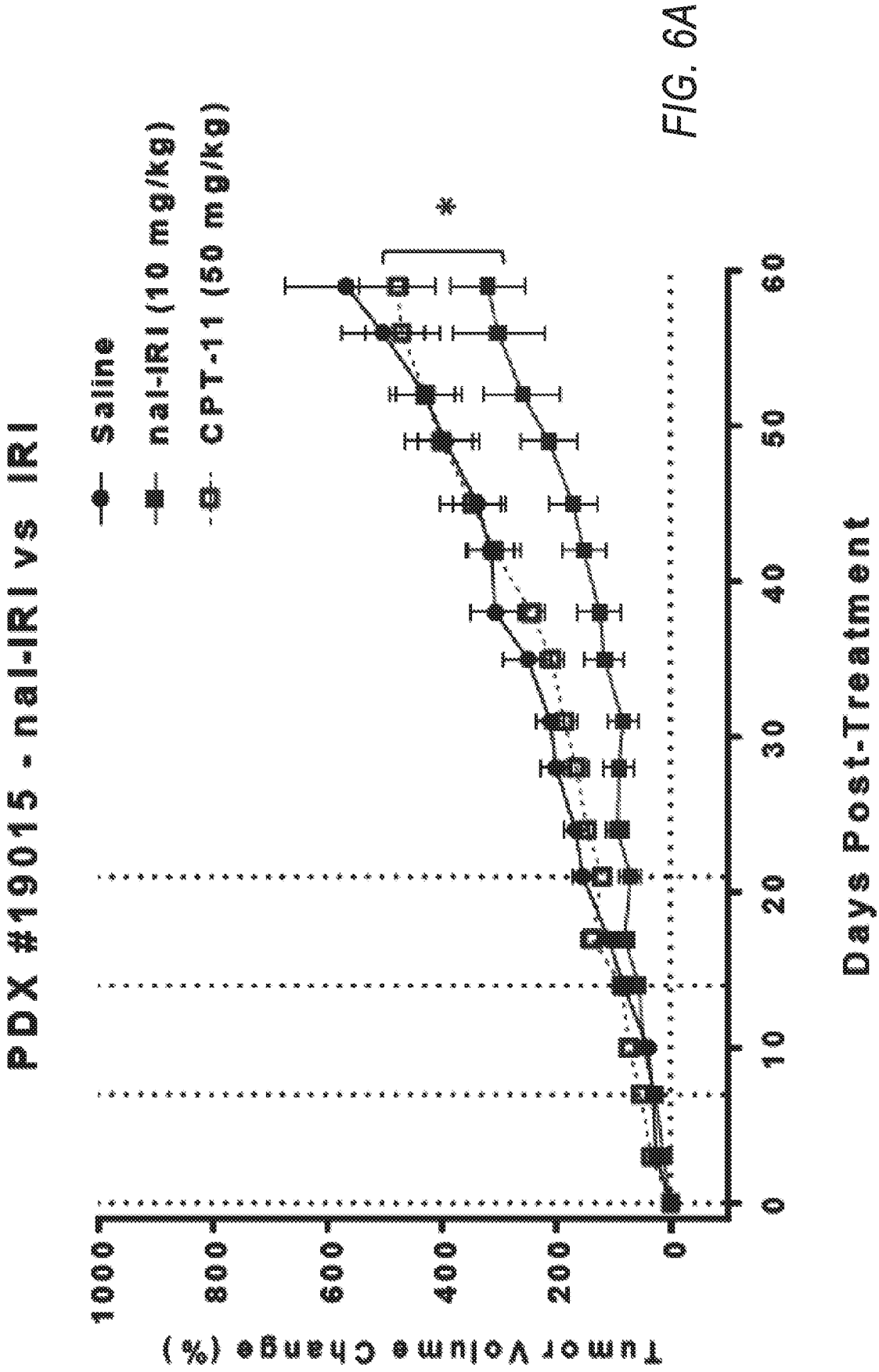

PDX #19015 - nal-IRI vs IRI
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6A

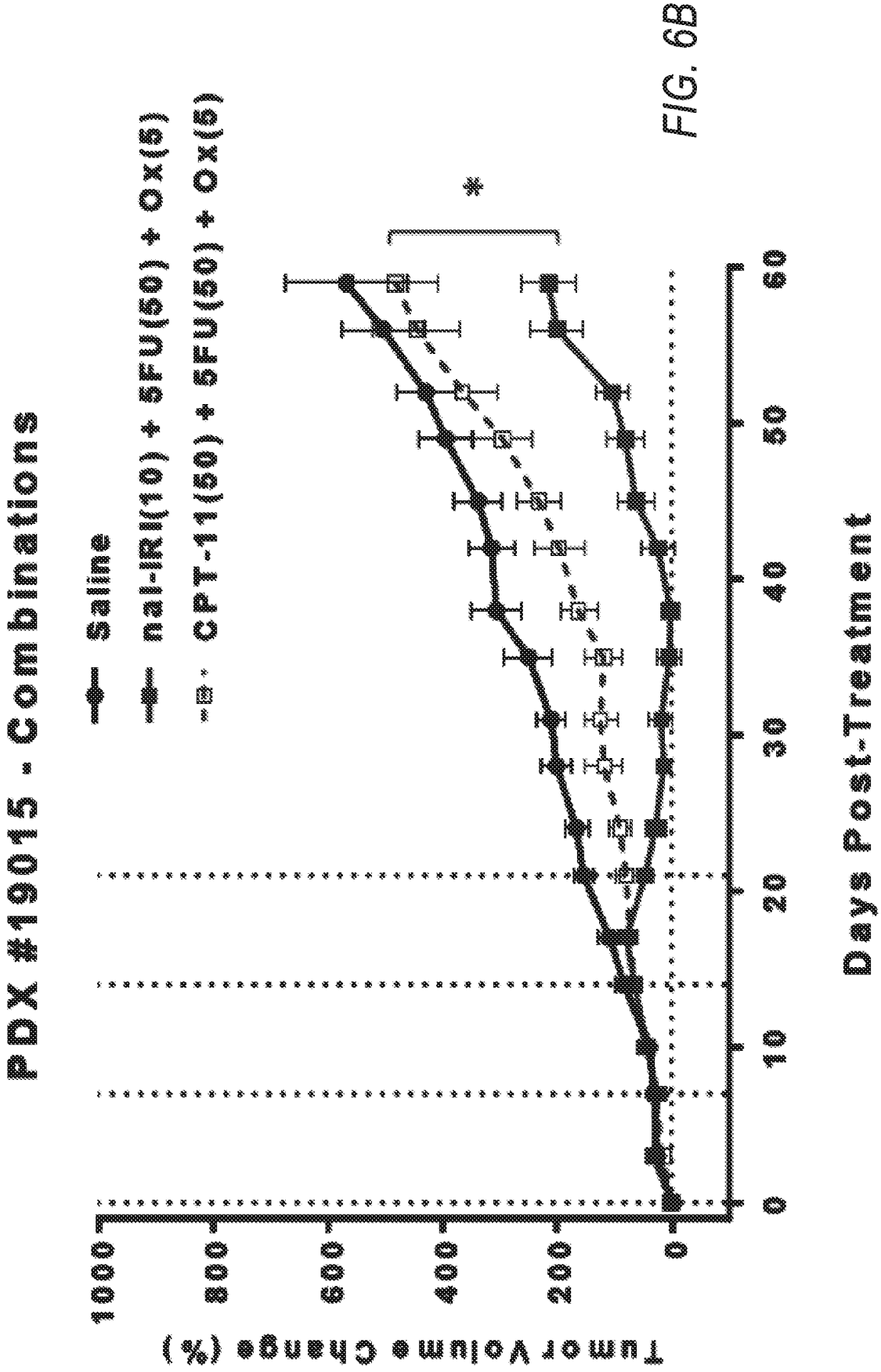

PDX #19015 - Combinations
Saline
nal-IRI(10) + 5FU(50) + Ox(5)
CPT-11(50) + 5FU(50) + Ox(5)
*
Tumor Volume Change (%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
Days Post-Treatment

FIG. 6B

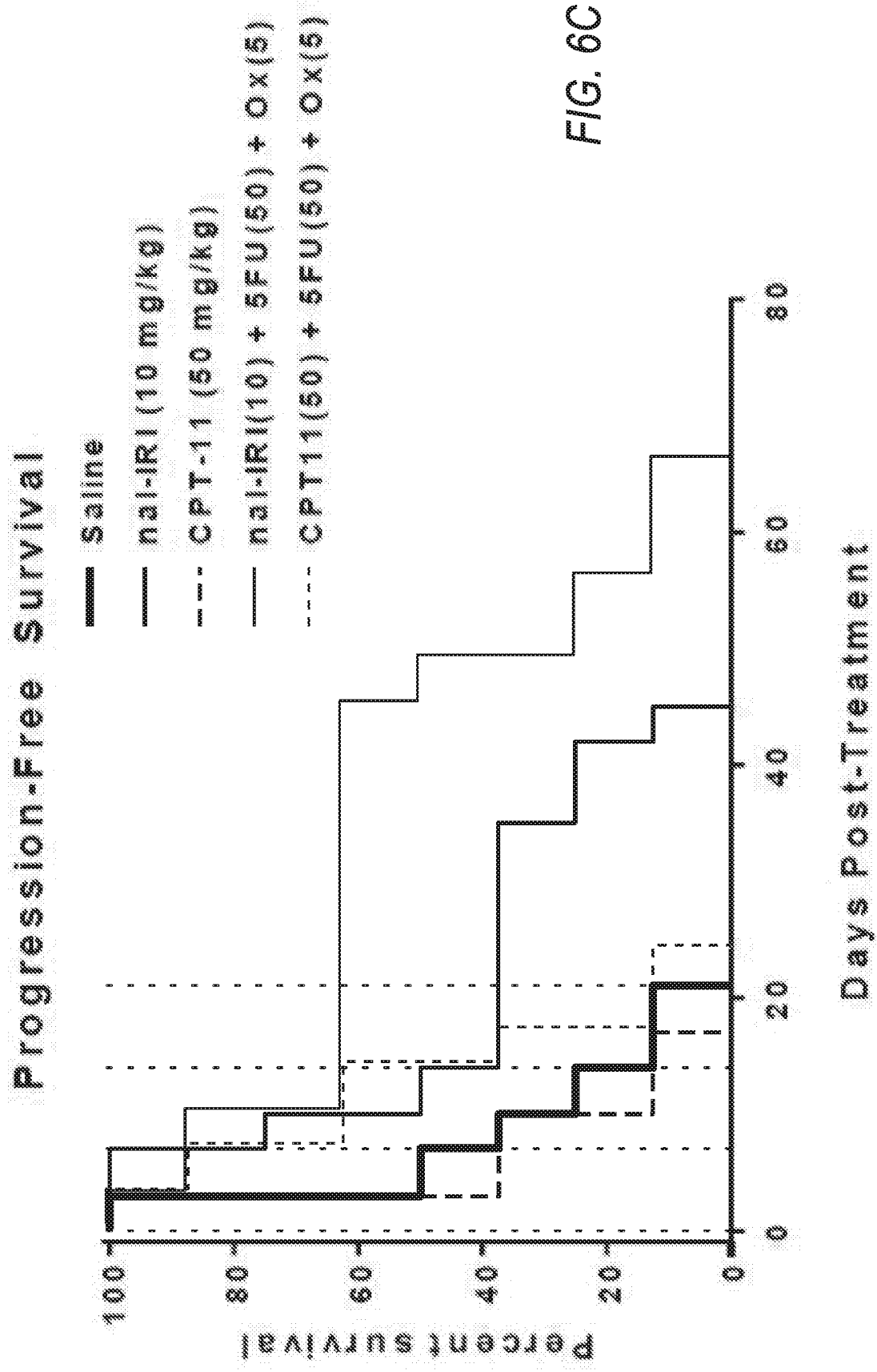
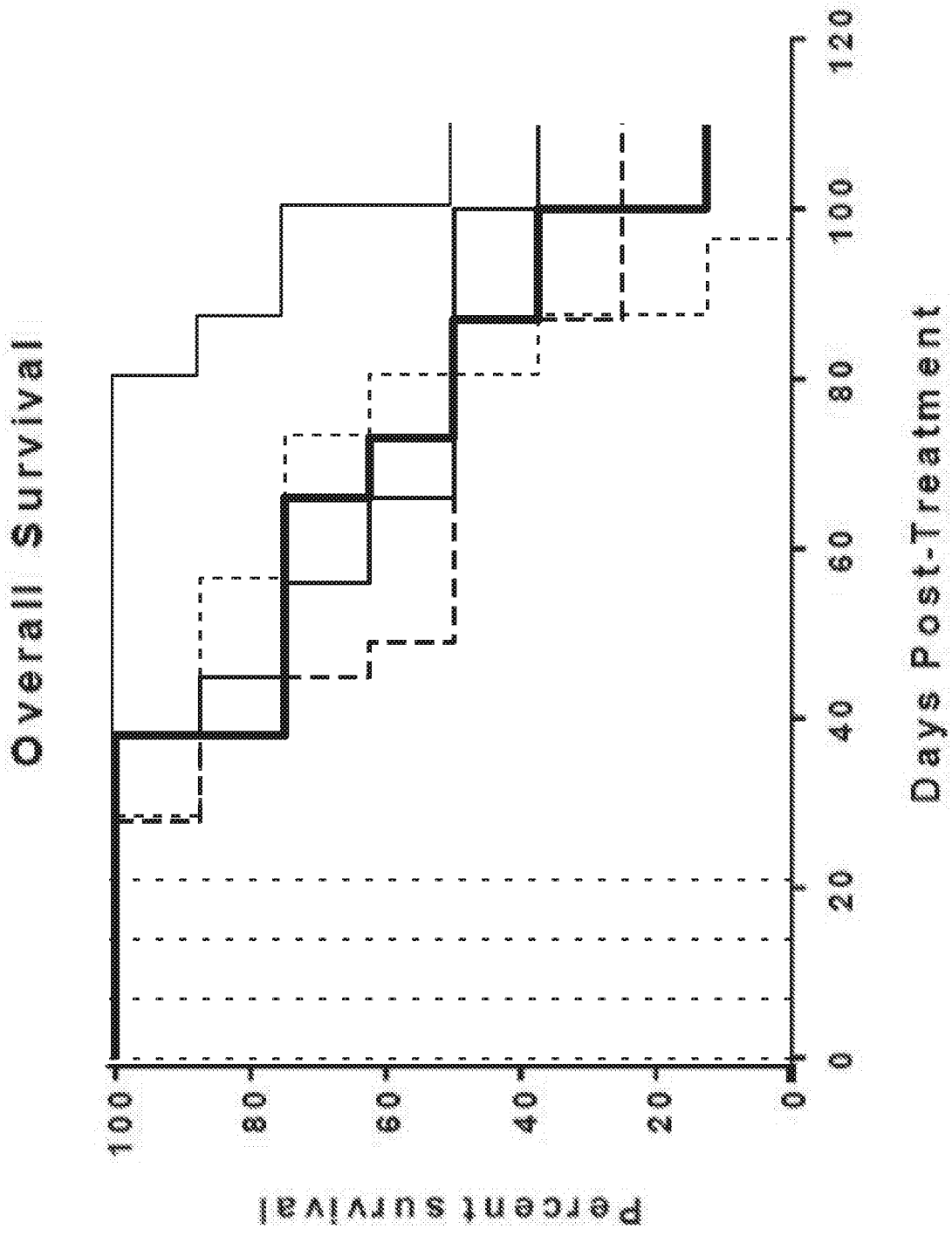

Progression-Free Survival
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(50) + Ox(5)
Percent survival
100
80
60
40
20
0
0
20
40
60
80
Days Post-Treatment

FIG. 6C

FIG. 6D


Overall Survival
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
120
Days Post-Treatment

G1 – Control
G2 – MM-398 10 mpk
G3 – Irinotecan 50 mg/kg
G4 – MM-398 10 mpk + 5FU 50 mpk
G5 – Irinotecan 50 mpk + 5FU 50 mpk
G6 – MM-398 10 mpk + 5FU 50 mpk + Ox 5 mpk
G7 – Irinotecan 50 mpk + 5FU 50 mpk + Ox 5 mpk

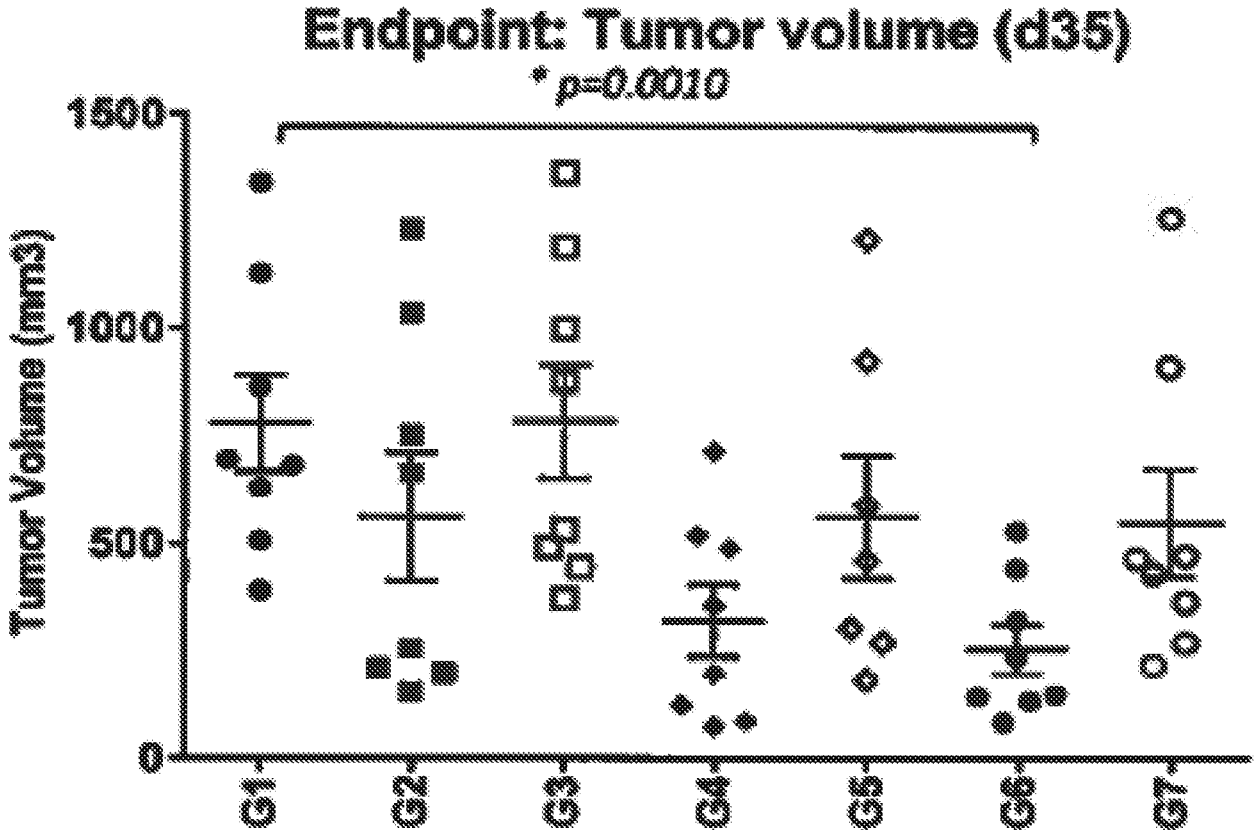


FIG. 7

	Control	MM-398	IRI	NAPOLI	FOLFIRI	NAPOX	FOLFIRINOX
Tumor Vol (mean mm^3,d35)	779	562	753	321	523	255	445
TGI (% at d35)	n/a	27.9%	3.4%	58.8%	32.9%	67.3%	42.9%
Median Days to $1000mm^3$	50.5 (n=8 of 8)	68 (6 of 8, 2 est)	43.5 (8 of 8)	70 (6 of 8, 2 est)	56 (7 of 7)	77 (8 of 8)	56 (8 of 8)
Stable Disease (-30% - +30%)	0	3	1	2	3	2	4
PR (30%-95% reduction)	0	0	0	3	0	4	0
CR (≥95% reduction)	0	0	0	0	0	0	0
Response Rate (≥30% reduction)	0%	0%	0%	38%	0%	50%	0%
Disease Control	0%	38%	13%	63%	38%	75%	50%
Rate (ORR + SD)							
Median Progression Free Survival (days)	5	12	3	36.5	10	47	14
Median OS(days)	80	83	68	100	80	105	80

FIG. 8

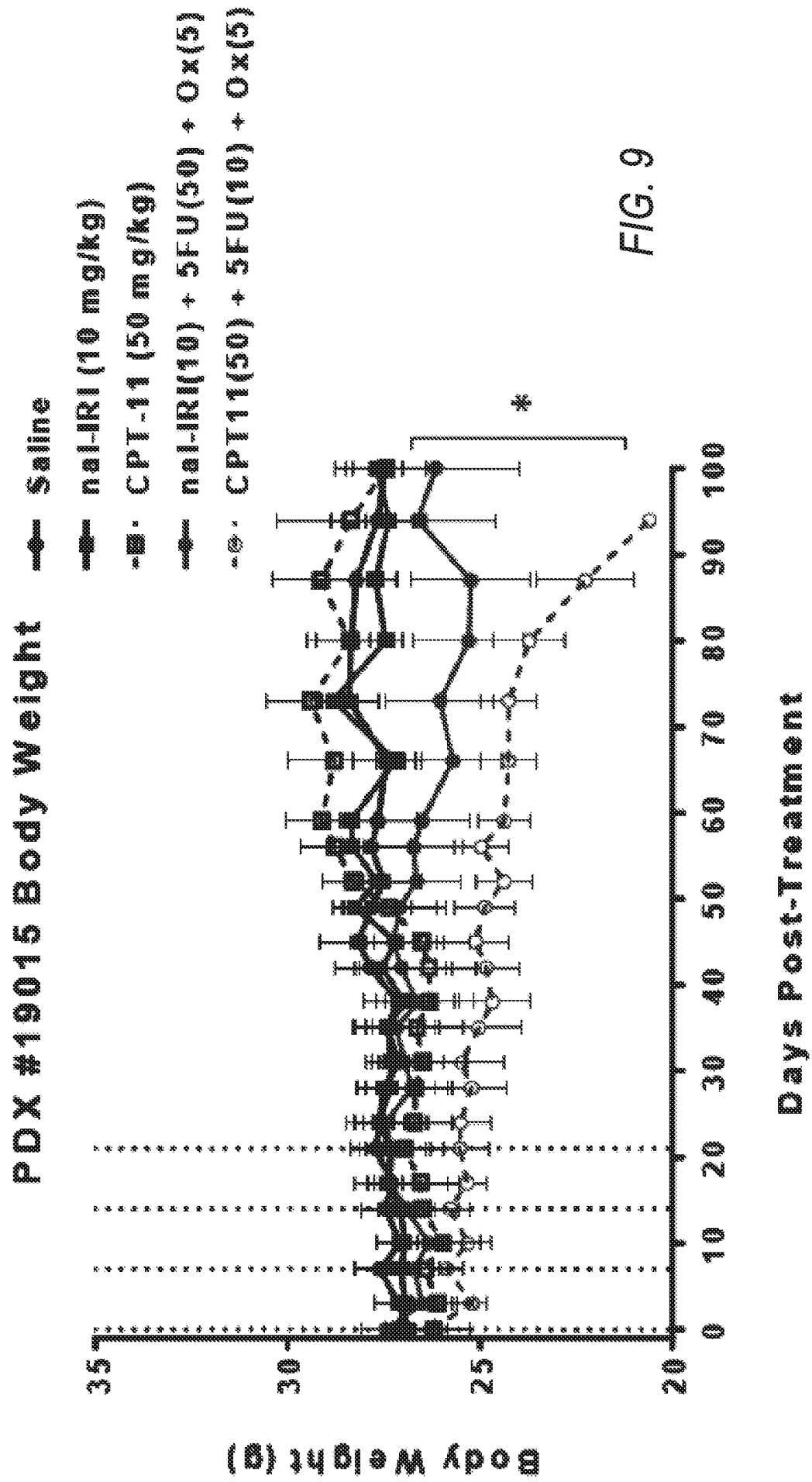

PDX #19015 Body Weight
Saline
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(10) + Ox(5)
*
Body Weight (g)
Days Post-Treatment
35
30
25
20
0
10
20
30
40
50
60
70
80
90
100

FIG. 9

FIG. 10A

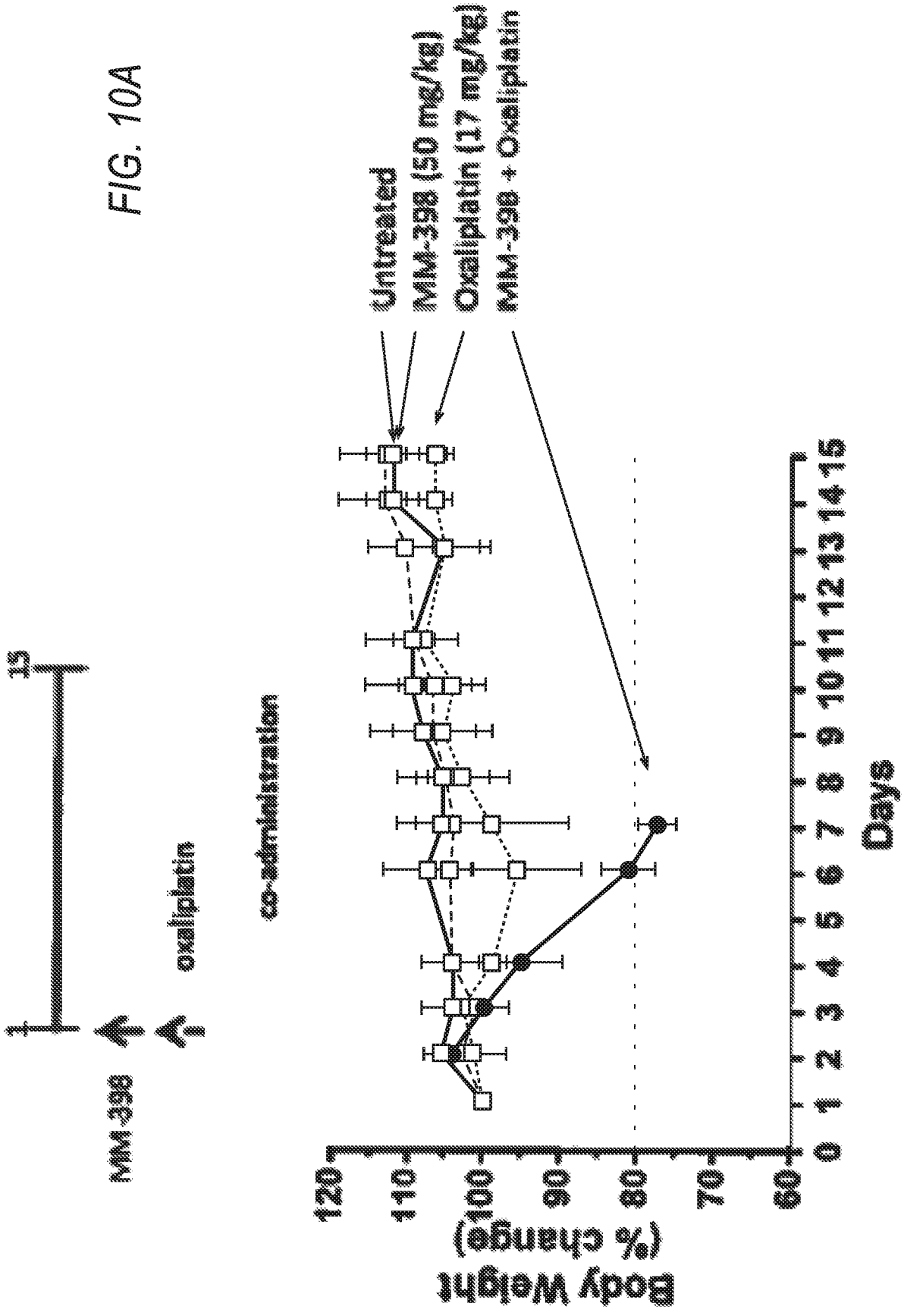
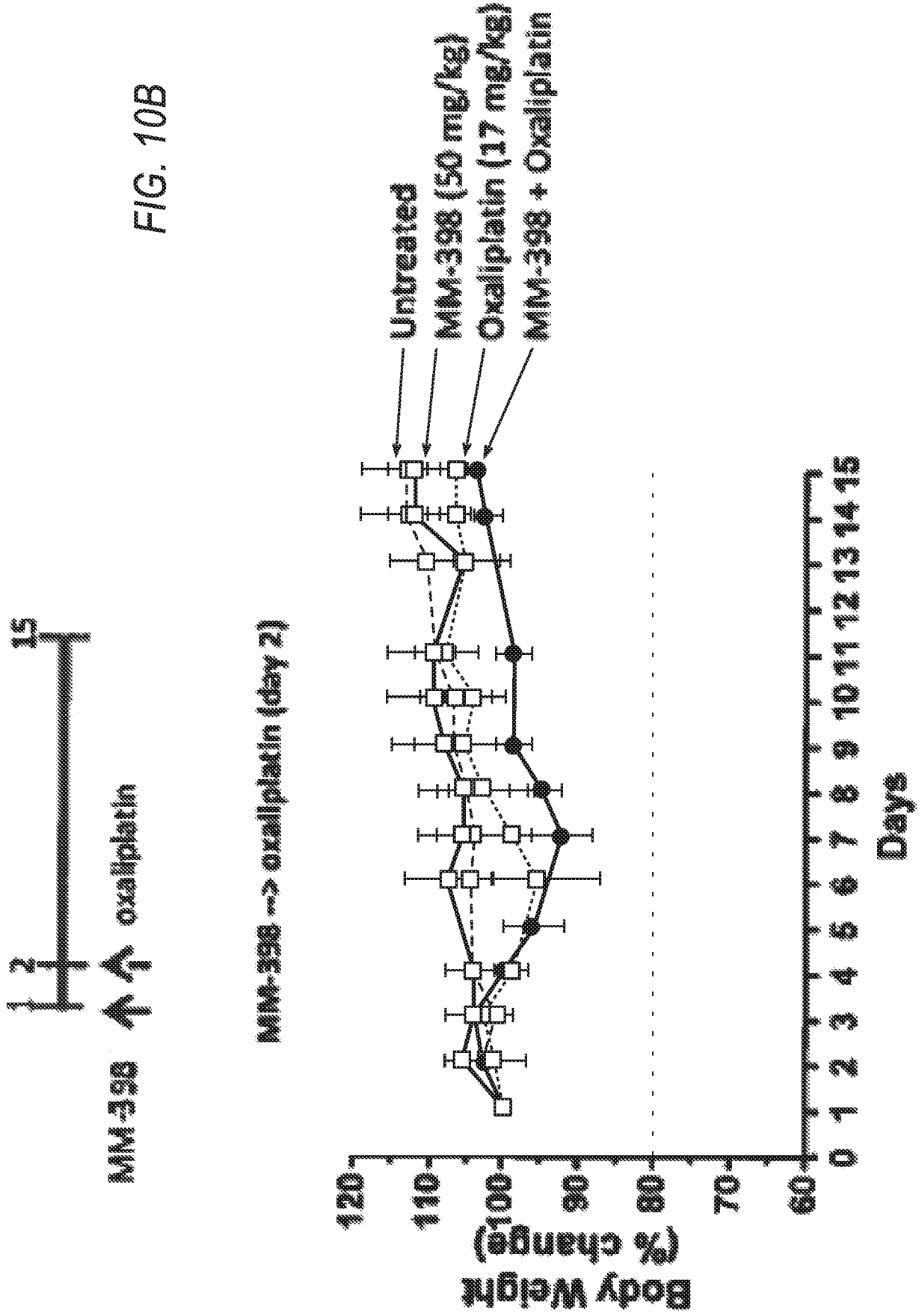

Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin
Body Weight (% change)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days
co-administration
MM-398
oxaliplatin
1
13

FIG. 10B


1 2 15
MM-398
oxaliplatin
MM-398 --> oxaliplatin (day 2)
Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin
Body Weight (% change)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days

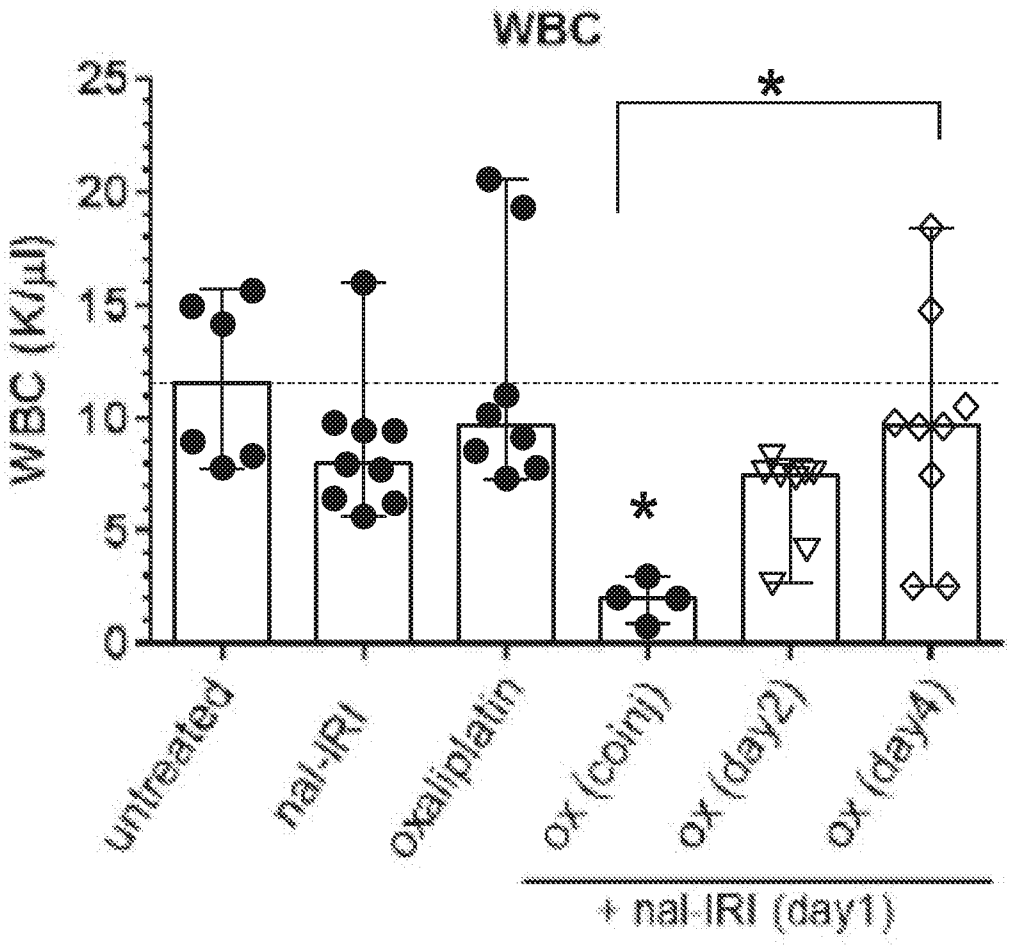


FIG. 11A

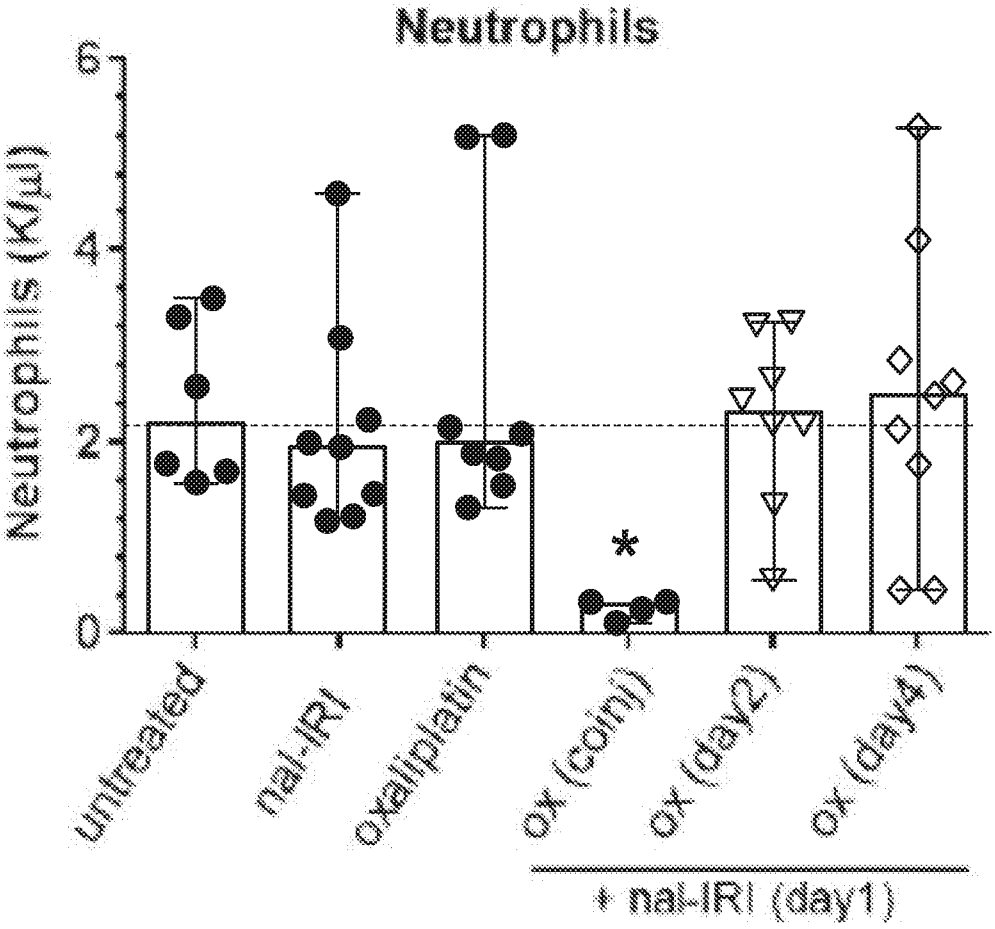


FIG. 11B

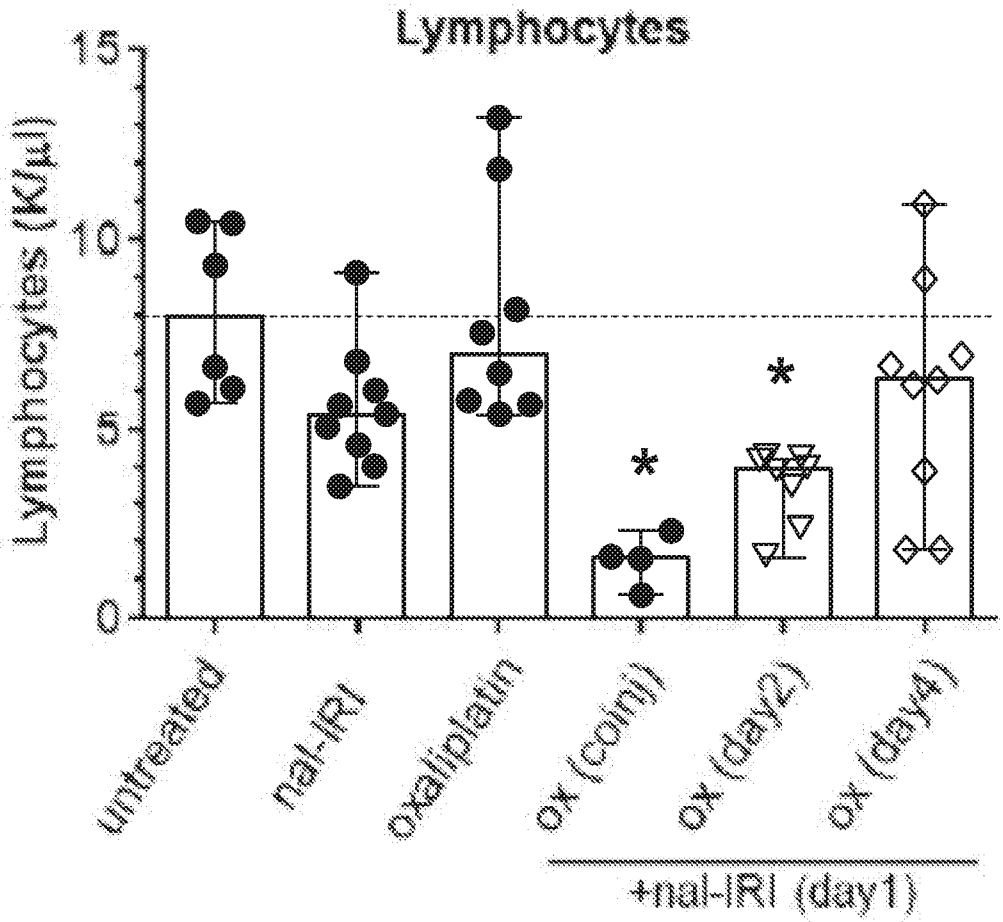


FIG. 11C

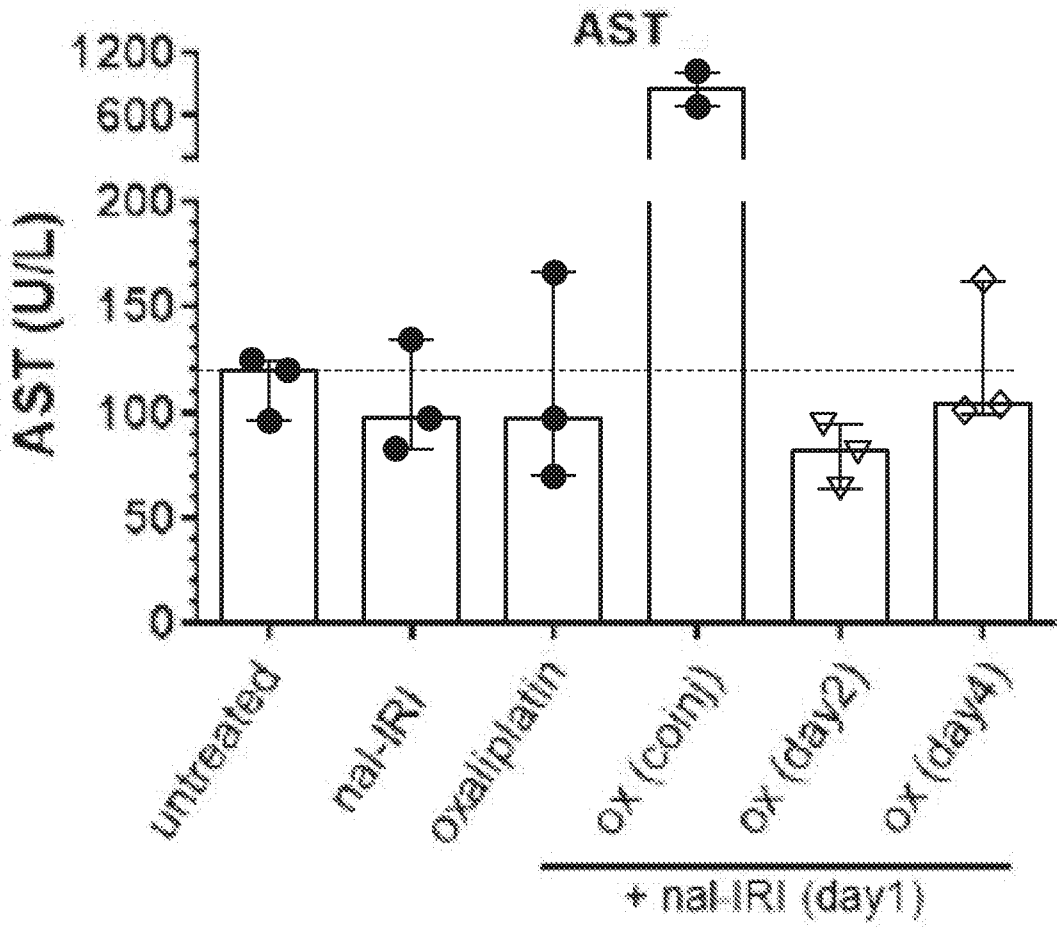


FIG. 11D

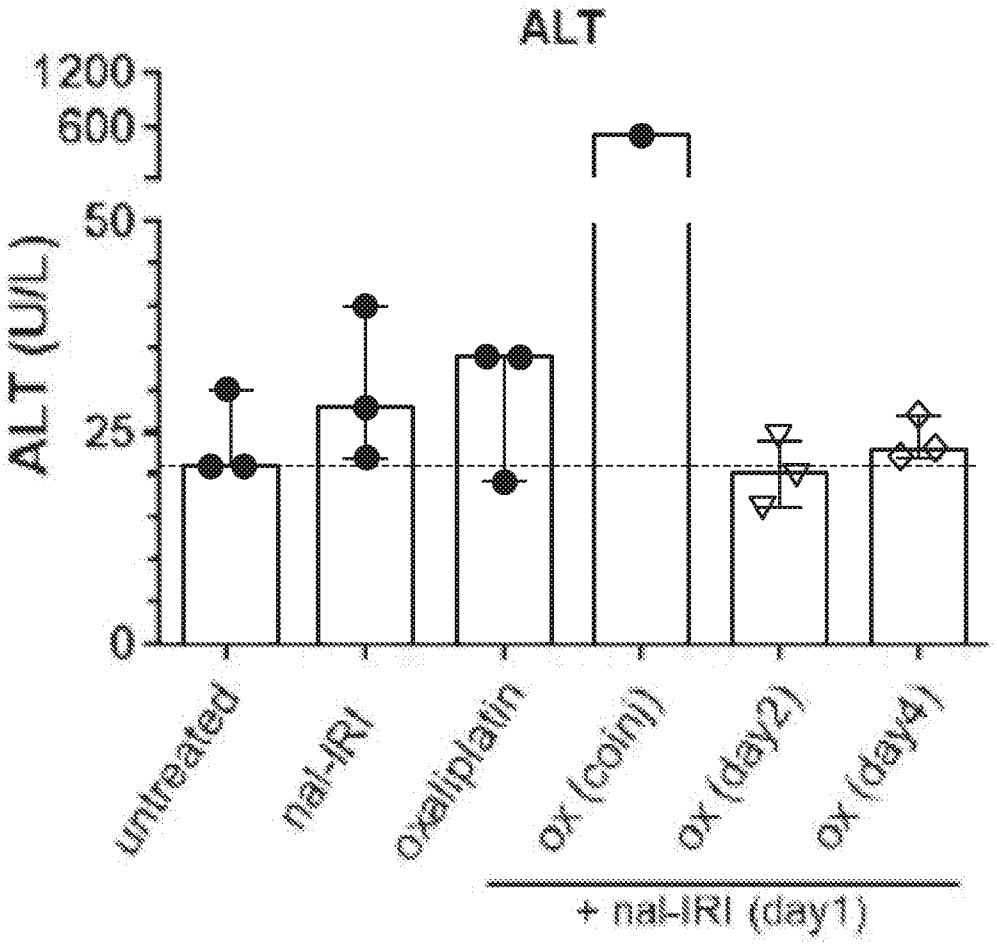


FIG. 11E

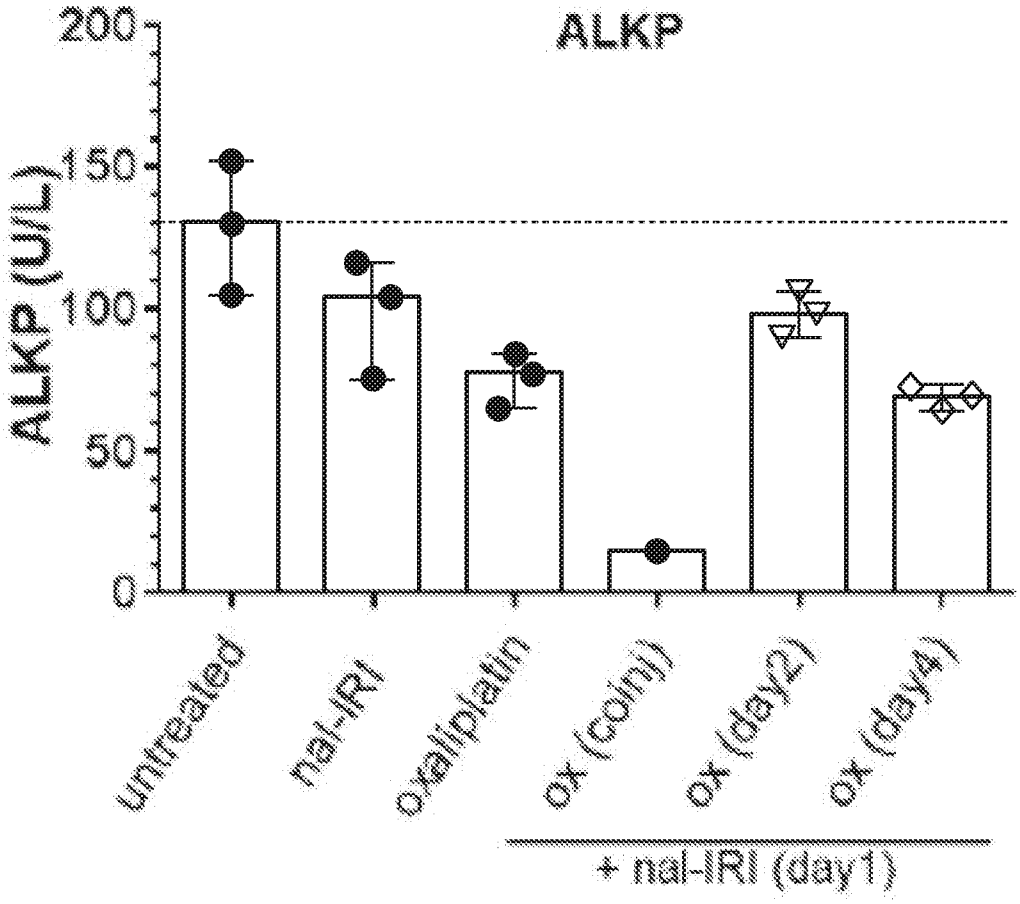


FIG. 11F

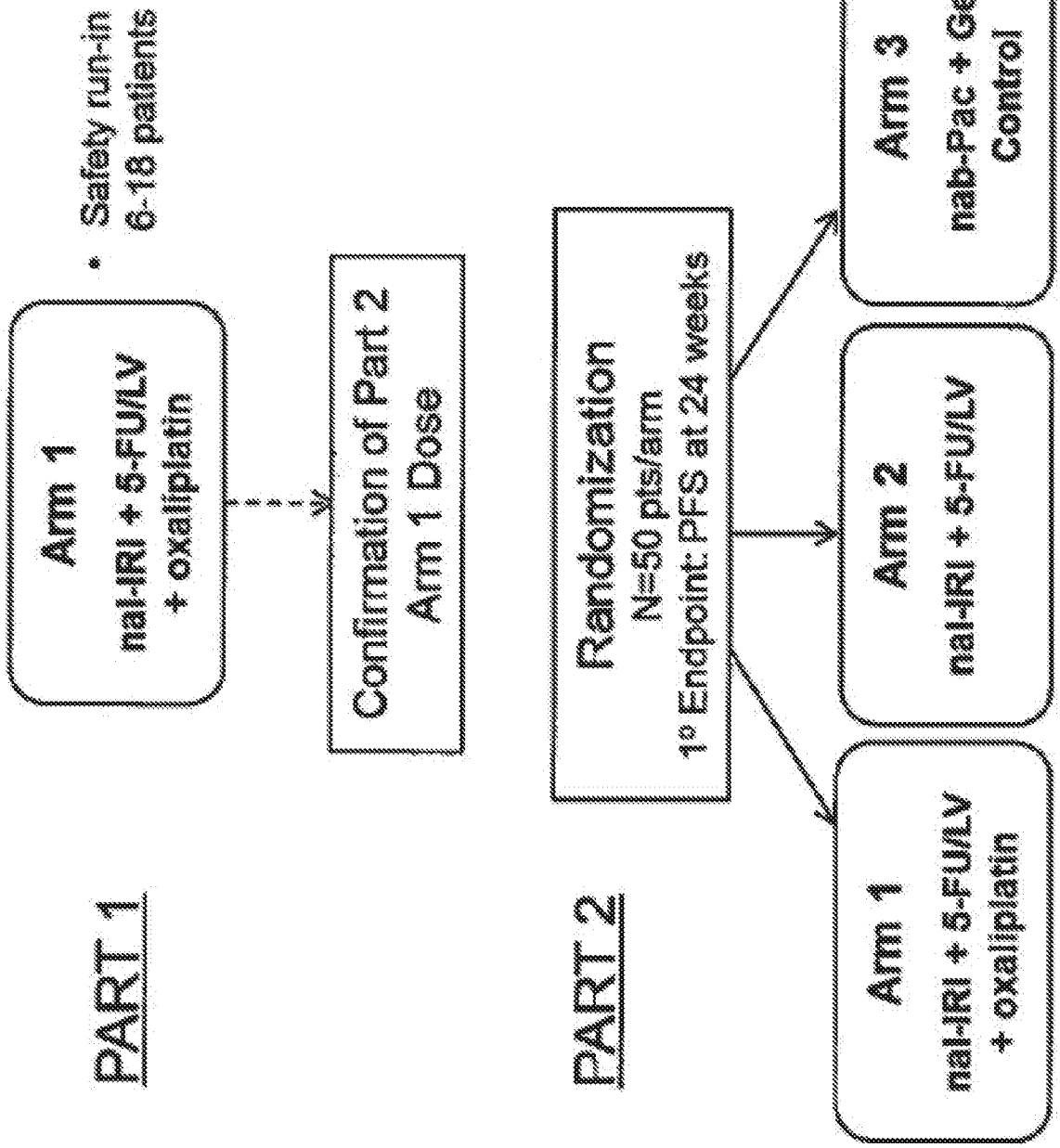

PART 1
Arm 1
nal-IRI + 5-FU/LV
+ oxaliplatin
Safety run-in
6-18 patients
Confirmation of Part 2
Arm 1 Dose
PART 2
Randomization
N=50 pts/arm
1º Endpoint: PFS at 24 weeks
Arm 1
nal-IRI + 5-FU/LV
+ oxaliplatin
Arm 2
nal-IRI + 5-FU/LV
Arm 3
nab-Pac + Gem
Control

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/047727

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/436 A61K9/127 A61K31/282 A61K31/4745 A61K31/475
A61K31/513 A61K31/519 A61P35/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHANG T C ET AL: "Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients", CANCER CHEMOTHERAPY AND PHARMACOLOGY, SPRINGER VERLAG, BERLIN, vol. 75, no. 3, 11 January 2015 (2015-01-11), pages 579-586, XP035456963, ISSN: 0344-5704, DOI: 10.1007/S00280-014-2671-X [retrieved on 2015-01-11] the whole document ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2016	16/11/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Engl, Brigitte

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L. Chen, H. Shiah, T. Chao, R. K. Hsieh, G. Chen, J. Chang, G. Yeh: "Phase I study of liposome irinotecan (PEP02) in combination with weekly infusion of 5-FU/LV in advanced solid tumors", Journal of Clinical Oncology, vol. 28, no. 15_Suppl., E13024, 2010, XP002763720, DOI: 10.1200/jco.2010.28.15_suppl.e13024 Retrieved from the Internet: URL:http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.e13024 [retrieved on 2016-11-02] abstract -----	1-15
Y	KO A H ET AL: "A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer", BRITISH JOURNAL OF CANCER 20 AUG 2013, vol. 109, no. 4, 20 August 2013 (2013-08-20), pages 920-925, XP002763721, ISSN: 1532-1827 page 920, left-hand column, line 1 - page 921, left-hand column, line 43 page 923, right-hand column, line 12 - page 924, left-hand column, line 67 -----	1-15
Y	PETER J HOSEIN ET AL: "A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma", BMC CANCER, BIOMED CENTRAL, LONDON, GB, vol. 12, no. 1, 29 May 2012 (2012-05-29), page 199, XP021126474, ISSN: 1471-2407, DOI: 10.1186/1471-2407-12-199 the whole document -----	1-15

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BOTT, Cynthia M.
Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
02 June 2017 (02.06.2017)

Applicant's or agent's file reference
263266-411935

IMPORTANT NOTIFICATION

International application No.
PCT/US2016/047727

International filing date *(day/month/year)*
19 August 2016 (19.08.2016)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
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One Kendall Square, Suite B7201
Cambridge, MA 02139
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address: patents@honigman.com

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
IPSEN BIOPHARM LTD.
Ash Road, Wrexham Industrial Estate
Wrexham Gb LL13 9UF
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
E-mail address: patents@hongman.com
☒ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 2 has been recorded as applicant for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☒ other: MERRIMACK PHARMACEUTICALS, INC.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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(19)中华人民共和国国家知识产权局

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(21)申请号 201680046873.3

(22)申请日 2016.08.19

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62/273,244 2015.12.30 US
62/281,473 2016.01.21 US
62/302,341 2016.03.02 US
62/323,245 2016.04.15 US
62/343,313 2016.05.31 US

(85)PCT国际申请进入国家阶段日
2018.02.08

(86)PCT国际申请的申请数据
PCT/US2016/047727 2016.08.19

(87)PCT国际申请的公布数据
WO2017/034957 EN 2017.03.02

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(51)Int.Cl.
A61K 31/436(2006.01)
A61K 9/127(2006.01)
A61K 31/282(2006.01)
A61K 31/4745(2006.01)
A61K 31/475(2006.01)
A61K 31/513(2006.01)
A61K 31/519(2006.01)
A61P 35/04(2006.01)

权利要求书2页 说明书38页 附图25页

(54)发明名称

使用包含脂质体伊立替康和奥沙利铂的组合疗法治疗转移性胰腺癌的方法

(57)摘要

包括脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合疗法方案可用于治疗胰腺癌,包括治疗诊断患有先前未治疗的转移性胰腺腺癌的患者。所述组合疗法可包括每两周一次施用脂质体伊立替康、奥沙利铂、亚叶酸和5-氟尿嘧啶。

CN 108495629 A

1.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.60mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌。

2.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.85mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌。

3.如权利要求1-2中任一项所述的用途，其中所述5-氟尿嘧啶以输注形式在46小时内施用。

4.如权利要求1-3中任一项所述的用途，其中施用所述亚叶酸后立即施用所述5-氟尿嘧啶。

5.如权利要求1-4中任一项所述的用途，其中所述脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用。

6.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.60mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌

其中所述脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用。

7.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.85mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌。

8.如权利要求1-7中任一项所述的用途，其中所述脂质体伊立替康以输注形式在总共约90分钟内施用。

9.如权利要求1-8中任一项所述的用途，其中施用所述脂质体伊立替康，之后施用所述奥沙利铂，之后施用所述亚叶酸，之后施用所述5-氟尿嘧啶。

10.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.60mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌

其中施用所述脂质体伊立替康，之后施用所述奥沙利铂，之后施用所述亚叶酸，之后施用所述5-氟尿嘧啶。

11.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.85mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌

其中施用所述脂质体伊立替康，之后施用所述奥沙利铂，之后施用所述亚叶酸，之后施用所述5-氟尿嘧啶。

12.如权利要求1-9中任一项所述的用途，其中在完成所述脂质体伊立替康的每次施用后2小时开始施用所述奥沙利铂。

13.一种脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合在治疗先前未接受治疗转移性胰腺腺癌的化疗的人类患者的转移性胰腺腺癌中的用途，所述用途包括总共每两周一次将抗肿瘤疗法施用到所述患者，所述抗肿瘤疗法由以下组成：

a.60mg/m^2的脂质体伊立替康、

b.60mg/m^2-85mg/m^2奥沙利铂、

c.200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，以及

d.2,400mg/$m^2$5-氟尿嘧啶以治疗所述人类患者的所述转移性胰腺腺癌

其中所述脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用，其中施用所述脂质体伊立替康，之后施用所述奥沙利铂，之后施用所述亚叶酸，之后施用所述5-氟尿嘧啶，其中在完成所述脂质体伊立替康的每次施用后2小时开始施用所述奥沙利铂。

14.如权利要求1-11中任一项所述的用途，其中所述脂质体伊立替康包含被封装在脂质体中的伊立替康蔗糖八硫酸酯。

15.如权利要求1-8中任一项所述的用途，其中所述脂质体伊立替康包含封装在脂质体载体中的伊立替康，所述载体由1,2-二硬脂酰-sn-甘油-3-磷酸胆碱(DSPC)、胆固醇和N-(羰基甲氧基聚乙二醇-2000)-1,2-二硬脂酰-sn-甘油-3-磷酸乙醇胺(MPEG-2000-DSPE)组成。

使用包含脂质体伊立替康和奥沙利铂的组合疗法治疗转移性胰腺癌的方法

[0001] 相关申请

[0002] 本专利申请要求以下待审的各美国临时专利申请的优选权，每个全文以引用方式并入本文中：62/208,209(2015年8月21日提交)、62/216,736(2015年9月10日提交)、62/273,244(2015年9月30日提交)、62/281,473(2016年1月21日提交)、62/302,341(2016年3月2日提交)、62/323,245(2016年4月15日提交)以及62/343,313(2016年5月31日提交)。

技术领域

[0003] 本公开涉及可用于治疗胰腺癌的新型疗法，包括使用脂质体伊立替康与5-氟尿嘧啶和奥沙利铂的组合用于(第一线)治疗诊断患有先前未治疗的胰腺癌的患者。

[0004] 背景

[0005] 胰腺癌对化疗有抗性，其预后极差。它是美国癌症死亡的第四大原因；5年存活率为6％。在过去的几十年期间，胰腺癌的发病率有所增加，并且在2014年，估计有46,420个患者被诊断为胰腺癌，并且39,590人死亡。预计到2030年，胰腺癌将超过肝癌、乳腺癌、前列腺癌以及结直肠癌，成为癌症相关死亡的第二大原因。这些统计数据反映了这种疾病的严重性并且缺乏有效疗法。肿瘤的位置几乎不引起早期症状，并且因此常常在晚期被诊断。缺乏有效的筛查工具和对风险因素的了解有限，意味着患者在诊断时已发展成晚期或转移性疾病。鉴于患有转移性疾病的患者预后差和少于1年的低中位存活率，仍需要新的治疗选项。

[0006] 多药方案的耐受性在癌症治疗中是重要的。可控治疗的持续时间越长，结果就越好，这是因为药物暴露时间较长。在过去的5年中，作为转移性胰腺癌的一线治疗的护理标准出现的一种组合化疗方案是5-氟尿嘧啶(5-FU)/亚叶酸(LV)+伊立替康+奥沙利铂(FOLFIRINOX)。然而，已知FOLFIRINOX具有显著的毒性，并且使用仅限于具有更好表现状态(即0或1的ECOG表现评分)的患者。随着FOLFIRINOX治疗延长，奥沙利铂常常因为毒性而从方案中停用。因此，如果可以确定同样有效的双重方案，患者可更好地耐受长时间的治疗，并且甚至表现低下的患者也可获益。虽然FOLFIRINOX方案自2011年以来一直被美国国家综合癌症网络(NCCN)推荐为一线转移性疾病的优先选择，但对于与FOLFIRINOX相关的毒性有一些担忧。FOLFIRINOX的一个剂量方案是通过IV推注施用85mg/m^2奥沙利铂、180mg/m^2伊立替康和400mg/m^2的剂量的氟尿嘧啶，随后连续输注2400mg/m^2。然而，由于毒性，常常使用修改的FOLFIRINOX方案(例如消除5-FU推注)，其中对修改方案的功效和安全性具有未知影响。

[0007] CPT-11是盐酸伊立替康三水合物，在美国以Camptosar®销售。MM-398是脂质体伊立替康，并且与5-氟尿嘧啶和亚叶酸组合在美国以美国FDA批准的产品ONIVYDE®销售，用于治疗基于吉西他滨的疗法后疾病进展后的转移性胰腺腺癌的患者。

[0008] 发明概述

[0009] 用于治疗胰腺癌的改善的抗肿瘤疗法提供了将脂质体伊立替康与奥沙利铂和5-氟尿嘧啶组合施用到患有先前未治疗的胰腺癌(例如未治疗的转移性胰腺癌或mPAC)的患

者。5-氟尿嘧啶可与亚叶酸组合施用。与先前的FOLFIRINOX方案相比，改善的抗肿瘤疗法可提供改善的治疗指数(例如，改善的毒性概况)。

[0010] 治疗胰腺癌的方法可包括每两周一次将脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的抗肿瘤疗法施用到患者。任选地，亚叶酸也可在每次施用5-氟尿嘧啶之前施用。脂质体伊立替康的每次施用可以以60mg/m^2脂质体伊立替康的总剂量(基于如本文定义的伊立替康盐酸盐三水合物的量的剂量)施用。当施用脂质体伊立替康时，每天开始46小时内可施用总共2,400mg/m^2的5-氟尿嘧啶。在施用脂质体伊立替康的每一天，可施用总共60mg/m^2、75mg/m^2或85mg/m^2的奥沙利铂。在每次施用5-氟尿嘧啶之前施用总共200mg/m^2(l)亚叶酸(例如任选以400mg/m^2的(l+d)亚叶酸施用)。抗肿瘤疗法可在28天治疗周期的第1天和第15天开始施用，其中在第1天和第15天施用脂质体伊立替康、奥沙利铂和任选地叶酸，并且在第1天和第15天开始5-氟尿嘧啶的46小时施用。

[0011] 本发明部分基于若干临床前的发现。首先，相对于暴露匹配剂量的非脂质体伊立替康，脂质体伊立替康提高了拓扑异构酶1抑制剂SN-38(伊立替康的活性代谢物)的抗肿瘤活性。其次，相对于非脂质体伊立替康，与5-氟尿嘧啶和奥沙利铂组合的脂质体伊立替康，在胰腺癌的小鼠异种移植模型中一致地改善肿瘤生长抑制和存活，而不加剧这些药剂的基线毒性。

[0012] 此外，本发明部分基于以下发现：当与60mg/m^2奥沙利铂、2400mg/m^2 5-氟尿嘧啶和400mg/m^2(l+d)亚叶酸组合施用时，施用80mg/m^2的剂量的脂质体伊立替康在人体中的耐受性不好。因此，治疗(先前未治疗)胰腺癌的优选方法是每两周一次提供人耐受的抗肿瘤疗法的施用，其中抗肿瘤疗法的每次施用是本文提供的抗肿瘤药剂脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合。优选地，每两周一次施用的抗肿瘤疗法由以下组成：(a)60mg/m^2总剂量的脂质体伊立替康(如本文所定义，基于伊立替康盐酸盐三水合物的量的剂量)，(b)60mg/m^2-85mg/m^2总剂量的奥沙利铂(包括例如60mg/m^2或85mg/m^2)和(c)总共2,400mg/m^2的5-氟尿嘧啶，任选地与亚叶酸组合施用。任选地，所述组合可包括施用总共200mg/m^2(l)亚叶酸(任选地以400mg/m^2的(l+d)亚叶酸施用)，然后开始施用5-氟尿嘧啶。优选地，在抗肿瘤疗法期间，在施用脂质体伊立替康后，除了脂质体伊立替康在患者体内产生的一定量的SN-38以外，没有其他抗肿瘤剂被施用。例如，抗肿瘤疗法可在没有(非脂质体)CPT-11伊立替康的情况下施用。优选地，脂质体伊立替康、奥沙利铂和(任选)亚叶酸在单个(第一)天作为单独的输液连续施用，并且5-氟尿嘧啶在施用亚叶酸(如果施用)后的第一天开始施用并且继续到第二天(例如，总共46小时)。

[0013] 附图简述

[0014] 图1A是示出了基于脂质体伊立替康人体临床活检数据和人体临床试验数据的活性伊立替康代谢物SN-38随时间的模拟水平的图。

[0015] 图1B是示出了与来自非脂质体伊立替康(CPT-11)的SN-38肿瘤暴露相比，使用脂质体伊立替康(MM-398)观察到的SN-38随时间的肿瘤暴露如何延长的示意图。

[0016] 图1C是示出了基于5种不同细胞系的总SN-38细胞暴露的不同时间，SN-38的相对细胞生长抑制百分比的图。

[0017] 图1D是与5-氟尿嘧啶(5-FU)或奥沙利铂(oxali)的不同的组合在不同的暴露时间(4小时或48小时)下图1C中测试的细胞系的相对细胞生长抑制百分比的图。

[0018] 图2A是示出了BxPC-3胰腺癌细胞的作为SN-38暴露的函数的细胞活力的图。

[0019] 图2B是示出了CFPAC-1胰腺癌细胞的作为SN-38暴露的函数的细胞活力的图。

[0020] 图3A是示出了在使用以下单个抗肿瘤药剂治疗后，在BxPC-3胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积的图：包括5-氟尿嘧啶(5FU)、奥沙利铂(Ox)、(非脂质体)伊立替康(IRI)以及MM-398脂质体伊立替康(nal-IRI)。

[0021] 图3B是示出了在使用以下抗肿瘤药剂的各种组合治疗后，在BxPC-3胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积的图：(非脂质体)伊立替康(IRI)和5FU；(非脂质体)伊立替康(IRI)、奥沙利铂和5FU；MM-398脂质体伊立替康(nal-IRI)和5FU；以及398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU。

[0022] 图4A是示出了在使用以下治疗后，在BxPC-3胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积的图：奥沙利铂单一疗法、MM-398脂质体伊立替康(nal-IRI)单一疗法和MM-398脂质体伊立替康(nal-IRI)和奥沙利铂(Ox)的组合。

[0023] 图4B是示出了在使用以下治疗后，在CFPAC-1胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积的图：奥沙利铂单一疗法、MM-398脂质体伊立替康(nal-IRI)单一疗法和MM-398脂质体伊立替康(nal-IRI)和奥沙利铂(Ox)的组合。

[0024] 图5A是示出了在使用以下治疗后，在源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量随时间推移的肿瘤体积的图：MM-398脂质体伊立替康(nal-IRI)单一疗法、(非脂质体)伊立替康单一疗法(伊立替康)，和各种组合疗法：MM-398脂质体伊立替康(nal-IRI)和5-氟尿嘧啶(5FU)；(非脂质体)伊立替康(伊立替康)和5FU；MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0025] 图5B是示出了在使用包含MM-398的图5A中示出的组合疗法治疗后，在来源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量随时间推移的肿瘤体积的图：MM-398脂质体伊立替康(nal-IRI)和5-氟尿嘧啶(5FU)、MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0026] 图5C是示出了在使用包含奥沙利铂的图5A中示出的组合疗法治疗后，在来源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量随时间推移的肿瘤体积的图：MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0027] 图6A是示出了在使用以下治疗后，在源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量随时间推移的肿瘤体积变化百分比的图：盐水对照、MM-398脂质体伊立替康(nal-IRI)单一疗法或(非脂质体)伊立替康单一疗法(伊立替康)。

[0028] 图6B是示出了在使用以下治疗后，在源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量随时间推移的肿瘤体积变化百分比的图：盐水对照或两种包含奥沙利铂的疗法：MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0029] 图6C是示出了在使用以下治疗后，在来源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量的无进展存活的图：两种包含奥沙利铂组合疗法：MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0030] 图6D是示出了在使用以下治疗后，在来源于患者的异种移植(PDX#19015)胰腺癌

小鼠功效模型中测量的总体存活的图:两种包含奥沙利铂组合疗法:MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU;以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0031] 图7是示出了在使用以下治疗后,在源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型中测量的肿瘤体积的图:MM-398脂质体伊立替康(nal-IRI)单一疗法、(非脂质体)伊立替康单一疗法(伊立替康),和各种组合疗法:MM-398脂质体伊立替康(nal-IRI)和5-氟尿嘧啶(5FU);(非脂质体)伊立替康(伊立替康)和5FU;MM-398脂质体伊立替康(nal-IRI)、奥沙利铂和5FU;以及(非脂质体)伊立替康、奥沙利铂和5FU。

[0032] 图8是示出了在使用以下治疗后,从来源于患者的异种移植(PDX#19015)胰腺癌小鼠功效模型获得的结果的表:仅MM-398脂质体伊立替康、仅非脂质体伊立替康(单一疗法)、MM-398脂质体伊立替康与5FU(NAPOLI,双疗法)组合、MM-398脂质体伊立替康与5FU+奥沙利铂(NAPOX,三疗法)组合以及非脂质体伊立替康与奥沙利铂和5-氟尿嘧啶(FOLFIRINOX)组合。

[0033] 图9是示出了在施用以下后第0天、7天、14天以及21天,通过记录小鼠的体重测量的小鼠模型中各种疗法的耐受性的图:盐水对照、脂质体伊立替康(nal-IRI)、纳米脂质体伊立替康、5-FU和奥沙利铂的组合或非脂质体伊立替康(CPT11)、5FU和奥沙利铂的组合。

[0034] 图10A是示出了在施用以下后,通过记录小鼠的体重测量的小鼠模型中各种疗法的耐受性的图:高剂量的MM-398脂质体伊立替康(nal-IRI)、奥沙利铂以及在相同日期一起给予的MM-398脂质体伊立替康和奥沙利铂的组合。

[0035] 图10B是示出了在施用以下后,通过记录小鼠的体重测量的小鼠模型中各种疗法的耐受性的图:高剂量的MM-398脂质体伊立替康(nal-IRI)、奥沙利铂以及在分开的连续日期顺序给予的MM-398脂质体伊立替康和奥沙利铂的组合(其中MM-398在第1天施用并且奥沙利铂在第2天施用)。

[0036] 图11A、11B和11C是描述了在施用以下后在小鼠中观察的血液毒性的柱状图:高剂量的在相同日期施用的MM-398脂质体伊立替康(nal-IRI)和奥沙利铂或奥沙利铂在施用MM-398后至少一天施用:A.白细胞;B.中性粒细胞;以及C.淋巴细胞。

[0037] 图11D、11E和11F是描述了在施用以下后在小鼠中观察的肝酶水平的柱状图:高剂量的在相同日期施用的MM-398脂质体伊立替康(nal-IRI)和奥沙利铂或奥沙利铂在施用MM-398后至少一天施用:D.天冬氨酸转氨酸(AST);E.丙氨酸转氨酶(ALT);F.碱性磷酸酶(ALKP)。

[0038] 图12是治疗胰腺癌的方法的流程图,其包括包含施用脂质体伊立替康、奥沙利铂、5-氟尿嘧啶以及亚叶酸的方法。

[0039] 详细描述

[0040] 除非另外指明,否则如本文所述的脂质体伊立替康或伊立替康脂质体的剂量是指提供被封装在脂质体伊立替康的脂质体或伊立替康脂质体中的伊立替康的量的伊立替康盐酸盐三水合物的量。例如,60mg/m^2的剂量的脂质体伊立替康是指提供存在于60mg/m^2的伊立替康盐酸盐三水合物中的脂质体封装的伊立替康的相同的量的脂质体伊立替康的量,并且基于封装在伊立替康脂质体中的伊立替康游离碱的量,等同于约50mg/m^2的脂质体伊立替康。

[0041] 如本文所用,除非另外指明,否则术语“nal-IRI”(纳米脂质体伊立替康)和“MM-

398”是指脂质体伊立替康的形式。术语“CPT-11”是指(非脂质体)伊立替康盐酸盐三水合物。

[0042] 如本文所用,“5-FU”和“5FU”可互换使用并且是指5-氟尿嘧啶。

[0043] 所有引用的文献都是以引用的方式并入本文。

[0044] 使用胰腺癌细胞系(实施例1),我们展示当使用与5-FU和奥沙利铂组合的SN-38(伊立替康的活性代谢物)的延长暴露模拟脂质体伊立替康治疗时,细胞死亡增强。图1示出了SN-38的延长暴露模拟体外MM-398治疗。参考图1A,相比于非脂质体伊立替康(CPT-11),MM-398治疗导致活性代谢物SN-38的延长肿瘤暴露。参考图1B,SN-38的延长的低剂量暴露模拟体外MM-398肿瘤递送。参考图1C,延长的低剂量暴露导致多胰腺癌细胞系细胞生长抑制更大。图包括四个部分,并且针对每个部分,细胞系数据在顶部以AsPC-1数据呈现,接下来是BxPC-3、Capan-2、CFPAC-1,并且最后是底部的MaPaCa-2。参考图1D,当与5-FU(20.7mM,持续48小时)或奥沙利铂(12.3mM,持续4小时)组合时,还观察到延长暴露于低浓度的SN-38的益处。这两种组合也均增加了抗性细胞系对延长的低剂量SN-38的敏感性。

[0045] 图2是描绘将SN-38作为单一药剂或SN-38与奥沙利铂的组合进行治疗后的细胞活力的两个条线图。将BxPC-3(图2A)或CFPAC-1(图2B)细胞处理4小时或72小时,洗涤,并且然后使用新鲜培养基再孵育24小时或144小时,随后评定细胞活力。数据跟踪标记为“1”单独SN-38 4小时,然后孵育24小时;“2”SN-38+奥沙利铂4小时,然后孵育24小时;“3”SN-38单独72小时,然后孵育144小时;和“4”SN-38+奥沙利铂72小时,然后孵育144小时。当细胞仅处理4小时时,相比于在两种测试细胞系中用单一药剂治疗,SN-38和奥沙利铂的组合的细胞治疗降低了IC-50。

[0046] 实施例2中细胞系来源的和患者来源的胰腺癌异种移植模型的测试展示,相对于暴露匹配剂量的非脂质体伊立替康,脂质体伊立替康的抗肿瘤活性提高。在实施例2的小鼠动物研究中,“x”mg/kg剂量的脂质体伊立替康提供与“5x”剂量的非脂质体伊立替康(CPT-11)对拓扑异构酶1抑制剂(伊立替康和/或SN-38)大约相同的暴露。在临床前模型中,相对于非脂质体伊立替康,脂质体伊立替康持续提高肿瘤生长抑制和存活,无论作为单一疗法还是与5-FU和奥沙利铂组合。将MM-398添加到5-FU和/或奥沙利铂不加剧这些药剂的基线毒性,包括体重减轻和中性粒细胞减少症,并且耐受性可通过延迟施用奥沙利铂至MM-398后1天进一步改善。这些发现说明了脂质体伊立替康与5-FU/LV和奥沙利铂组合的治疗潜力,并且支持一线PDAC(实施例2)中这种三联方案的正在进行的2期试验(NCT02551991)。

[0047] 在胰腺肿瘤异种移植小鼠模型中,针对MM-398+5-FU/LV+奥沙利铂方案测试FOLFIRINOX方案的动物模型。相比于常规(非脂质体)伊立替康(CPT-11),脂质体伊立替康(MM-398)在等同的暴露剂量(5mg/kg MM-398对25mg/kg游离IRI)下,在BxPC-3胰腺异种移植癌症模型(实施例2)中表现更佳,无论单独(例如,图3A)或与奥沙利铂和/或5-FU组合(例如,图3B)。

[0048] 在实施例2中测试的小鼠模型中,评定MM-398在5-FU不敏感的胰腺癌模型(BxPC-3)中的功效。将癌细胞皮下植入小鼠中;当肿瘤建立良好并达到平均体积～300mm^{3}时,开始使用游离伊立替康(IRI)、MM-398、5-FU、奥沙利铂(Ox)或对照进行IV治疗。每种治疗的剂量如上所示,并且每周给药x4周,在图上用虚线表示的时间点。图3A描述了代表在使用各种单个治疗剂治疗后肿瘤生长的线图。图3B描述了代表在使用治疗剂的各种组合治疗后肿瘤生

长的线图。

[0049] 5-FU不敏感胰腺癌模型(BxPC-3)中MM-398的功效。将癌细胞皮下植入小鼠中;当肿瘤建立良好并达到平均体积～300mm^{3}时,开始使用包含与奥沙利铂和/或5-FU组合的IRI或MM-398的双方案或三方案进行IV治疗。每种治疗的剂量如上所示,并且每周给药x4周,在图上用虚线表示的时间点。相比于图4A(以下讨论),包含与奥沙利铂和/或5-FU组合的IRI或MM-398的双方案或三方案展示包含MM-398的双方案或三方案显著优于包含IRI方案抑制肿瘤生长。将奥沙利铂添加到FOLFIRI或MM-398+5-FU/LV的双组合使得肿瘤生长抑制轻微增加(图3B:针对FOLFIRI对FOLFIRINOX,比较IRI+5FU与IRI+5FU+Ox;针对MM-398+5-FU/LV对MM-398+5-FU/LV+Ox,比较nal-IRI+5FU与nal-IRI+5FU+Ox,)。然而,FOLFIRI对MM-398+5-FU/LV双方案(IRI+5FU对nal-IRI+5FU)和FOLFIRINOX对MM-398+5-FU/LV+Ox三方案(IRI+5FU+Ox对nal-IRI+5FU+Ox),比包含MM-398的方案展示显著更多的肿瘤生长抑制。另外,包含MM-398的双方案表现优于FOLFIRINOX三方案(nal-IRI+5FU对IRI+5FU+Ox),这是由于与常规伊立替康相比,MM-398的改善的功效。

[0050] 单个治疗的单药剂结果在图4A中示出,从而展示MM-398比游离IRI显著抑制肿瘤生长。图4A和4B是描绘了使用以下静脉内治疗后,小鼠异种移植模型中肿瘤生长的两张线图(BxPC-3(图4A)或CFPAC-1(图4B)肿瘤细胞):盐水(对照,圆形)、5mg/kg奥沙利铂(三角形)、5mg/kg MM-398(亮方框)或组合,所述肿瘤细胞皮下植入小鼠。在肿瘤建立良好后开始治疗,并且治疗在由图上虚线所指示的时间点处给予四次(BxPC-3模型)或三次(CFPAC-1模型)。

[0051] 图5A、5B、5C、6A、6B、6C、6D以及7是通过在各种治疗后在小鼠中测量肿瘤生长抑制获得的图。将肿瘤细胞(PDX模型19015)皮下植入小鼠。当肿瘤建立良好并且已达到～250mm^{3}的平均体积时,使用仅MM-398或非脂质体伊立替康或与5-FU或5-FU+奥沙利铂组合开始IV治疗。治疗剂量在每个治疗旁边的图中标出,并且给予4次。

[0052] 图5A-5C是描绘了在各种治疗后小鼠中肿瘤生长抑制的图。将肿瘤细胞,PDX 19015模型,皮下植入小鼠。当肿瘤建立良好并且已达到～250mm^{3}的平均体积时,将MM-398或非脂质体伊立替康用作单一疗法或与5-FU和奥沙利铂组合开始IV治疗。治疗剂量在每个治疗旁边的图例中指出,并且在图上由虚线指示的时间点给予四次。相对各自单一疗法,将5-FU添加到MM-398或非脂质体伊立替康显著改善肿瘤生长抑制。如相比于MM-398单一疗法,将奥沙利铂添加到MM-398+5-FU还通过显著延迟肿瘤进展改善了响应。在使用MM-398+5-FU的双疗法治疗的组中,肿瘤进展延迟不显著。图5A是包括来自所有组合(具有MM-398的那些和具有伊立替康的那些)的数据的线图,并且显示MM-398、奥沙利铂和5-FU的组合使得最大地抑制肿瘤生长(最低线),虽然MM-398和5-FU的组合也抑制肿瘤生长(第二低线)。出于比较的目的,图5B是仅包括来自MM-398组合(无伊立替康组合或对照线)的数据的线图。如图中可见,三联组合治疗使得最大地抑制肿瘤生长抑制(最低线),并且在抑制肿瘤生长方面,伊立替康和5-FU(中间线)的双联组合优于仅MM-398(最高线)。图5C是允许将奥沙利铂组合与盐水对照进行比较的相同数据的子集。

[0053] 图6A是示出了在使用以下治疗后,在PDX 19015胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积变化百分比的图:盐水对照、MM-398脂质体伊立替康(MM-398)单一疗法或(非脂质体)伊立替康单一疗法(伊立替康)。图6A中的数据显示,通过观察总共

约60天后，在第0天、7天、14天以及21天各自施用，相比于50mg/kg的非脂质体伊立替康(CPT-11)，施用10mg/kg脂质体伊立替康(MM-398)，肿瘤体积变化百分比显著减少更大。图6B是示出了在使用以下治疗后，在PDX 19015胰腺癌异种移植小鼠功效模型中测量随时间推移的肿瘤体积变化百分比的图：盐水对照或两种包含奥沙利铂的疗法：MM-398脂质体伊立替康(MM-398)、奥沙利铂和5FU；以及(非脂质体)伊立替康、奥沙利铂和5FU。通过约60天的观察时间段，相比于在第0天、7天、14天以及21天接受非脂质体伊立替康(CPT-11)与奥沙利铂和5-FU的组合的小鼠，在第0天、7天、14天以及21天接受脂质体伊立替康(MM-398，也称为MM-398)与5FU和奥沙利铂的组合的小鼠显示肿瘤体积百分比变化显著减少。参考图6C，相比于对照组和MM-398单一疗法，将奥沙利铂添加到MM-398+5-FU显著改善了具有PDX 19015肿瘤的小鼠的无进展存活。MM-398+5FU与MM-398单一疗法之间的差值不具有统计意义上的显著性。参考图6D，相对对照组，将5-FU和奥沙利铂添加到MM-398显著改善了总存活率。用非脂质体伊立替康观察不到添加的5-FU或奥沙利铂的益处。参考图7，相对MM-398单一疗法，将奥沙利铂添加到MM-398+5-FU显著延迟肿瘤进展，如第35天显著减少的肿瘤体积所示。

[0054] 图8是示出了在各种治疗后小鼠中肿瘤生长和存活的结果的表。将肿瘤细胞(PDX 19015模型)皮下植入小鼠。当肿瘤建立良好并且已达到～250mm^{3}的平均体积时，使用仅MM-398或非脂质体伊立替康(单一疗法)或与5-FU(NAPOLI，双联疗法)或5-FU+奥沙利铂(NAPOX，三联疗法)组合开始IV治疗。如相比于双联NAPOLI(38％)或单一疗法MM-398单一疗法(0％)，使用三联疗法NAPOX(50％)治疗的小鼠具有最佳总缓解率(ORR)。另外，三联疗法治疗的小鼠还具有更佳的疾病控制率(DCR)：NAPOX(75％)、NAPOLI(63％)、MM-398单一疗法(38％)和无进展存活(PFS)：NAPOX是47天，相对NAPOLI的36.5天和MM-398单一疗法的12天。NAPOX PFS显著优于单一疗法，而NAPOLI不显著优于单一疗法。值的注意的是，在100天的小鼠耐受性研究中，脂质体伊立替康与5FU和奥沙利铂的组合的耐受性优于SN-38暴露匹配剂量的非脂质体伊立替康与5FU和奥沙利铂的组合。图9是示出了在施用以下各种方案后小鼠的体重的图：盐水对照、脂质体伊立替康(MM-398)、纳米脂质体伊立替康、5-FU和奥沙利铂的组合或非脂质体伊立替康(CPT11)、5FU和奥沙利铂的组合。当与5-FU和奥沙利铂组合时，相对非脂质体伊立替康，在重复给药后，脂质体伊立替康改善了小鼠模型的耐受性。通过普通的双向方差分析(ANOVA)确定显著性。方案在研究的第0、7、14以及21天施用。施用10mg/kg脂质体伊立替康和50mg/kg剂量的非脂质体游离伊立替康(CPT11)在小鼠模型中向肿瘤细胞提供相当剂量的SN-38。

[0055] 当奥沙利铂在施用MM-398后一天施用时，MM-398脂质体伊立替康和奥沙利铂的组合的耐受性在小鼠模型中有所改善。图10A和10B描绘了与MM-398和奥沙利铂作为单一疗法给予或作为组合疗法同时(A)或交错(1天给予奥沙利铂，然后施用MM-398)(B)相关的毒性的线图。MM-398和奥沙利铂的共施用导致显著的毒性，如通过体重减轻所测量，而延迟奥沙利铂施用24小时然后MM-398不导致体重显著变化。

[0056] 图11A-11F是描述用MM-398同时或按序给予MM-398与或不与奥沙利铂一起给予后的血液学和肝脏毒性的柱状图。通过延迟给予奥沙利铂，改善了血液学毒性(A-C)。当奥沙利铂施用延迟时，肝酶(D-F)保持与单一疗法相当。

[0057] 这些临床前发现支持脂质体伊立替康与5-FU/LV和奥沙利铂组合的治疗用途和一

线PDAC(实施例2)中这种三联方案的正在进行的2期试验(NCT02551991)。图12描绘了采用MM-398+5-FU/LV+奥沙利铂(第1组)和MM-398+5-FU/LV(第2组)以及nab-紫杉醇+吉西他滨(第3组)的组合的研究设计的图形表示。

[0058] 例如,使用脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的组合来治疗先前未接受化疗以治疗转移性胰腺腺癌的人类患者转移性胰腺腺癌,所述使用包括总共每两周一次将抗肿瘤疗法施用到患者,所述抗肿瘤疗法由以下组成:(a)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌;(b)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌;(c)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌,其中脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用;(d)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌,其中脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用;(e)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌,其中施用脂质体伊立替康,之后施用奥沙利铂,之后施用亚叶酸,之后施用5-氟尿嘧啶;(f)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌,其中施用脂质体伊立替康,然后施用奥沙利铂,之后施用亚叶酸,之后施用5-氟尿嘧啶;或(g)60mg/m^2的脂质体伊立替康、60mg/m^2-85mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌,其中脂质体伊立替康、奥沙利铂和亚叶酸在28天治疗周期的第1和15天施用,其中施用脂质体伊立替康,之后施用奥沙利铂,之后施用亚叶酸,之后施用5-氟尿嘧啶,其中在完成脂质体伊立替康的每次施用后2小时,开始施用奥沙利铂。可以对这些示例性用途中的每一个进行修改,以在以下关于这些特定组分的段落中替换本文公开的脂质体依立替康、奥沙利铂、亚叶酸以及5-氟尿嘧啶的剂量。有时脂质体伊立替康包含封装在脂质体中的伊立替康蔗糖八硫酸盐。有时,脂质体伊立替康包含封装在脂质体载体中的伊立替康,所述载体由1,2-二硬脂酰-sn-甘油-3-磷酸胆碱(DSPC)、胆固醇和N-(羰基甲氧基聚乙二醇-2000)-1,2-二硬脂酰-sn-甘油-3-磷酸乙醇胺(MPEG-2000-DSPE)组成。

[0059] 如本文所提供,伊立替康可在伊立替康脂质体制剂中施用。优选地,脂质体伊立替康是伊立替康蔗糖硫酸酯脂质体注射剂(另外称为"伊立替康蔗糖八硫酸酯盐脂质体注射剂"或"伊立替康蔗糖硫酸酯脂质体注射剂"),本文称为"MM-398"(也称为PEP02,参见US 8,147,867)的制剂是"纳米脂质体伊立替康"(也称为"伊立替康脂质体"或"脂质体伊立替康")的一种形式。MM-398是作为封装在纳米脂质体药物递送系统中的伊立替康蔗糖八硫酸酯盐的伊立替康。

[0060] 脂质体伊立替康可以是制备以用于人类静脉施用的药物组合物。例如,脂质体伊

立替康可作为静脉内注射的无菌可注射肠胃外液体提供。所需量的脂质体伊立替康可以例如在500mL的5％右旋糖注射液USP中稀释以提供各种浓度，例如5mg/mL，并且可在90分钟时间段内输注。

[0061] MM-398注射液伊立替康的活性成分是拓扑异构酶I抑制剂类药物的一个成员并且是天然存在的生物碱喜树碱(camptothecin)的半合成水溶性类似物。拓扑异构酶I抑制剂通过抑制DNA解旋并由此防止DNA复制来阻止不受控制的细胞生长。伊立替康的药理学很复杂，涉及药物的活化、失活和消除的广泛代谢转化。伊立替康是前药，它通过非特异性羧酸酯酶转化成具有100-1000倍更高活性的代谢物SN-38。SN-38是经由葡萄糖醛酸反应(对此，已经显示主要药物遗传变化)和胆汁排泄来清除。这些药物特性引起了临床上观察到的伊立替康在功效和毒性方面的明显差异。

[0062] 脂质体伊立替康可以封装有含水空间的直径为约80nm-140nm的单层脂质双层囊泡，所述含水空间包含与蔗糖八硫酸酯络合形成盐的呈胶凝或沉淀状态的伊立替康。脂质体的脂质膜由磷脂酰胆碱、胆固醇和聚乙二醇衍生化的磷脂酰乙醇胺(其量为约一个聚乙二醇(PEG)分子对200个磷脂分子)构成。

[0063] 当与奥沙利铂和5-氟尿嘧啶组合施用用于治疗胰腺癌时，施用到人类患者的脂质体伊立替康的量在可约40mg/m^2至约180mg/m^2的范围内，优选地60mg/m^2(剂量以伊立替康盐酸盐三水合物盐的量为单位表达)。使用群体药代动力学分析，在接受MM-398的患有癌症的患者和353个患有癌症的患者中评估总伊立替康和总SN-38的血浆药代动力学，所述MM-398作为单一药剂或组合化疗的一部分，在50mg/m^2和155mg/m^2的剂量之间(伊立替康碱的量，等同于以伊立替康盐酸盐三水合物盐的量为单位表达的60mg/m^2-180mg/m^2剂量)。在50mg/m^2至155mg/m^2的剂量范围内，总伊立替康的$C_{最大}$和AUC随剂量增加。另外，总SN-38的$C_{最大}$与剂量成比例增加；然而总SN-38的AUC增加小于与剂量成比例增加。

[0064] 本文描述的组合治疗涵盖将MM-398脂质体伊立替康与多个其他活性药剂的组合：奥沙利铂、亚叶酸和5-氟尿嘧啶以如本文所述的转移性环境的剂量和计划表施用到先前未使用之前的化疗剂治疗的患有转移性胰腺癌的人类患者。

[0065] 5-氟尿嘧啶是干扰核酸生物合成的嘧啶拮抗剂。所述药物的脱氧核糖核苷酸抑制胸苷酸合成酶，由此抑制由脱氧尿苷酸形成胸苷酸，从而干扰DNA的合成。它还干扰RNA合成。施用到人类患者的5-氟尿嘧啶的示例性有效量可以在约2,000mg/m^2至约3,000mg/m^2的范围内。在一些实施方案中，施用到人类患者的5-氟尿嘧啶的量是2,400mg/m^2。

[0066] 任选地在5-氟尿嘧啶前，施用亚叶酸。亚叶酸在嘌呤和嘧啶的合成中充当1-碳转移反应的生物化学辅因子。亚叶酸转化成四氢叶酸不需要二氢叶酸还原酶(DHFR)。亚叶酸抑制甲氨蝶呤和其他DHFR-拮抗剂的作用。亚叶酸可增强氟化嘧啶(即，氟尿嘧啶和氟尿苷)的细胞毒性作用。当5-FU在细胞内活化之后，它由叶酸辅因子伴随并且抑制酶胸苷酸合成酶，从而抑制嘧啶合成。亚叶酸使叶酸池增加，借此增加叶酸辅因子和活性5-FU与胸苷酸合成酶的结合。亚叶酸具有右旋异构体和左旋异构体，只有左旋异构体在药理学上是有用的。因此，具有生物活性的左旋异构体("左亚叶酸")还被FDA批准用于治疗癌症。亚叶酸的剂量典型地为包含右旋(d)异构体和左旋(l)异构体的外消旋混合物剂量的一半，或任选地(l+d)外消旋形式的剂量的一半的(l)形式的亚叶酸。施用到人类患者的亚叶酸的示例性有效量可包括在约100mg/m^2至约300mg/m^2.范围内的(l)形式的亚叶酸的量。在一些实施方案中，

施用到人类患者的量的(l)形式的亚叶酸是200mg/m^2。在其他实施方案中,所施加的亚叶酸是(l+d)形式的亚叶酸,其量在约200mg/m^{2}至约600mg/m^{2}的范围内。在一些实施方案中,所施加的(l+d)形式的亚叶酸的量是400mg/m^2。

[0067] 奥沙利铂是铂类药物,其可作为DNA交联剂以有效抑制DNA复制和转录,从而导致细胞毒性,这是细胞周期非特异性的。奥沙利铂通常与输注5-FU/LV组合使用,并且被批准用于晚期结直肠癌(详情请参阅包装说明书)。施用到人类患者的奥沙利铂的有效量的范围可在约30mg/m^{2}至约150mg/m^2,例如约40mg/m^{2}至约100mg/m^2,或可以是50mg/m^2、55mg/m^2、60mg/m^2、65mg/m^2、70mg/m^2、75mg/m^2、80mg/m^2、85mg/m^2、90mg/m^{2}或95mg/m^{2}的量的奥沙利铂。

[0068] 作为不良事件(包括血液学和非血液学不良事件)的结果,可以对施用本文描述的组合治疗的方法进行剂量修改。

[0069] 在一些实施方案中,将本文所述的组合治疗施用到具有一个或多个特征的患者的方法可包括减少或以其他方式修改根据本文实施方案施用的MM-398的剂量。在一些实施方案中,根据表1修改MM-398的剂量。

[0070] 表1A:MM-398(盐)的剂量修改的实施例

[0071]

毒性 NCI CTCAE v4.0	发生	在接受 60 mg/m^{2‡} (盐)的患者中 MM-398 调整	先前未增加到 60 mg/m^2 (盐)的具有纯合型 UGT1A1*28 的患者
3 级或 4 级不良反应	停用 MM-398。 开始洛哌丁胺以用于任何严重的迟发性腹泻。 静脉内或皮下施用 0.25 mg 至 1 mg 的阿托品(除非有临床禁忌)用于任何严重的早发性腹泻。 在恢复至≤1 级或基线级后, 重新开始 MM-398:		
	第一	45 mg/m^2	35 mg/m^2
	第二	35 mg/m^2	30 mg/m^2
	第三	停止 MM-398	停止 MM-398
间质性肺病	第一	停止 MM-398	停止 MM-398
过敏反应	第一	停止 MM-398	停止 MM-398

[0072] 在一些实施方案中,响应于患者耐受性考虑因素诸如对第一或后续剂量的MM-398和/或其他抗肿瘤剂的不良反应和/或确定患者为具有纯合型UGT1A1*28等位基因,MM-398的第一、第二或任何后续剂量可减少20%-30%(包括20%、25%和/或30%的剂量减少)。在一些实施方案中,MM-398的第二或后续剂量减少约20%、25%或30%(例如,60mg/m2至的剂量减少)。在一些实施方案中,MM-398的剂量减少25%。在一些实施方案中,MM-398的剂量减少30%。在一些实施方案中,MM-398的减少的剂量在从30mg/m^{2}开始至(并且包括)55mg/m^{2}的范围内。在一些实施方案中,MM-398的剂量减少到60mg/m^2。在一些实施方案中,MM-398的剂量减少到45mg/m^2。在一些实施方案中,MM-398的剂量减少到35mg/m^2。

[0073] 其他剂量减少时间表在下表1B-1E中提供。当MM-398的开始(起始)剂量是60mg/m^2,5FU 2400mg/m^2,LV(l+d)400mg/m^{2}并且奥沙利铂是85mg/m2或60mg/m2时,则响应于III或IV级血液毒性的第一剂量减少优选地为针对抗肿瘤疗法的每次施用,MM-398、5-FU和奥沙

利铂剂量中的每个剂量减少25％。对于持续的毒性，尽管第一次剂量减少，MM-398、5-氟尿嘧啶和奥沙利铂的抗肿瘤剂中的每一种的另外的25％剂量减少是优选的。然后进一步的毒性将导致在某些情况下停止治疗。对于非血液学毒性，除了与药物相关的特定毒性(即5FU手足综合征和奥沙利铂神经病)外，可遵循与血液毒性相同的剂量减少方案，这可以基于患者的医学上适合剂量来选择。

[0074] 表1B MM-398和奥沙利铂的减少的剂量的实施例

[0075]

剂量	MM-398 (mg/m2) (盐)	奥沙利铂 (mg/m2)	5-氟尿嘧啶(5FU) (mg/m2)
初始	60	60	2400
第一减少	45	45	1800
第二减少	35	35	1350

[0076] 表1C MM-398和奥沙利铂的减少的剂量的实施例

[0077]

剂量	MM-398 (mg/m2) (盐)	奥沙利铂 (mg/m2)	5-氟尿嘧啶(5FU) (mg/m2)
初始	60	80	2400
第一减少	45	60	1800
第二减少	35	45	1350

[0078] 表1D MM-398和奥沙利铂的减少的剂量的实施例

[0079]

剂量	MM-398 (mg/m2) (盐)	奥沙利铂 (mg/m2)	5-氟尿嘧啶(5FU) (mg/m2)
初始	60	60	2400
第一减少	45	45	2400

[0080]

第二减少	35	35	1800

[0081] 表1E MM-398和奥沙利铂的减少的剂量的实施例

[0082]

剂量	MM-398 (mg/m2) (盐)	奥沙利铂 (mg/m2)	5-氟尿嘧啶(5FU) (mg/m2)
初始	60	80	2400
第一减少	45	60	2400
第二减少	35	45	1800

[0083] 在一些实施方案中，将本文所述的组合治疗施用到具有一个或多个特征的患者的方法可包括减少或以其他方式修改根据本文实施方案施用的奥沙利铂的剂量。在一些实施方案中，奥沙利铂的剂量减少20％-30％。在一些实施方案中，奥沙利铂的剂量减少20％。在一些实施方案中，奥沙利铂的剂量减少25％。在一些实施方案中，奥沙利铂的剂量减少30％。在一些实施方案中，奥沙利铂的减少的剂量在30mg/m^2至75mg/m^2的范围内。在一些实施方案中，奥沙利铂的剂量减少到75mg/m^2。在一些实施方案中，奥沙利铂的剂量减少到65mg/m^2。在一些实施方案中，奥沙利铂的剂量减少到60mg/m^2。在一些实施方案中，奥沙利铂的剂量减少到45mg/m^2。在一些实施方案中，奥沙利铂的剂量减少到45mg/m^2。在一些实施方案中，奥沙利铂的剂量减少到34mg/m^2。

[0084] 在一些实施方案中，将本文所述的组合治疗施用到具有一个或多个特征的患者的

方法可包括减少或以其他方式修改根据本文实施方案施用的5-氟尿嘧啶的剂量。在一些实施方案中,5-氟尿嘧啶的剂量减少20%-30%。在一些实施方案中,5-氟尿嘧啶的剂量减少20%。在一些实施方案中,5-氟尿嘧啶的剂量减少25%。在一些实施方案中,5-氟尿嘧啶的剂量减少30%。在一些实施方案中,5-氟尿嘧啶的减少的剂量在1000mg/m^2至1800mg/m^2的范围内。在一些实施方案中,5-氟尿嘧啶的剂量减少到1800mg/m^2。在一些实施方案中,5-氟尿嘧啶的剂量减少到1350mg/m^2。在一些实施方案中,5-氟尿嘧啶的剂量减少到1200mg/m^2。

[0085] 在一些实施方案中,将本文所述的组合治疗施用到具有一个或多个特征的患者的方法可包括另外减少或以其他方式修改根据本文实施方案施用的MM-398、奥沙利铂和/或5-氟尿嘧啶的剂量。

[0086] 在一些实施方案中,将本文所述的组合治疗施用到具有一个或多个特征的患者的方法可包括减少或以其他方式修改根据本文实施方案施用的MM-398、奥沙利铂和5-氟尿嘧啶中多于一个的剂量。

[0087] MM-398、奥沙利铂和/或5-氟尿嘧啶的另外的剂量修改可见于各自的包装说明书中,其通过引用并入本文。

[0088] 在一个实施方案中,施用组合治疗的方法包括34mg/m^2、45mg/m^2或60mg/m^2的脂质体伊立替康、34mg/m^2、42mg/m^2、45mg/m^2、60mg/m^2、或85mg/m^2奥沙利铂、200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸以及1,200mg/m^2、1,350mg/m^2、1,800mg/m^2或2,400mg/m^2 5-氟尿嘧啶以治疗人类患者的转移性胰腺腺癌。

[0089] 因此在一些实施方案中,施用组合治疗以治疗人类患者的转移性胰腺腺癌的方法包括:

[0090] (A)(i)35mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(ii)35mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(iii)35mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(iv)35mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(v)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(vi)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/$m^2$5-FU;(vii)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(viii)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(ix)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(x)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xi)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(xii)35mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/$m^2$5-FU;(xiii)35mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(xiv)35mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xv)35mg/m^2的脂质体伊立替康、60mg/m^2奥

沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(xvi)35mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(xvii)35mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(xviii)35mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/$m^2$5-FU;(xix)35mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;或(xx)35mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(B)(i)45mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(ii)45mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(iii)45mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(iv)45mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(v)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/$m^2$5-FU;(vi)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(vii)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(viii)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(ix)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(x)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/$m^2$5-FU;(xi)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(xii)45mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(xiii)45mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(xiv)45mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xv)45mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(xvi)45mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/$m^2$5-FU;(xvii)45mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(xviii)45mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xix)45mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;或(xx)45mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;或(C)(i)60mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(ii)60mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(iii)60mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/$m^2$5-FU;(iv)60mg/m^2的脂质体伊立替康、35mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸

以及2,400mg/m^2 5-FU;(v)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(vi)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(vii)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(viii)60mg/m^2的脂质体伊立替康、45mg/m2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(ix)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/$m^2$5-FU;(x)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xi)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/m^2 5-FU;(xii)60mg/m^2的脂质体伊立替康、45mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(xiii)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/$m^2$5-FU;(xiv)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xv)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/$m^2$5-FU;(xvi)60mg/m^2的脂质体伊立替康、60mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU;(xvii)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,200mg/m^2 5-FU;(xviii)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,350mg/m^2 5-FU;(xix)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及1,800mg/$m^2$5-FU;或(xx)60mg/m^2的脂质体伊立替康、85mg/m^2奥沙利铂、200mg/m^2(l)形式或400mg/m^2外消旋亚叶酸以及2,400mg/m^2 5-FU。

[0091] 脂质体伊立替康优选地与奥沙利铂、5-氟尿嘧啶(5-FU)和亚叶酸组合静脉内施用。在一个实施方案中,脂质体伊立替康在奥沙利铂、5-FU和亚叶酸之前施用。在另一个实施方案中,亚叶酸在5-FU之前施用。在另一个实施方案中,施用MM-398脂质体伊立替康,之后施用奥沙利铂,之后施用亚叶酸并且之后施用5-氟尿嘧啶。在某些实施方案中,在90分钟内,将脂质体伊立替康静脉内施用到患者。在另一个实施方案中,在120分钟内,将奥沙利铂静脉内施用到患者。在另一个实施方案中,在46小时内,静脉内施用5-FU。在一个实施方案中,在施用脂质体伊立替康后约6至约72小时,施用奥沙利铂。在另一个实施方案中,在施用脂质体伊立替康后例如,6小时、12小时、24小时、36小时、48小时、60小时或72小时,施用奥沙利铂。在另一个实施方案中,在30分钟内,静脉内施用亚叶酸。在各种实施方案中,脂质体伊立替康是MM-398。在各种实施方案中,在施用MM-398脂质体伊立替康和其他活性药剂之前,将地塞米松和5-HT3拮抗剂或其他止吐药前驱给药到患有转移性胰腺癌的人类患者。

[0092] 本发明的进一步实施方案

[0093] 下面的方法和实施方式可以单独考虑,在本部分中与其他实施方案组合,或者与上面公开的方法组合。本发明提供用于治疗人类患者(诸如例如先前未在转移性环境中使用化疗剂治疗的患者)的胰腺癌的方法,所述方法包括向患者施用与奥沙利铂、亚叶酸和5-FU组合的脂质体伊立替康,也被称为MM-398(例如,伊立替康蔗糖八硫酸酯盐脂质体注射液)。

[0094] 1.一种用于治疗先前未接受化疗以治疗胰腺癌的人类受试者的胰腺癌的方法，所述方法包括向受试者施用治疗有效量的与奥沙利铂、亚叶酸和5-FU组合的MM-398脂质体伊立替康以治疗所述人类受试者的胰腺癌。

[0095] 2.根据实施方案1所述的方法，其中施用的MM-398脂质体伊立替康所施用的量为60mg/m^2或80mg/m^2。

[0096] 3.一种用于治疗先前未接受化疗以治疗胰腺癌的人类受试者的胰腺癌的方法，所述方法包括向受试者施用60mg/m^2的与奥沙利铂、亚叶酸和5-FU组合的MM-398脂质体伊立替康以治疗所述人类受试者的胰腺癌。

[0097] 4.如实施方案1-3中任一项所述的方案，其中奥沙利铂的施用量为约50mg/m^2至约100mg/m^2，诸如约60mg/m^2至约85mg/m^2，例如60mg/m^2、75mg/m^2或85mg/m^2。

[0098] 5.如实施方案1-4中任一项所述的方案，其中亚叶酸以400mg/m^2的(l+d)外消旋形式或200mg/m^2的(l)形式的剂量施用。

[0099] 6.如实施方案1-5中任一项所述的方案，其中5-FU以2,400mg/m^2的量施用。

[0100] 7.如实施方案1-6中任一项所述的方案，其中MM-398脂质体伊立替康、奥沙利铂、亚叶酸以及5-FU至少施用一次，诸如其中MM-398、奥沙利铂、亚叶酸以及5-FU在28天周期中在第1和15天施用。

[0101] 8.如实施方案1-7中任一项所述的方案，其中施用多个周期。

[0102] 9.如实施方案1-8中任一项所述的方案，其中胰腺癌是胰的腺癌，诸如胰腺的不可切除、局部晚期或转移性腺癌，例如其中胰腺癌是胰的转移性腺癌；或其中转移性胰腺癌是外分泌性转移性胰腺癌，选自由以下组成的组：导管细胞癌、腺泡细胞癌、腺鳞癌、囊肿腺癌(浆液性和粘液性)、巨细胞癌、与囊性黏液性肿瘤或导管内乳头状黏液性肿瘤相关的侵袭性腺癌、混合型(导管内分泌或腺泡内分泌)、粘液癌、胰母细胞瘤，乳头状囊性肿瘤(Frantz肿瘤)、乳头状粘液癌、印戒细胞癌、小细胞癌、未分类的未分化癌、浆液性囊腺癌以及实性和假乳头状肿瘤。

[0103] 11.如实施方案1-10中任一项所述的方案，其中奥沙利铂在亚叶酸前施用到患者，诸如其中亚叶酸在5-FU前施用到患者，任选地其中MM-398脂质体伊立替康在奥沙利铂、亚叶酸和5-FU前施用到患者。

[0104] 12.如实施方案11所述的方法，其中MM-398在90分钟内施用，之后在120分钟内施用奥沙利铂，之后在30分钟内施用亚叶酸，之后在46小时内施用5-FU。

[0105] 在具体实施方案中，使用本公开的组合方案治疗先前未在转移性环境中使用任何化疗剂治疗的患有胰的转移性腺癌的人类患者，所述方法包括静脉内施用到患者，在2周周期的第1天开始，在90分钟内，80mg/m^2的MM-398脂质体伊立替康，之后60mg/m^2-85mg/m^2奥沙利铂，之后200mg/m^2的(l)形式的亚叶酸或400mg/m^2的(l+d)消旋形式的亚叶酸，之后2,400mg/m^2 5-FU，其中人类患者接受一个或多个周期的治疗。在本文公开的实施方案中，施用到人类患者的MM-398脂质体伊立替康的有效量可在约40mg/m^2至约100mg/m^2，例如约60mg/m^2至约80mg/m^2的范围内。在各种实施方案中，施用到人类患者的MM-398脂质体伊立替康的量为60mg/m^2或80mg/m^2。在本文公开的实施方案中，施用到人类患者的奥沙利铂的有效量可在约40mg/m^2至约100mg/m^2，例如约60mg/m^2至约85mg/m^2的范围内。在各种实施方案中，施用到人类患者的奥沙利铂的量为60mg/m^2或85mg/m^2。在此实施方案的一个变体中，在120

分钟内施用奥沙利铂,在30分钟内施用亚叶酸并且在46小时内施用5-FU。

实施例

[0106] 实施例1:体外胰腺癌细胞暴露于拓扑异构酶1抑制剂

[0107] 图1A中示出了使用游离伊立替康或MM-398施用的患者中SN-38的模仿肿瘤暴露。相比于游离伊立替康(CPT-11),MM-398显示使得肿瘤的SN-38持续时间延长。在一组胰细胞系(AsPC-1、BxPC-3、Capan-2、CFPAC-1以及MiaPaCa-2)中研究各种SN-38持续时间对细胞生长抑制的效应。图1B显示模拟这2种药物的临床上可比较的SN-38暴露的体外条件,其中在短时间内以高浓度暴露于SN-38的细胞接近游离伊立替康,并且在长时间内以低浓度暴露接近MM-398。图1C中汇总了结果和试验条件。例如,在患者肿瘤中,使用139nM的SN-38孵育144小时对使用417nM孵育24小时的细胞具有类似的MM-398对游离伊立替康的SN-38肿瘤暴露比率。在这些临床相关的条件下,相比于高浓度下的短暴露(即游离伊立替康),延长的暴露(即MM-398)主要使得胰腺癌细胞生长抑制更多。当SN-38与5-FU或奥沙利铂组合时也获得了类似的结果,从而展示当与用于FOLFIRINOX方案中的这些其他化疗剂组合时,延长的暴露还导致细胞生长抑制增加。

[0108] 实施例2:动物模型中组合疗法的体内耐受性和功效的评估

[0109] BxPC-3和CFPAC-1小鼠异种移植研究(功效):

[0110] 组织培养物:将BxPC-3细胞在补充有10%FBS和1%青霉素/链霉素的RPMI生长培养基中培养。将CFPAC-1细胞也在补充有10%FBS和1%青霉素/链霉素的RPMI生长培养基中培养。

[0111] 动物:试验根据批准的准则进行。雌性NOD.scid小鼠获自CharlesRiver Laboratories(Wilmington,MA)。将BxPC-3或CFPAC-1细胞接种到5e6细胞处右后侧面,总体积为50uL/小鼠。除非另外指明,每组治疗八只动物。除非另外指明,当肿瘤达到200mm^3-250mm^3的平均体积(范围100mm^3-400mm^3)时,将动物随机化并开始给药。

[0112] 治疗功效:静脉内施用MM-398、伊立替康和奥沙利铂。腹膜内施用5-FU。当肿瘤达到200mm^3-250mm^3的平均体积时,开始施用指定剂量的每种药剂并且持续总共4周的剂量。如所示,每周测量肿瘤体积,直到肿瘤达到1000mm^3-2000mm^3,动物处于较差的总体健康状况,或在最终剂量后2周。

[0113] PDX19015小鼠异种移植研究(功效和耐受性):

[0114] 动物:试验根据批准的准则进行。雌性CB.17SCID小鼠获自Roswell Park癌症研究所(Buffalo,NY),最初6-8周龄。除非另外指明,每个治疗组治疗8只动物。肿瘤块来源于供体小鼠并且皮下移植。除非另外指明,当肿瘤达到200mm^3-250mm^3的平均体积(范围100mm^3-400mm^3)时,将动物随机化并开始给药。

[0115] 治疗功效:静脉内施用MM-398、伊立替康和奥沙利铂。腹膜内施用5-FU。当肿瘤达到200mm^3-250mm^3的平均体积时,开始施用指定剂量的每种药剂并且持续总共4周的剂量。如所示,在给药周期过程中,每周两次测量肿瘤体积,然后每周一次,直到肿瘤达到1000mm^3-2000mm^3,动物处于较差的总体健康状况,或在第一给药后100天。耐受性:每周一次测量小鼠体重以监测治疗耐受性。当体重下降到比基线低≥20%或者它们显示总体健康状况不佳的明显迹象时,小鼠被安乐死。

[0116] 延迟给药奥沙利铂：

[0117] 动物：试验根据批准的准则进行。雌性CD-1小鼠获自Charles River Laboratories(Wilmington,MA)。在幼稚(不具有肿瘤)小鼠中进行耐受性研究。每组治疗三只动物。

[0118] 治疗耐受性：以它们预先定义的最大耐受剂量(MM-398，50mg/kg；奥沙利铂，17mg/kg)静脉内施用药剂。每种药物单独或组合施用。以3个独立的给药计划表中的一个给予组合：共注射(同时施用药物)，第1天给予MM-398并且第2天给予奥沙利铂(延迟24小时)，或第1天给予MM-398并且第4天给予奥沙利铂(延迟72小时)。给予每种药物单次施用。每天测量小鼠体重至治疗后2周。当体重下降到比基线低≥20％、它们显示总体健康状况不佳的明显迹象或治疗后2周(研究结束)时，小鼠被安乐死。

[0119] 血液学和肝毒性的测量：在研究结束时，通过心脏穿刺对每只小鼠进行末端出血。根据制造商的方案，通过Hemavet(Drew Scientific,Miami Lakes,FL)测量血液学功能(血细胞计数)。根据制造商的方案，通过CatalystDx(Idexx Laboratories,Westbrook,ME)测量肝功能(酶水平)。

[0120] 实施例3：胰腺癌的治疗

[0121] 如图12示意性所示，本研究是开放标签的2期比较研究，用于评定相比于nab-紫杉醇+吉西他滨，MM-398组合其他抗癌疗法在之前未接受化疗的患有转移性胰腺癌的患者中的安全性、耐受性和功效。此研究评定以下方案：(1)MM-398+5-FU/LV+奥沙利铂(第1组)，(2)MM-398+5-FU/LV(第2组)和(3)nab-紫杉醇+吉西他滨(第3组)。

[0122] 这项2期研究评估了MM-398+5-FU/LV在具有或不具有奥沙利铂的情况下相对nab-紫杉醇+吉西他滨在患有先前未治疗的mPAC的患者中的初步安全性和功效。所述研究还可提供关于MM-398组合治疗对患者HRQL的影响的重要信息，并且确定潜在的响应生物标志物。

[0123] 在研究中，MM-398代替常规的伊立替康施用以改善FOLFIRINOX方案的安全性、耐受性和最终功效。将奥沙利铂添加到NAPOLI-1方案被包括以增加DNA损伤并且增强功效。此外，由于MM-398延长的PK特性和持续的肿瘤暴露，使用MM-398代替常规的依立替康被设计为进一步改善FOLFIRINOX的功效。

[0124] 本文提供了脂质体伊立替康、奥沙利铂、5-氟尿嘧啶(5-FU)/亚叶酸的修改的三联组合方案，由此将不施用5-FU的推注。在使用连续输注剂量的5-FU(排除推注)的第1组组合方案中评估奥沙利铂的靶剂量(60mg/m^2-85mg/m^2)，并且与5-FU组合，MM-398的每2周剂量先前显示为可耐受且有效的。请注意，相比于使用游离伊立替康的标准给药所预计的，在MM-398给药的情况下，预计SN-38的$C_{最大}$更低。

[0125] 所述研究分两部分进行，如图12的示意图所示：1)MM-398+5-FU/LV+奥沙利铂方案的安全性运行，和2)MM-398+5-FU/LV+奥沙利铂方案的随机功效研究，MM-398+5-FU/LV组合先前在3期NAPOLI-1试验(即NAPOLI方案)中显示功效，和nab-紫杉醇+吉西他滨对照组。

[0126] 第1部分：

[0127] 第一部分由第1组：MM-398+5-FU/LV+奥沙利铂组合方案的开放标签的安全性运行组成。第2组和第3组的方案已建立剂量，并且MM-398+5-FU/LV已被证明是可耐受的，从而在患有复发的转移性胰腺癌的患者的3期研究中产生抗肿瘤反应，并且因此不包括在所述研

究的这部分中。按照传统的3+3剂量提高设计，安全运行招募了小批患者，以确认奥沙利铂的目标剂量。在治疗的第一个周期过程(即，28天/周期；或在研究治疗的第2次给药后14天，如果小批患者中存在治疗延迟，以确定是否目标组合剂量是可耐受的(注意：目标组合剂量是基于FOLFIRINOX方案的建立剂量))中评估剂量限制性毒性(DLT)。如果在安全评估期内没有DLT，则在研究者、医疗监护人和发起者之间达成协议后开始后续队列。如果发生一个DLT，则所述队列扩大至6位患者。如果2个或更多的患者在给定的剂量水平内有DLT，则认为所述剂量超过组合的安全性和耐受性标准，并且剂量不进一步升高；然而，可探索更低的剂量。然后将第2部分剂量定义为下一个较低的剂量水平，其中治疗6位患者，并且≤1位患者经历了达到DLT的毒性。

[0128] 另外，在评估DLT时考虑UGT1A1*28等位基因状态。基于以前伊立替康的经验，UGT1A1*28等位基因纯合型(UGT1A1 7/7基因型)的个体在伊立替康治疗开始后中性粒细胞减少症的风险增加。根据伊立替康的处方信息，在接受单剂伊立替康(每3周一次350mg/m^2)的66个患者的研究中，UGT1A1*28等位基因纯合型患者中4级中性粒细胞减少症的发生率高达50％，并且此等位基因杂合子(UGT1A16/7基因型)的患者的发生率为12.5％。重要的是，在野生型(WT)等位基因(UGT1A1 6/6基因型)的纯合型患者中未观察到4级中性粒细胞减少症。在其他研究中，描述了伴随的危及生命的中性粒细胞减少症的患病率较低(详情参见伊立替康的处方信息)。MM-398的群体PK研究尚未确定UGT1A1*28纯合性与SN-38暴露增加之间的关系(参见研究者手册)。在I期研究中，在杂合子或WT患者队列中没有观察到毒性差异，并且在两个队列中均可见到伴有或不伴有脱水或疲劳的腹泻的DLT。由于这些原因，并且因为UGT1A1*28纯合型的患病率相对较低，所以在此研究的MM-398的第一次给药之前不需要测试结果，并且所有患者的开始剂量将是80mg/m^2。但是，如果已知患者是UGT1A1*28纯合型，则MM-398的剂量可如本文所述降低。

[0129] 第2部分：

[0130] 第二部分由开放标签随机的2期研究组成，其中患者将被随机化以使用MM-398+5-FU/LV+奥沙利铂、MM-398+5-FU/LV或nab-紫杉醇+吉西他滨治疗(1:1:1)。随机化是根据地区(东亚对世界其他地区)和表现状态(ECOG 0对1)分层。

[0131] 对于与5-FU/LV组合的以往奥沙利铂治疗以下不良事件是常见的(≥40％)并且预计包含MM-398的组合方案：外周感觉神经病变、中性粒细胞减少症、血小板减少症、贫血、恶心、转氨酶和碱性磷酸酶增加、腹泻、疲劳、呕吐以及口腔炎。如奥沙利铂包装说明书中所述，可预见另外的不良事件，包括过敏和过敏性反应。在FOLFIRINOX组合的3期研究中，最常见(>5％)3-4级不良事件为：中性粒细胞减少症、疲劳、呕吐、腹泻、血小板减少症、感觉神经病变、贫血、丙氨酸转氨酶(ALT)水平升高、血栓栓塞以及热性中性粒细胞减少症。考虑到这些预期毒性，如下所述，在研究的第1部分中评估第1组的安全性和耐受性。

[0132] 85mg/m^2的奥沙利铂剂量是本研究第2部分的目标剂量。第一部分的目的是确认当使用MM-398代替常规伊立替康时，这个剂量是否相容。在没有无预期毒性的情况下，在施用85mg/m^2的最高建议剂量的奥沙利铂之前，开始以较低剂量的奥沙利铂(60mg/m^2，参见表1)治疗3至6个患者。在研究的第2部分中施用的三联组合的剂量被定义为3至6个患者队列中少于2个患者经历DLT的最高剂量水平。如果一个患者经历了达到DLT的治疗相关毒性，则在所述剂量水平上最多招募3个另外的患者，每个队列不超过总共6个患者。如果没有观察到

另外的DLT，则重新开始提高剂量。如果第二个患者在所述剂量下经历达到DLT的治疗相关毒性，则认为所述剂量超过组合的最佳安全性和耐受性标准。然后将第2部分中待使用的剂量定义为下一个较低的剂量水平，其中治疗6位患者，并且≤1位患者经历了达到DLT的毒性。

[0133] 患者队列的给药从剂量水平-1开始，计划提高至剂量水平-2B(目标剂量)，其中三种药物中的一种的剂量增加，而另外两种药物将维持恒定剂量。如果-1剂量水平被评估并且被认为是安全的，则可开始提高到-2B剂量水平。如本文所述，必须根据所确定的用于剂量提高的建立的决定过程来做出任何降低提高的决定以及在降低提高后的替代剂量的招募。第1组组合方案的计划剂量提高概述于下表2中；如在本文“研究治疗”部分中所述的关于剂量施用的其他细节。

[0134] 表2第1部分：剂量提高表(MM-398+5-FU/LV+奥沙利铂)

[0135]

水平	奥沙利铂		5-FU/LV		MM-398 (nal-IRI)	
	剂量 (mg/m^2)[a]	给药天[c]	剂量 (mg/m^2)[b]	给药天[c]	剂量 (mg/m^2)	给药天[c]
-1	60	1、15	2400/400	1、15	60	1、15
-2B	85	1、15	2400/400	1、15	60	1、15

[0136] a与第一剂量的MM-398一起的第一剂量施用；在第1部分中nal-IRI输注完成后2小时施用奥沙利铂。

[0137] b 46小时输注，不给予推注；在完成奥沙利铂输注后，将最后施用亚叶酸和5-FU

[0138] c所指示的日期是28天周期的一部分

[0139] 第1组：MM-398+5-FU/LV+奥沙利铂

[0140] 临床上待施用的输注的顺序如下：首先施用MM-398，之后奥沙利铂，然后LV，之后5-FU。

[0141] 在第1部分中，患者在MM-398输注完成后2小时接受奥沙利铂输注。如果没有看到输注反应，则在MM-398输注完成后，第2部分患者可直接接受奥沙利铂。如果在第2部分患者中发现任何3级或更高级别的输注反应，则在MM-398输注完成后2小时，DSMB可选择恢复施用奥沙利铂。

[0142] 第1组预先用药

[0143] 在MM-398输注、5-FU/LV输注和奥沙利铂输注前，所有患者必须使用标准剂量的地塞米松和5-HT3拮抗剂或根据伊立替康、5-FU和奥沙利铂施用的标准体系实践或位于欧盟(EU)的网站的产品特性摘要(SmPC)的等同的其他止吐药进行预先用药。阿托品可预防性地开处方以用于在之前的周期中经历急性胆碱能症状的患者。

[0144] 第2组：MM-398+5-FU/LV

[0145] 临床上待施用的输注的顺序将如下：首先施用MM-398，之后LV，之后5-FU。

[0146] 第2组术前用药法

[0147] 在MM-398输注和5-FU/LV输注前，所有患者必须使用标准剂量的地塞米松和5-HT3拮抗剂或根据伊立替康和5-FU施用的标准体系实践或位于EU的网站的SmPC的等同的其他止吐药进行术前用药。根据标准体系实践，阿托品可预防性地开处方以用于在之前的周期中经历急性胆碱能症状的患者。

[0148] MM-398的剂量和施用(第1组和第2组)

[0149] 每两周在90分钟(±10分钟)内通过静脉(IV)输注施用MM-398。第1个周期第1天是固定的一天;后续剂量应在每个周期的第1天+/-2天施用。

[0150] 在施用之前,适当剂量的MM-398必须在5%右旋糖注射液(D5W)或生理盐水中稀释至500mL的最终体积。应注意不要使用在线过滤器或D5W或生理盐水以外的任何稀释剂。MM-398可以以高达1mL/sec(30mg/sec)的速率施用。

[0151] 待施用的MM-398的实际剂量将通过计算每个周期开始时患者的体表面积来确定。在计算的总剂量中将允许+/-5%的变化以便于剂量施用。由于MM-398小瓶是一次性使用的小瓶,因此现场人员不得储存小瓶的任何未使用部分以备将来使用,并且必须丢弃产品的未使用部分。

[0152] 5-FU和亚叶酸的剂量和施用(第1组和第2组)

[0153] 在每个28天周期的第1天和第15天,亚叶酸以400mg/m^2的(l+d)-外消旋形式或(l)形式200mg/m^2的剂量,作为IV输注在30分钟(±5分钟)施用

[0154] 在每个28天周期的第1天和第15天,在46小时(±60分钟)内,以2400mg/m^2的剂量以IV输注施用5-FU

[0155] 亚叶酸应根据包装说明书、SmPC或亚叶酸的标准体系准则进行重构。

[0156] 亚叶酸应在5-FU输注之前施用(第1组,亚叶酸将与奥沙利铂同时给予)。在每个周期之前,通过计算患者的体表面积来确定待施用的5-FU和亚叶酸的实际剂量。在计算的总剂量中将允许+/-5%的变化以便于剂量施用。

[0157] 奥沙利铂的剂量和施用(仅第1组)

[0158] 在第1部分中,在每个28天周期的第1天和第15天,奥沙利铂在120分钟(±10分钟)内以增加的剂量水平IV施用,如表2中所示(从60mg/m^2-85mg/m^2)

[0159] 在第2部分中,在每个28天周期的第1天和第15天,奥沙利铂在120分钟(±10分钟)内以85mg/m^2的剂量IV施用(如果根据本文所述的方法确认目标剂量)。

[0160] 奥沙利铂应根据包装说明书上的说明书、SmPC或奥沙利铂的制备和施用标准体系准则进行制备。

[0161] 应在MM-398输注后施用奥沙利铂;在第1部分中,在剂量水平1的前3名患者在MM-398输注完成两小时后开始奥沙利铂输注。在每个周期之前,通过计算患者的体表面积来确定待施用的奥沙利铂的实际剂量。在计算的总剂量中允许+/-5%的变化以便于剂量施用。

[0162] 第3组:nab-紫杉醇+吉西他滨

[0163] 临床待施用的输注的顺序如下:首先将施用nab-紫杉醇,之后吉西他滨。

[0164] 第3组预先用药

[0165] 所有接受nab-紫杉醇和吉西他滨的患者应根据相应的包装说明书进行预先用药。如果针对每周nab-紫杉醇和/或吉西他滨的预先用药存在不同的体系准则,则研究者应该使用他们的标准实践或位于欧盟站点的SmPC。

[0166] nab-紫杉醇和吉西他滨的剂量和施用(第3组)

[0167] 在每个28天周期的第1、8和15天,将在35分钟(±5分钟)内以125mg/m^2IV施用nab-紫杉醇。

[0168] 在每个28天周期的第1、8和15天,将在30分钟(±5分钟)内以1000mg/m^2IV施用吉

西他滨。

[0169] 剂量限制性毒性(DLT)

[0170] 对于与5-FU/LV和奥沙利铂组合施用的MM-398,如果在第1个治疗周期过程中发生以下不良事件,则将它们认为是剂量限制性毒性反应(DLT),并且认为与研究治疗方案有关:

[0171] ●4级中性粒细胞减少症或血小板减少症,即使最佳治疗也不能在7天内消退(停用研究药物并且同时施用药物,例如施用用于治疗中性粒细胞减少症的G-CSF);

[0172] ●4级中性粒细胞减少症并发有发热≥38.5℃即(即发热性中性粒细胞减少症)和/或伴有感染的3级中性粒细胞减少症;

[0173] ●由于药物相关毒性,无法在计划日期的14天内开始后续治疗过程;以及

[0174] ●任何4级非血液学毒性,其中具体排除:疲劳/乏力持续时间<2周,碱性磷酸酶水平升高,恶心并且呕吐持续时间≤3天(如果使用最佳止吐药方案治疗后,持续>72小时,则仅考虑剂量限制),以及腹泻持续时间≤3天(使用最佳抗腹泻方案治疗后,腹泻持续>72小时才考虑剂量限制)

[0175] 任何与疾病进展有关的毒性将不被视为DLT。

[0176] 用于DLT评估和剂量提高决定的目的的安全性评定阶段是一个治疗周期(即28天;或者如果存在根据本文所述的治疗延迟,则在研究治疗的第2剂量后14天)。只有安全性数据在当前剂量水平被评估(一旦被招募到队列中的最后一名患者完成第一个治疗周期),并且未超过最佳剂量的安全性和耐受性标准(参见段落第2部分剂量定义)后,剂量可提高到下一个水平。另外,针对在第1周期(如果适用)后产生的3级或更高级别的任何药物相关的毒性,评定与累积MM-398或组合疗法剂量的潜在关系,并且在决定提高剂量进行考虑。PK数据可能是可用的,但是对于剂量提高的决定不是必需的。

[0177]

纳入标准	排除标准
为了被纳入研究中,患者必须具有/是: ● 先前未在转移性环境中治疗的病理证实的胰的腺癌 ○ 第 1 部分: 不能切除的局部晚期或转移性疾病是允许的, 在招募前 6 周内诊断 ○ 第 2 部分: 必须在随机化前 6 周内诊断患有转移性疾病; 局部晚期疾病是不允许的 ● 如通过 RECIST v1.1 所定义的可测量或不可测量的疾病	患者必须满足所有纳入标准, 并且不满足以下所有的排除标准: ● 先前在转移性环境中, 使用手术、放疗、化疗或研究性疗法(注意: 允许放置胆道支架)治疗胰腺癌 ● 先前使用细胞毒性剂量的化疗治疗胰腺癌(如果在治疗结束后患者经过≥6 个月, 则接受先前使用化疗作为放射增敏剂的治疗的患者是符合条件的) ● 已知转移到中枢神经系统 ● 临床显著的胃肠道疾病, 包括肝脏疾病、出血、炎症、闭塞、腹泻>1 级、吸收不良综合征、溃疡性结肠炎、炎性肠病或部分肠梗阻

[0178]

● 0 或 1 的 ECOG 表现状态 ● 通过以下血液计数证明有足够的生物学参数: ○ ANC > 1,500 个细胞/μl, 不使用造血生长因子, ○ 血小板计数> 100,000 个细胞/μl, 并且 ○ 血红蛋白 > 9 g/dL ● 胜任的肝功能可通过以下得到证实: ○ 血清总胆红素≤ ULN(针对胆道梗阻, 允许胆道引流)和 ○ AST 和 ALT ≤ 2.5 x ULN (≤ 5 x ULN 是可接受的, 如果存在肝脏癌细胞转移) ● 胜任的肾功能可通过以下得到证实: 针对具有高于或低于规定正常值的血清肌酸酐的患者, 血清肌酸酐≤ 1.5 x ULN, 并且计算清除率 ≥60 mL/min/1.72 m^2。计算肌酸酐清除率应使用实际体重, 使用 Cockcroft-Gault 公式(肌酸酐清除率 = 性别 * ((140 - 年龄) / (血清肌酸酐)) * (体重/72)); 对于身体质量指数(BMI) >30 kg/m2 的患者, 应该用瘦体重来代替。 ● 正常的 ECG 或没有任何临床意义的发现的 ECG ● 从任何以前的手术或放疗的影响中恢复 ● ≥ 18 岁 ● 同意提交未染色的存档肿瘤组织进行分析, 如果可以的话 ● 能够理解并签署知情同意书(或具有能够这样做的法定代表人)	● 过去 3 年内任何第二次恶性肿瘤的病史; 具有原发癌或基底或鳞状细胞皮肤癌既往病史的患者符合条件。有其他恶性肿瘤病史的患者如果他们持续至少 3 年无病, 则符合条件。 ● 已知对 MM-398、其他脂质体产物的任何组分或 5-FU、亚叶酸或奥沙利铂的任何组分超敏 ● 已知对 nab-紫杉醇或吉西他滨(仅第 2 部分)的任何组分超敏 ● 将是实验参与的相对禁忌症的同时发生的疾病, 诸如活动性心脏病或肝脏疾病等, 包括: ○ 被纳入前少于 6 个月的严重动脉血栓栓塞事件(心肌梗塞、不稳定型心绞痛、中风) ○ NYHA III 或 IV 类充血性心力衰竭、室性心律失常或血压不受控制 ○ 已知具有 HIV、乙型肝炎或丙型肝炎的历史或活动性感染 ● 在筛查访视期间或给药的第一个计划日(在研究者的判断下, 可招募患有肿瘤发热的患者)中, 活动性感染或不明原因的发热> 38.5 ℃研究者认为这可能损害患者的参与实验或影响研究结果 ● 使用强效 CYP3A4 抑制剂或诱导剂, 或存在伊立替康的任何其他禁忌症 ● 5-FU、亚叶酸或奥沙利铂的任何禁忌症的存在 ● 使用强效 CYP2C8 抑制剂或诱导剂, 或存在 nab-紫杉醇或吉西他滨的任何其他禁忌症(仅第 2 部分) ● 研究者认为可能干扰患者签署知情同意、合作和参与研究或干扰结果解释的任何其他医学或社会状况 ● 怀孕或哺乳: 育龄妇女必须在招募时基于尿或血清妊娠测试检测怀孕阴性。具有生殖潜力的男性和女性患者均必须同意在研究期间和最后一次剂量的研究药物后 3 个月使用高效的节育方法。

[0179] 剂量修改

[0180] 必须在施用后续周期并且分级根据美国国家癌症研究所通用不良事件术语标准(NCI CTCAE)(4.03版)分级前记录每个周期的毒性。所有组的所有剂量减少都应基于最差

先前毒性。

[0181] 当它是由于允许从研究治疗相关的毒性中恢复时,给药可以保持最多至2周。如果从毒性恢复所需的时间超过2周,除非患者从研究治疗中受益,否则患者应从研究停止,在这种情况下,研究者和发起者之间应关于继续的风险和益处来讨论患者在研究上的继续。如果奥沙利铂在第1组招募的患者中耐受性不好,则可停止奥沙利铂,并且患者可根据研究者的判断继续接受MM-398+5-FU/LV。

[0182] 如果在研究期间患者的剂量由于毒性而减少,则在研究期间应该保持减少;剂量再提高至较早的剂量是不允许的。任何有2次剂量减少并经历了需要第三次剂量减少的不良事件的患者必须从研究治疗停止。

[0183] 剂量修改

[0184] 在每次给药前,患者必须具有:ANC≥1500/mm^3,WBC≥3500/mm^3,血小板计数≥100,000/mm^3并且腹泻≤1级。

[0185] 应延迟治疗以提供充足时间来恢复至上述水平,并且在恢复之后,应根据下表中的准则施用治疗。如果患者患有发热性中性粒细胞减少症,则ANC必须消退到≥1500/mm^3并且患者必须从感染恢复。对于3级或4级非血液毒性,治疗应延迟,直到它们消退到1级或基线。以下第1组(表3)和第2组(表6至14)的表中存在方案内每种单独治疗剂量调整的准则。在患者经历输注反应的情况下,应遵循体系准则或针对输注反应管理所提供的准则。

[0186] 对于以下所有表格,如果需要减少2次以上的剂量,或如果需要MM-398减少低于35mg/m^2,患者应从研究治疗退出。亚叶酸不需要对毒性进行剂量调整。必须在每次5-FU给药之前立即给予亚叶酸;因此,如果5-FU剂量持续,亚叶酸剂量也应该保持。

[0187] 由于MM-398或5-FU毒性导致需要治疗停止将导致研究停止。然而,对于第1组,仅需要停止奥沙利铂(例如神经病)的毒性将导致可以选择继续使用MM-398+5-FU/LV进行研究治疗,仅用于所有未来的给药。

[0188] 第1组剂量修改

[0189] ONIVYDE的开始剂量将是60mg/m^2,5FU 2400mg/m^2,LV400mg/m^2以及奥沙利铂85mg/m^2或60mg/m^2。对于任何III-IV级血液毒性,所有药剂的剂量减少将减少25%。对于持续的毒性,尽管第一次剂量减少,并且所有试剂将发生另外25%的剂量减少。然后进一步的毒性将导致试验停止。

[0190] 对于非血液学毒性来说,除了与药物相关的特定毒性(即5FU手足综合征和奥沙利铂神经病),剂量减少将是与针对血液毒性的相同剂量方案,将如表3所示。

[0191] 表3:第1组剂量修改

[0192]

CTCAE 等级的最差毒性	MM-398	5-FU	奥沙利铂
血液毒性			
2 级中性粒细胞减少症 (ANC <1500 个细胞/ mm^3 - 1000 个细胞/ mm^3)	先前剂量的 100 %	先前剂量的 100 %	第 1 次发生: 先前剂量的 100%
3 级或 4 级中性粒细胞减少症 (ANC ≤ 1000/mm^3) 或发热性中性粒细胞减少症 [a]	第 1 次发生: 剂量减少到 45 mg/m^2 第 2 次发生: 剂量减少到 35 mg/m^2	第 1 次发生: 剂量减少 25% 第 2 次发生: 剂量再减少 25%	第 1 次发生: 剂量从 85 mg/ m^2 减少至 65 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 第 2 次发生: 剂量从 65 mg/ m^2 减少至 50 mg/m^2 或从 45 mg/m^2

[0193]

			减少至 35 mg/m^2
≥2 级血小板减少症 (2 级：血小板≤ 75,000/mm^3 – 50,000/mm^3 或者 3-4 级：血小板< 50,000/mm^3)	如果 2 级：先前剂量的 100% 如果≥3 级： 第 1 次发生：剂量减少到 45 mg/m^2 第 2 次发生：剂量减少到 35 mg/m^2	如果 2 级：先前剂量的 100% 如果≥3 级： 第 1 次发生：剂量减少 25% 第 2 次发生：剂量再减少 25%（原始剂量的 50%）	第 1 次发生：剂量从 85 mg/ m^2 减少至 65 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 第 2 次发生：剂量从 65 mg/ m^2 减少至 50 mg/m^2 或从 45 mg/m^2 减少至 35 mg/m^2
其他血液学毒性未在上面具体列出	如果≤2 级：先前剂量的 100% 如果≥3 级： 第 1 次发生：剂量减少到 45 mg/m^2 第 2 次发生：剂量减少到 35 mg/m^2	如果≤2 级：先前剂量的 100% 如果≥3 级： 第 1 次发生：剂量减少 25% 第 2 次发生：剂量再减少 25%	如果≤2 级：先前剂量的 100% 如果≥3 级： 第 1 次发生：剂量从 85 mg/ m^2 减少至 65 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 第 2 次发生：剂量从 65 mg/ m^2 减少至 50 mg/m^2 或从 45 mg/m^2 减少至 35 mg/m^2
除了虚弱的非血液毒性和 3 级厌食 [b]			
1 级或 2 级，包括腹泻 [c]	先前剂量的 100 %	先前剂量的 100%，除了 2 级手足综合征、2 级心脏毒性或任何级别的神经小脑毒性	先前剂量的 100 %
3 级或 4 级，包括腹泻 [d] (除恶心和呕吐)	第 1 次发生：剂量减少到 45 mg/m^2 第 2 次发生：剂量减少到 35 mg/m^2	第 1 次发生：剂量减少 25% 第 2 次发生：剂量再减少 25% *除 3 级或 4 级手足综合征	第 1 次发生：剂量从 85 mg/ m^2 减少至 65 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 第 2 次发生：剂量从 65 mg/ m^2 减少至 50 mg/m^2 或从 45 mg/m^2 减少至 35 mg/m^2
3 级或 4 级恶心和/或呕吐，虽然进行止吐疗法	优化止吐药疗法和第 1 次发生：剂量减少到 45	优化止吐疗法并且将剂量减少 25%；如何患者已	第 1 次发生：剂量从 85 mg/ m^2 减少至 65 mg/m^2

[0194]

	mg/m^2 第 2 次发生: 剂量减少到 35 mg/m^2	接受减少的剂量, 则再将剂量减少 25%	或从 60 mg/m^2 减少至 45 mg/m^2 第 2 次发生: 剂量从 65 mg/m^2 减少至 50 mg/m^2 或从 45 mg/m^2 减少至 35 mg/m^2
2 级手足综合征	先前剂量的 100%[d]	第 1 次发生: 剂量减少 25% 第 2 次发生: 剂量再减少 25%	先前剂量的 100%
3 级或 4 级手足综合征	第 1 次发生: 剂量减少到 45 mg/m^2 第 2 次发生: 剂量减少到 35 mg/m^2	停止疗法	无剂量需要修改
任何等级的神经小脑或≥2 级心脏毒性	无剂量需要修改[e]	停止疗法	无剂量需要修改
感觉神经病	无剂量需要修改[e]	无剂量需要修改[e]	2 级, 持续: 剂量从 85 mg/m^2 减少至 60 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 3 级, 在下一个周期前恢复: 剂量从 85 mg/m^2 减少至 60 mg/m^2 或从 60 mg/m^2 减少至 45 mg/m^2 3 级, 持续: 停止疗法 4 级: 停止疗法

[0195] [a]考虑针对经历≥3级中性粒细胞减少症或发热性中性粒细胞减少症的患者使用G-CSF。

[0196] [b]虚弱和3级厌食无需剂量修改

[0197] [c]1级腹泻:2-3次大便/天>治疗前;2级腹泻:4-6次大便/天>治疗前

[0198] [d]3级腹泻:7-9次大便/天>治疗前;4级腹泻:>10次大便/天>治疗前

[0199] 第2组剂量修改

[0200] 当它是由于允许从研究治疗相关的毒性中恢复时,给药可以保持最多至3周。如果从毒性恢复所需的时间超过3周,除非患者从研究治疗中受益,否则患者应从研究停止,在这种情况下,研究者和发起者或其设计者之间应关于继续的风险和益处来讨论患者在研究上的继续。

[0201] 如果在研究期间患者的剂量由于毒性而减少,则在研究期间应该保持减少;剂量

再提高至较早的剂量是不允许的。任何有2次剂量减少并经历了需要第三次剂量减少的不良事件的患者必须从研究治疗停止。

[0202] 将监测输注反应。输注反应将根据美国国家癌症研究所CTCAE(4.0版)关于过敏反应/输注反应和过敏性反应的定义进行定义,如以下所定义:

[0203] 表4

[0204]

1级: 短时间潮红或皮疹，药物热 <38 °C (<100.4 °F)；提示干预
2级: 提示干预或输注中断；立即对症状治疗做出反应(例如，抗组织胺、NSAIDS、镇静剂)；提示预防性用药<24小时
3级: 有症状的支气管痉挛，发生或不发生风疹；提示不经肠干预；过敏相关性浮肿/血管性水肿；血压过低
4级: 危及生命的后果；提示紧急干预

[0205] 对于输注反应的管理,应使用研究场所政策或以下治疗准则。

[0206] 表5

[0207]

1级 ● 输注速率减慢50% ● 每15分钟监测患者的病况恶化情况

[0208]

2级 ● 停止输注 ● 静脉内施用50 mg盐酸苯海拉明，口服对乙酰氨基酚650 mg和氧气 ● 一旦输注反应消退，以先前速率的50%重新开始输注 ● 每15分钟监测患者的病况恶化情况 ● 对于所有后续输注，预先静脉内施用盐酸苯海拉明25 mg-50 mg
3级 ● 停止输注并且从患者取下输注管 ● 施用盐酸苯海拉明50 mg(静脉内)，地塞米松10 mg(静脉内)，针对支气管痉挛的支气管扩张剂，以及根据医疗需要施用其他药物或氧气 ● 不允许再用MM-398进行治疗
4级 ● 停止输注并且从患者取下输注管 ● 如提示支气管痉挛，则施用肾上腺素、支气管扩张剂或氧气 ● 施用盐酸苯海拉明50 mg(静脉内)、地塞米松10 mg(静脉内) ● 考虑留院观察 ● 不允许再用MM-398进行治疗

[0209] 对于经历1级或2级输注反应的患者,遵医嘱,将来输注可以减低速率(120分钟内)施用。

[0210] 对于经历第2次1级或2级输注反应的患者,静脉内施用地塞米松10mg。所有后续输注都应当预先给与盐酸苯海拉明50mg(静脉内)、地塞米松10mg(静脉内)和对乙酰氨基酚650mg(口服)。

[0211] 针对血液毒性的MM-398剂量调整

[0212] 在开始新一周期的疗法之前,患者必须具有:

[0213] ●ANC>1500/mm^3

[0214] ●血小板计数>100,000/mm^3

[0215] 应延迟治疗以提供充足时间来恢复,并且在恢复之后,应根据下表中的准则施用治疗。如果患者患有发热性中性粒细胞减少症,则ANC必须消退到>1500/mm^3并且患者必须从感染恢复。

[0216] 表6:针对中性粒细胞计数的MM-398剂量调整

[0217]

ANC: 细胞/mm^3 (最差CTCAE 等级)	新周期的 MM-398 剂量		
	A 组: 非 UGT1A1*28 纯合型患者	A 组: UGT1A1*28 纯合型患者 C 组: UGT1A1*28 纯合型患者	C 组: UGT1A1*28 纯合型患者
≥1000 至 1999 (1 级或 2 级)	先前剂量的 100%	先前剂量的 100%	先前剂量的 100%
< 1000 (3/4 级)或发热性中性粒细胞减少症	剂量减少 20 mg/m^2 至最低剂量 40 mg/m^2	对于第 1 次发生, 剂量减少到 45 mg/m^2, 并且对于第 2 次发生, 剂量减少到 35 mg/m^2	对于第 1 次发生, 剂量减少到 45 mg/m^2, 并且对于第 2 次发生, 剂量减少到 35 mg/m^2

[0218] 表7:针对其他血液学毒性MM-398剂量调整

[0219]

最差毒性 CTCAE 等级	新周期的 MM-398 剂量		
	A 组: 非 UGT1A1*28 纯合型患者	A 组: UGT1A1*28 纯合型患者 C 组: UGT1A1*28 纯合型患者	C 组: UGT1A1*28 纯合型患者
≤2 级	先前剂量的 100%	先前剂量的 100%	先前剂量的 100%
3/4 级	剂量减少 20 mg/m^2 至最低剂量 40 mg/m^2	对于第 1 次发生, 剂量减少到 45 mg/m^2, 并且对于第 2 次发生, 剂量减少到 35 mg/m^2	对于第 1 次发生, 剂量减少到 45 mg/m^2, 并且对于第 2 次发生, 剂量减少到 35 mg/m^2

[0220] 针对非血液毒性的MM-398剂量调整

[0221] 应延迟治疗直到腹泻消退到≤1级,并且对于其他3级或4级非血液毒性,直到其消退到1级或基线。有关针对药物相关性腹泻和其他3级或4级非血液毒性的MM-398剂量调整准则提供于下。应如以上所描述来处理输注反应。

[0222] 表8:针对腹泻的MM-398剂量调整

[0223]

最差毒性 CTCAE 等级	新周期的 MM-398 剂量 [a]		
	A 组: 非 UGT1A1*28	A 组:	C 组:

[0224]

	纯合型患者	UGT1A1*28 纯合型患者 C 组：非 UGT1A1*28 纯合型患者	UGT1A1*28 纯合型患者
1 级或 2 级(2-3 次大便/天>治疗前或 4-6 次大便/天>治疗前)	先前剂量的 100%	先前剂量的 100%	先前剂量的 100%
3 级(7-9 次大便/天> 治疗前)或 4 级(>10 次大便/天> 治疗前)	剂量减少 20 mg/m^2 至最低剂量 40 mg/m^2	对于第 1 次发生，剂量减少到 45 mg/m^2，并且对于第 2 次发生，剂量减少到 35 mg/m^2	对于第 1 次发生，剂量减少到 45 mg/m^2，并且对于第 2 次发生，剂量减少到 35 mg/m^2

[0225] 表9：针对除腹泻、虚弱和3级厌食外的其他非血液毒性的MM-398剂量调整

[0226]

最差毒性 CTCAE 等级	新周期的 MM-398 剂量		
	A 组：非 UGT1A1*28 纯合型患者	A 组：UGT1A1*28 纯合型患者 C 组：非 UGT1A1*28 纯合型患者	C 组：UGT1A1*28 纯合型患者
1 级或 2 级	先前剂量的 100%	先前剂量的 100%	先前剂量的 100%
3 级或 4 级(除恶心和呕吐)	剂量减少 20 mg/m^2 至最低剂量 40 mg/m^2	对于第 1 次发生，剂量减少到 45 mg/m^2，并且对于第 2 次发生，剂量减少到 35 mg/m^2	对于第 1 次发生，剂量减少到 45 mg/m^2，并且对于第 2 次发生，剂量减少到 35 mg/m^2
3 级或 4 级恶心和或呕吐，虽然进行止吐疗法	优化止吐疗法并且剂量减少 20 mg/m^2 至最低剂量 40 mg/m^2	优化止吐疗法**并且**将剂量减少到 40 mg/m^2	优化止吐疗法**并且**将剂量减少到 40 mg/m^2

[0227] 5-FU和亚叶酸剂量修改

[0228] 有关5-FU剂量调整的准则提供于下。亚叶酸不需要对毒性进行剂量调整。必须在每次5-FU给药之前立即给予亚叶酸；因此，如果5-FU剂量持续，亚叶酸剂量也应该保持。在患者经历输注反应的情况下，应使用体系准则或针对MM-398输注反应管理所提供的准则。

[0229] 针对血液毒性的5-FU剂量调整

[0230] 在一个周期的下一次剂量之前或在起始新一周期的疗法之前，患者必须具有：

[0231] ●ANC≥1500/mm^3

[0232] ●WBC≥3500/mm^3

[0233] ●血小板计数≥75,000/mm^3(根据欧洲有关5-FU的产品特征说明书,血小板在起始疗法之前应恢复到≥100,000/mm^3)

[0234] 应延迟治疗以提供充足时间来恢复,并且在恢复之后,应根据下表中提供的准则施用治疗。周期持续时间固定为6周,并且如果患者因毒性而不能接受D8、D15或D22剂量,则应考虑跳过所述剂量。

[0235] 表10:针对血液毒性的5-FU剂量调整(B组和C组)

[0236]

ANC (细胞/mm^3)		血小板(细胞/mm^3)	D8、D15、D22的5-FU剂量[a]	新周期的5-FU剂量[a]
≥1000	以及	≥50,000	先前剂量的100%	先前剂量的100%
500 - 999	或	<50,000 – 25,000	保持剂量;当消退时,剂量减少25%[b]	剂量减少25%[b]
< 500或发热性中性粒细胞减少症	或	<25,000或伴随出血的血小板减少症	保持剂量;当消退时,剂量减少25%[b]	剂量减少25%[b]

[0237] [a]所有剂量修改都应基于最差先前毒性

[0238] [b]需要超过2次剂量减少的患者必须退出研究

[0239] 针对非血液毒性的5-FU剂量调整

[0240] 应延迟治疗直到所有3级或4级非血液毒性消退到1级或基线。有关5-FU相关毒性的剂量调整准则提供于下。周期持续时间固定为6周,并且如果患者因毒性而不能接受D8、D15或D22剂量,则应考虑跳过所述剂量。

[0241] 表11:针对除虚弱和3级厌食外的其他非血液毒性的5-FU剂量修改[c]

[0242]

最差毒性CTCAE等级	D8、D15、D22的5-FU剂量[a]	新周期的5-FU剂量[a]
1级或2级	先前剂量的100%,除了2级手足综合征、2级心脏毒性或任何级别的神经小脑毒性	先前剂量的100%,除了2级手足综合征、2级心脏毒性或任何级别的神经小脑毒性
2级手足综合征	剂量减少25%[b]	剂量减少25%[b]
任何等级的神经小脑或≥2级心脏毒性	停止疗法	停止疗法
3级或4级	保持剂量;当消退时,剂量减少25%[b],除3级或4级手足综合征之外	剂量减少25%[b],除3级或4级手足综合征之外
3级或4级手足综合征	停止疗法	停止疗法

[0243] [a]所有剂量修改都应基于最差先前毒性

[0244] [b]需要超过2次剂量减少的患者必须退出研究

[0245] [c]虚弱和3级厌食无需剂量修改

[0246] UGT1A1*28阳性患者的MM-398剂量修改(第1组和第2组)

[0247] 在筛选期间针对UGT1A1*28状态对患者进行测试,但是在MM-398的初始剂量之前不需要测试的结果。所有患者将以80mg/m^2(盐)开始给药,但对于UGT1A1*28 7/7基因型为阳性(即纯合)的患者将来的剂量可能减少。对于接受80mg/m^2(盐)的MM-398的第1部分的患者:取决于第一次剂量后所见的总体安全性概况,在PI、发起者和医疗监测者之间讨论后,剂量可减少至60mg/m^2(盐)。由于UGT1A1*28纯合性,在第1周期期间接受剂量减少的任何第1部分患者将不能对所述队列进行评估并且被替换。

[0248] 第3组剂量修改

[0249] 由于与nab-紫杉醇和吉西他滨相关的毒性,所需的剂量水平减少应遵循表12中概述的准则。

[0250] 表12:nab-紫杉醇和吉西他滨的剂量水平减少

[0251]

剂量水平	Nab-紫杉醇(mg/m^2)	吉西他滨(mg/m^2)
全剂量	125	1000
第1次剂量减少	100	800
第2次剂量减少	75	600
如果需要另外的剂量减少	停止	停止

[0252] 表13提供了中性粒细胞减少症和血小板减少症的推荐剂量修改,并且表14提供了与其他毒性相关的调整。

[0253] 表13:在中性粒细胞减少症和/或血小板减少症的每个周期的开始或周期内的nab-紫杉醇和吉西他滨剂量修改。

[0254]

周期日期	ANC(细胞/mm^3)		血小板计数(细胞/mm^3)	Nab-紫杉醇 / 吉西他滨
第 1 天	<1500	或者	< 100,000	延迟给药, 直到恢复
第 8 天	500 至< 1000	或者	50,000 至 < 75,000	减少 1 剂量水平
	< 500	或者	< 50,000	停用剂量
第 15 天: 如果减少或不修改给予第 8 天剂量:				
	500 至< 1000	或者	50,000 至 < 75,000	从第 8 天减少 1 剂量水平
	< 500	或者	< 50,000	停用剂量
第 15 天: 如果停用第 8 天剂量:				
	≥ 1000	或者	≥ 75,000	从第 1 天减少 1 剂量水平
	500 至< 1000	或者	50,000 至 < 75,000	从第 1 天减少 2 剂量水平
	< 500	或者	< 50,000	停用剂量

[0255] ANC=绝对中性粒细胞计数

[0256] 表14:针对其他不良药物反应nab-紫杉醇和吉西他滨剂量修改

[0257]

不良药物反应	Nab-紫杉醇	吉西他滨
发热性中性粒细胞减少症: 3级或4级	停用直到发热消退并且ANC≥1500; 以下一个较低剂量水平重新开始	
周围神经病变: 3级或4级	停用直到改善≤1级; 以下一个剂量水平重新开始	无剂量减少
皮肤毒性: 2级或3级	减少到下一个较低剂量水平; 如果毒性持续则停止治疗	
胃肠毒性 3级粘膜炎或腹泻	停用直到改善至≤1级; 在下一个剂量水平重新开始	

[0258] 疾病评估

[0259] 根据实体肿瘤响应评估标准(RECIST)版本1.1评估肿瘤响应,以通过CT或MRI建立疾病进展。此外,可执行研究者认为适当的其他影像程序,以评定肿瘤介入的地点。整个研究过程中必须使用相同的评定方法。研究者应根据RECIST v1.1准则选择目标和非目标病灶。跟进测量和总体反应也应该符合这些准则。

[0260] 肿瘤评定应完成,直到确定患者患有进行性疾病(符合RECISTv1.1)。对于没有在治疗结束时根据RECIST v.1.1记录疾病进展的患者,影像研究应持续进行到每8周的随访期,直到记录疾病进展为止。建议继续按计划表进行影像学随访,以减少对疾病的实验性治疗的影响评估的潜在偏差。

[0261] EORTC-QLQ-C30和EQ-5D-5L(仅第2部分)

[0262] 健康相关生存质量(HRQL)通过EORTC-QLQ-C30和EQ-5D-5L仪器评定。EORTC-QLQ-C30是在多元文化临床研究情况下癌症患者的生活质量的可靠并且有效的量度。它合并了九个多项量表:五个功能量表(身体功能、角色功能、认知功能、情感功能以及社交功能);三个症状量表(疲劳、疼痛以及恶心和呕吐);以及一个总体健康和生活品质量表。还包括若干单项症状量度。EQ-5D是通用的、基于偏好的HRQL度量。EQ-5D-5L描述系统包括以下五个维度:移动性、自我照顾、日常活动,疼痛/不适和焦虑/抑郁。每个维度具有5个层次:没有问题、轻微的问题、中等问题、严重的问题、无法做到。

[0263] 要求患者在评定表中列出的时间点完成两份问卷。在研究药物施用前,评定应在患者将接受研究药物的那天完成。只有能够确认调查问卷翻译的那些患者将被要求完成调查问卷。

[0264] 功效分析

[0265] 在评定功效中,每个包含MM-398的组与对照组进行比较。功效比较使用分层分析,具有随机化阶层。每个比较使用0.10水平的单侧测试来评估包含MM-398的组是否改善了功效参数。为了描述的目的,置信区间呈双面95%的水平。假设测试验和置信区间不进行用于多重比较的调整。主要功效比较基于ITT人群,其中包括所有随机患者。

[0266] 根据RECIST v1.1测量肿瘤评估。对于每位患者,无进展存活时间被确定为从随机化的时间(对于第1部分患者,参考开始时间将是第一研究药物的日期)到首次记录的放射性病变进展(PD)(根据使用RECIST 1.1的研究者),或因任何原因死亡,以先到者为准。如果进展或死亡在非PD上次肿瘤评定后大于12周的时间点发生,则无进展存活时间在最后一次

非PD肿瘤评定时审查。

[0267] 当所有随机患者的第24周无进展状态可以被确定时进行主要分析，预期在最后一位患者被随机化后大约24周。当PFS事件发生在至少120名(即80％的随机患者)患者中时，对PFS和其他终点进行后续分析。

[0268] 主要功效分析

[0269] 在意向性治疗(ITT)分析中，如果患者有数据表明患者在24周没有进展，则认为患者在24周时已经达到无进展存活期。也就是说，如果在第24周或以后在进展或新的抗癌疗法之前至少有一次非PD评定，则认为患者是响应者。

[0270] 如果进展或死亡发生在非PD最后肿瘤评定后大于12周的时间点，则患者不符合24周无进展达成标准(例如，患者进展/死于第24周，患者在第24周之前被审查)。

[0271] 对于每一组，24周时的无进展存活达成率通过满足24周达成标准的患者数量除以组中ITT患者的数量来估计。速率估计值以相应的95％置信区间表示。测试评定每个包含MM-398的组相对于对照组的速率的增加，合并随机化分层因子，显著性水平为0.10。

[0272] 次要功效测量

[0273] 使用Kaplan-Meier方法，针对每个组，描述性总结无进展存活(PFS)。介绍中位PFS时间和相应的95％置信界限。对于每个包含MM-398的组，将PFS与对照组进行比较。使用单侧分层对数秩检验对PFS的差异进行假设测试。使用分层Cox模型估计PFS的危害比(95％置信区间)。

[0274] 最佳总体反应(BOR)被定义为从研究药物开始直到疾病进展记录的最佳反应。没有基线后肿瘤评定的患者被认为是不可评估BOR的。为了将BOR分类为稳定的疾病(SD)，应该从随机化至少6周后进行合格的SD评定。客观反应率(ORR)定义为相对于可评估患者总数，具有特征为完全反应(CR)或部分反应(PR)的BOR的患者比例。只有基线时患有可测量疾病的患者将被纳入客观反应的分析。对每个治疗组，计算客观反应率和其相应的95％CI估计。对于每个包含MM-398的组，将ORR与对照组进行比较。每个包含MM-398的组与对照组之间的客观反应率的差异提供了95％CI。Cochran-Mantel-Haenszel测试，通过随机阶层调整，用于比较客观反应率。

[0275] 计算CA19-9中的最大减少量(从基线的变化％)，包括按时间段的分析(直至第8、16和24周访视)。使用最大限度的减少的3个阈值进行CA 19-9响应分析：≥20％、≥50％、≥90％。无基线后CA19-9测量的患者被视为无响应者。只有基线下CA 19-9升高(>37U/mL)的患者被纳入CA19-9响应的分析中。对于每个阈值和时间段，通过治疗组估计CA19-9响应的比例以及相应的95％置信区间。

[0276] 总存活期(OS)是从随机化到由于任何原因死亡的日期的时间。分析时存活或失访的患者将在最后已知的存活日期进行审查。使用Kaplan-Meier方法，针对每个组，描述性总结OS。对于每个包含MM-398的组，将OS与对照组进行比较。使用单侧分层对数秩检验对OS的差异进行假设测试。使用分层Cox模型估计PFS的危害比(95％置信区间)。

[0277] 生活质量分析

[0278] 针对每种生活质量仪器，使用分析群体中的患者进行生活质量分析(EORTC-QLC-C30，EQ-5D-5L)。EORTC-QLQ-30和EQ-5D-5L结果将在治疗组的每次访视时进行总结。

[0279] 针对施用的每种EORTC QLQ-C30，分数计算为以下量表：总体健康状态、身体功能、

角色功能、情感功能、认知功能、社会功能、疲劳、恶心和呕吐、疼痛、呼吸困难、失眠、食欲不振、便秘、腹泻、经济困难。

[0280] 如EORTC QLQ-C30评分手册(Fayers,Aaronson,Bjordal,Curran,&Groenvald,2001)中所述进行评分。将线性变换应用于原始分数,以便所有量表的报告得分的范围将为0-100。汇总统计针对每个分量表呈现。为每个EQ-5D-5L评定计算健康状况指数汇总值。汇总统计针对汇总健康状态指数呈现。对于每个EQ-5D-5L属性(移动性、自我照顾、日常活动、疼痛/不适和焦虑/抑郁),将响应列表显示。

[0281] 安全性分析

[0282] 将使用安全性群体进行安全性分析(不良事件和实验室分析)。不良事件通过MedDRA 17.1版或更高版报告。根据NCI CTCAE 4.03版将毒性分级。

[0283] 第1部分的患者的安全性分析将包括剂量限制毒性事件的汇总。

[0284] 治疗紧急不良事件和安全性结果的时期是从第一次研究药物施用到最后次研究药物施用后30天。如果不良事件在第一次研究药物施用的日期开始,并且无时间记录,则事件被认为是治疗发生的。

[0285] 将呈现所有不良事件、治疗前不良事件、治疗发生的不良事件(TEAE)、严重不良事件、导致研究药物停止的不良事件、研究药物相关的TEAE以及3/4级TEAE的表格。通过系统器官分类和优选术语将汇总不良事件。患者将列出所有不良事件数据。

[0286] 实验室数据按周期显示。使用所有可用数据评定异常实验室值并且根据NCI CTCAE毒性等级指定毒性分级,如果标准可以这样做。报告连续实验室数据的最大和最小降低/增加。评定异常实验室值的频率和百分比(L/ULN,2*L/ULN)。汇总转向最严重的毒性等级。

[0287] 根据时间点,将生命体征和ECG从基线的变化列表显示。可如SAP中详细描述的那样进行另外分析。

[0288] 根据时间点,将生命体征从基线的变化列表显示。可如SAP中详细描述的那样进行另外分析。

[0289] 生物标记物亚组分析

[0290] 进行分析以评定潜在生物标记物(来自血浆和存档组织)与功效参数(ORR,目标病灶大小的变化百分比和PFS或视情况而定)之间的关系。当适当时进行图像显示。

[0291] 药代动力学分析

[0292] MM-398和奥沙利铂的血浆浓度可用于表征PK参数。由于稀稀落落的PK采样计划表,可基于先前估计(MM-398)或公开的(奥沙利铂)群体PK模型参数的经验贝叶斯估计方法估计个体患者的PK参数。通过比较药物暴露的最小二几何平均比(LS-GMR),使用模型模拟暴露,例如$C_{最大}$,AUC(曲线下面积)来检查MM-398与奥沙利铂之间的任何可能的相互作用。NONMEM®,7.3版,用于估计单个PK参数并且模拟血浆暴露。

[0293] 实施例4:人类临床实验的抗肿瘤疗法的耐受性

[0294] 使用两个不同的剂量,在实施例3中描述的人类临床实验中评估组合脂质体伊立替康、5-FU/亚叶酸和奥沙利铂的抗肿瘤疗法的耐受性:80mg/m^2(盐)的脂质体伊立替康(MM-398)和60mg/m^2(盐)的脂质体伊立替康(MM-398)。表15汇总了在28天治疗周期中用于治疗人类中先前未治疗的(前线)胰腺癌的三种给药方案。

[0295] 表15第1部分:剂量提高表(MM-398+5-FU/LV+奥沙利铂)

[0296]

水平	奥沙利铂		5-FU/LV		MM-398 (nal-IRI)	
	剂量 (mg/m^2)[a]	给药天[c]	剂量 (mg/m^2)[b]	给药天[c]	剂量 (mg/m^2)	给药天[c]
1	60	1、15	2400/400	1、15	80	1、15
2	85	1、15	2400/400	1、15	80	1、15
-2A[d]	75	1、15	2400/400	1、15	80	1、15

[0297] a与第一剂量的nal-IRI一起的第一剂量施用:在第1部分中nal-IRI输注完成后2小时施用奥沙利铂。

[0298] b 46小时输注,不给予推注;将最后施用亚叶酸和5-FU,然后完成奥沙利铂输注

[0299] c所指示的日期是28天周期的一部分

[0300] 注意:剂量水平1和2以上的nal-IRI和5-FU/LV的剂量是NAPOLI-1 3期研究中先前使用的相同的剂量和计划表。

[0301] 初始,奥沙利铂、MM-398脂质体伊立替康、亚叶酸以及5-氟尿嘧啶的组合是上表15中的剂量水平1。针对上表15中的剂量水平1(针对80mg/m^2(盐)M-398剂量),结果汇总于表16中,从而显示在剂量水平1下,80mg/m^2(盐)的剂量的脂质体伊立替康(MM-398)与奥沙利铂和5-氟尿嘧啶/亚叶酸组合在人类中是不耐受的。

[0302] 表16:抗肿瘤疗法,其中在人类临床实验中使用80mg/m^2脂质体伊立替康与奥沙利铂/5FU/亚叶酸的组合

[0303]

患者	周期1 第1天	周期1 第15天	周期2 第1天	周期2 第15天	周期3 第1天	周期3 第15天
1	✓	✓	X	X	X	X
2	✓	R	R	R	X	X
3	✓	X	X	X	X	X
4	✓	✓	X	X	X	X
5	✓	X	X	X	X	X
6	✓	✓	R	R	R	R
7	✓	X	X	X	X	X

[0304] 表16汇总了来自治疗总共七个(7)患者的结果,如图12所示第1组的第1部分的一部分。所有七个患者满足以下指定适用的纳入标准,包括胰腺癌的诊断。

[0305] 表16中的“选自选标记”(√)表示患者接受了上表15中的剂量水平1的抗肿瘤治疗,从3个连续28天治疗周期的指定天开始:80mg/m^2脂质体伊立替康(MM-398,基于伊立替康盐酸盐三水合物盐的对应的量的剂量)、60mg/m^2奥沙利铂、400mg/m^2(1+d)亚叶酸和2,400mg/m^2 5-氟尿嘧啶,如实施例3的规程中所述。

[0306] 表16中的“R”表示患者在相应的周期和日期接受表2中剂量水平-1(以上实施例3)的抗肿瘤疗法的减少的剂量:60mg/m^2脂质体伊立替康(MM-398,基于伊立替康盐酸盐三水合物盐的对应的量的剂量)、60mg/m^2奥沙利铂、400mg/m^2(1+d)亚叶酸和2,400mg/m^2 5-氟尿嘧啶,如实施例3的规程中所述。

[0307] 表16中的“X”表示患者未接受组合脂质体伊立替康、奥沙利铂、5-氟尿嘧啶以及亚叶酸或组合脂质体伊立替康、奥沙利铂和5-氟尿嘧啶的抗肿瘤疗法。在周期1,第1天后并且

在周期1，第15天前，患者2被确定具有纯合型UGT1A1*28等位基因，并且基于实施例3的规程，在表16中表示的日期接受后续减少的剂量的抗肿瘤疗法。患者1和3-7不具有纯合型UGT1A1*28等位基因。

[0308] 表15(实施例4)中的剂量水平1的抗肿瘤疗法仅在(28天)周期1的第15天施用到这些6个患者中的2个，无患者接受大于2个连续剂量的剂量水平1，并且没有患者在周期1后接受此疗法。

[0309] 因此，如表16中所提及，组合80mg/m^2的剂量的脂质体伊立替康和60mg/m^2奥沙利铂以及2,400mg/m^2和400mg/m^2的剂量的5-氟尿嘧啶和(l+d)亚叶酸的抗肿瘤疗法在人体临床实验中耐受性不佳(导致剂量限制性毒性)。组合80mg/m^2的剂量的脂质体伊立替康和60mg/m^2奥沙利铂以及2,400mg/m^2和400mg/m^2的剂量的5-氟尿嘧啶和(l+d)亚叶酸的抗肿瘤疗法的实施例包括表15中的疗法。

[0310] 相比之下，如下表18中所提及，组合60mg/m^2的剂量的脂质体伊立替康和60mg/m^2奥沙利铂以及2,400mg/m^2和400mg/m2的剂量的5-氟尿嘧啶和(l+d)亚叶酸的抗肿瘤疗法在人体临床实验中是耐受的。具体地，将表17中的剂量水平-1(60mg/m^2(盐)M-398剂量)两次或更多连续次在实施例3中所述的临床实验中施用到多个人类患者。包括减少的60mg/m^2(盐)的脂质体伊立替康(MM-398)与奥沙利铂和5-氟尿嘧啶/亚叶酸组合的这些抗肿瘤疗法比表15中的剂量水平1在人体中耐受性更佳。在其他实施方案中，向患者施用表17中的剂量水平-2B的疗法。

[0311] 表17第1部分：剂量提高表(MM-398+5-FU/LV+奥沙利铂)

[0312]

水平	奥沙利铂		5-FU/LV		MM-398 (nal-IRI)	
	剂量 (mg/m^2)[a]	给药天[c]	剂量 (mg/m^2)[b]	给药天[c]	剂量 (mg/m^2)	给药天[c]
-1	60	1、15	2400/400	1、15	60	1、15
-2B	85	1、15	2400/400	1、15	60	1、15

[0313] a与第一剂量的MM-398一起的第一剂量施用：在第1部分中nal-IRI输注完成后2小时施用奥沙利铂。

[0314] b 46小时输注，不给予推注；将最后施用亚叶酸和5-FU，然后完成奥沙利铂输注

[0315] c所指示的日期是28天周期的一部分

[0316] 表18：抗肿瘤疗法，其中在人类临床实验中使用60mg/m^2脂质体伊立替康与奥沙利铂/5FU/亚叶酸的组合

[0317]

患者	周期 1 第 1 天	周期 1 第 15 天	周期 2 第 1 天	周期 2 第 15 天	周期 3 第 1 天
1	✓	✓	R2	R2	R2
2	✓	✓	✓		
3	✓	✓	✓		
4	✓	✓			
5	✓	✓	✓		

[0318] 表18汇总了来自治疗总共五个(5)患者的结果，如图12所示第1组的第1部分的一部分。所有五个患者满足实施例3中指定适用的纳入标准，包括胰腺癌的诊断。表18中的“选自选标记”(✓)表示患者接受了上表17中的剂量水平1的抗肿瘤治疗，从3个连续28天治疗

周期的指定天开始:60mg/m^2脂质体伊立替康(MM-398,基于伊立替康盐酸盐三水合物盐的对应的量的剂量)、60mg/m^2奥沙利铂、400mg/m^2(l+d)亚叶酸和2,400mg/m^2 5-氟尿嘧啶,如实施例3的规程中所述。

[0319] 相比于表14中的剂量水平1的抗肿瘤疗法,将表2中剂量水平-1的抗肿瘤疗法(实施例3)重复地施用到患者2和6,持续至少3次连续施用(包括患者6的4次连续施用)。

[0320] 在此研究中,将表2中剂量水平-1的抗肿瘤疗法(实施例3)在(28天)周期1的第1天和第15天施用到5个患者中的5个,在(28天)的第1天和第15天施加到4个患者中的3个,其中无剂量限制性毒性。将剂量水平-1的抗肿瘤疗法重复地施用到所有5个患者,持续至少2个连续施用。

[0321] 表18中的"选自选标记"(√)表示患者接受了上表17中的剂量水平-1的抗肿瘤治疗,从3个连续28天治疗周期的指定天开始:80mg/m^2脂质体伊立替康(MM-398,基于伊立替康盐酸盐三水合物盐的对应的量的剂量)、60mg/m^2奥沙利铂、400mg/m^2(l+d)亚叶酸和2,400mg/m^2 5-氟尿嘧啶,如实施例3的规程中所述。

[0322] 表18中的"R2"表示患者在相应的周期和日期接受剂量的抗肿瘤疗法的减少的剂量:50mg/m^2脂质体伊立替康(MM-398,基于伊立替康盐酸盐三水合物盐的对应的量的剂量)、60mg/m^2奥沙利铂、400mg/m^2(l+d)亚叶酸和1,800mg/m^2 5-氟尿嘧啶(相比于剂量水平-1剂量,减少25%),如实施例3的规程中所述。表18中的一个患者响应于II级症状(非血液学)接受这种减少的剂量,但无剂量限制毒性。

[0323] 因此,如表18中所提及,组合60mg/m^2的剂量的脂质体伊立替康和60mg/m^2奥沙利铂以及2,400mg/m^2和400mg/m^2的剂量的5-氟尿嘧啶和(l+d)亚叶酸的抗肿瘤疗法在人体临床实验中是耐受的。组合80mg/m^2的剂量的脂质体伊立替康和60mg/m^2奥沙利铂以及2,400mg/m^2和400mg/m^2的剂量的5-氟尿嘧啶和(l+d)亚叶酸的抗肿瘤疗法的实施例包括表17中的疗法。

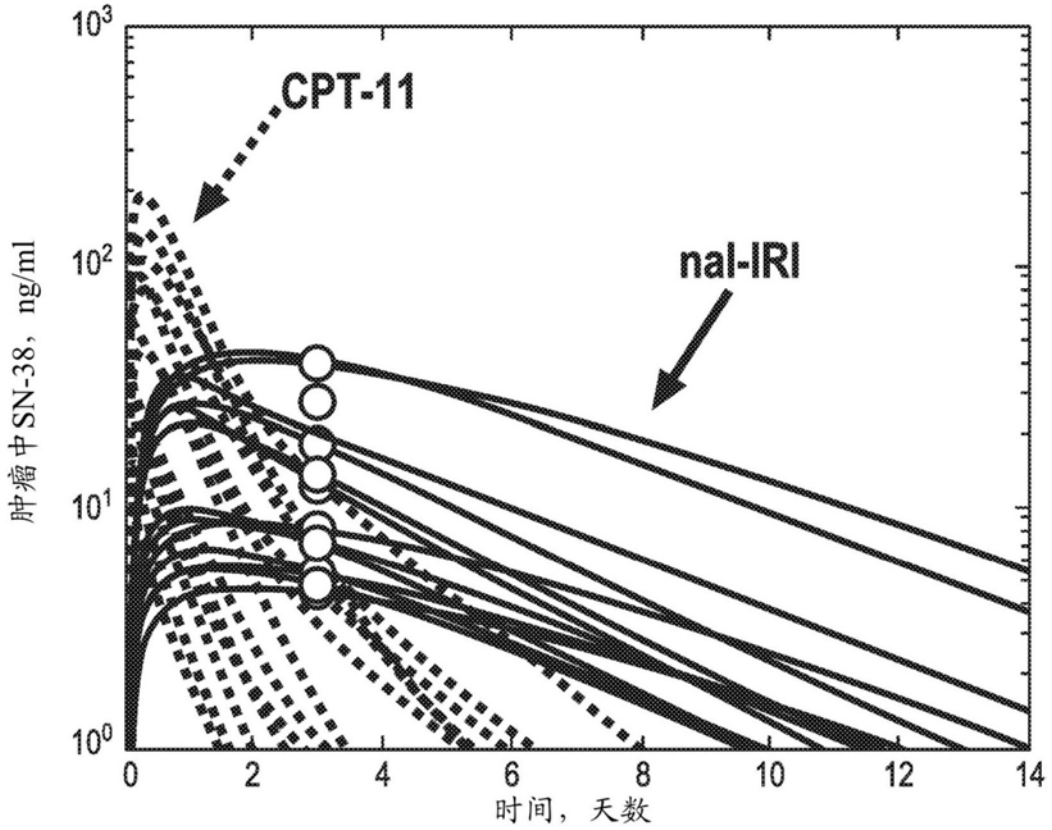
[0324] 实施例5:ONIVYDE®(伊立替康脂质体注射液)脂质体伊立替康

[0325] 本文所述的伊立替康脂质体的一个优选示例是作为ONIVYDE®销售的产品(伊立替康脂质体注射液)。ONIVYDE®是拓扑异构酶抑制剂,使用伊立替康在脂质体分散体中配制,以用于静脉使用。

[0326] 完成的ONIVYDE®产品是用于输注的白色至淡黄色不透明无菌浓缩物。它由包含伊立替康盐酸盐三水合物的脂质体的等渗分散体组成。脂质体是小的单层脂质双层囊泡,直径为大约110nm,包封作为蔗糖硫酸酯盐的呈胶凝或沉淀状态的伊立替康的含水空间。囊泡由1,2-二硬脂酰-sn-甘油-3-磷酸胆碱(DSPC)6.81mg/mL、胆固醇2.22mg/mL和甲氧基封端的聚乙二醇(MW 2000)-二硬脂酰基磷脂酰乙醇胺(MPEG-2000-DSPE)0.12mg/mL构成。每mL还包含作为缓冲液4.05mg/mL的2-[4-(2-羟乙基)哌嗪-1-基]乙磺酸(HEPES)和作为等渗剂的8.42mg/mL氯化钠。将脂质体分散在缓冲水溶液中。

[0327] ONIVYDE®产品包含封装在脂质体中的伊立替康蔗糖硫酸酯,获自伊立替康盐酸盐三水合物原料。伊立替康的化学名为(S)-4,11-二乙基-3,4,12,14-四氢-4-羟基-3,14-二氧代1H-吡喃并[3',4':6,7]-吲哚并[1,2-b]喹啉-9-基-[1,4'二哌啶]-1'-羧酸酯。ONIVYDE®的剂量可根据用于制备伊立替康脂质体的伊立替康三水合物盐酸盐原料的

等效量或基于脂质体中伊立替康的量计算。每克伊立替康三水合物盐酸盐中存在约866mg的伊立替康。例如，基于伊立替康盐酸盐三水合物原料的量，80mg的ONIVYDE®剂量在最终产品中实际上包含约约0.866x(80mg)的伊立替康(即，基于伊立替康盐酸盐原料的重量，80mg/m^2的剂量的ONIVYDE®在最终产品中临床上等于约70mg/m^2的伊立替康)。每个10mL单剂量小瓶包含43mg伊立替康游离碱，浓度为4.3mg/mL。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nal-IRI
肿瘤中SN-38，ng/ml
10^3
10^2
10^1
10^0
0
2
4
6
8
10
12
14
时间，天数

图1A

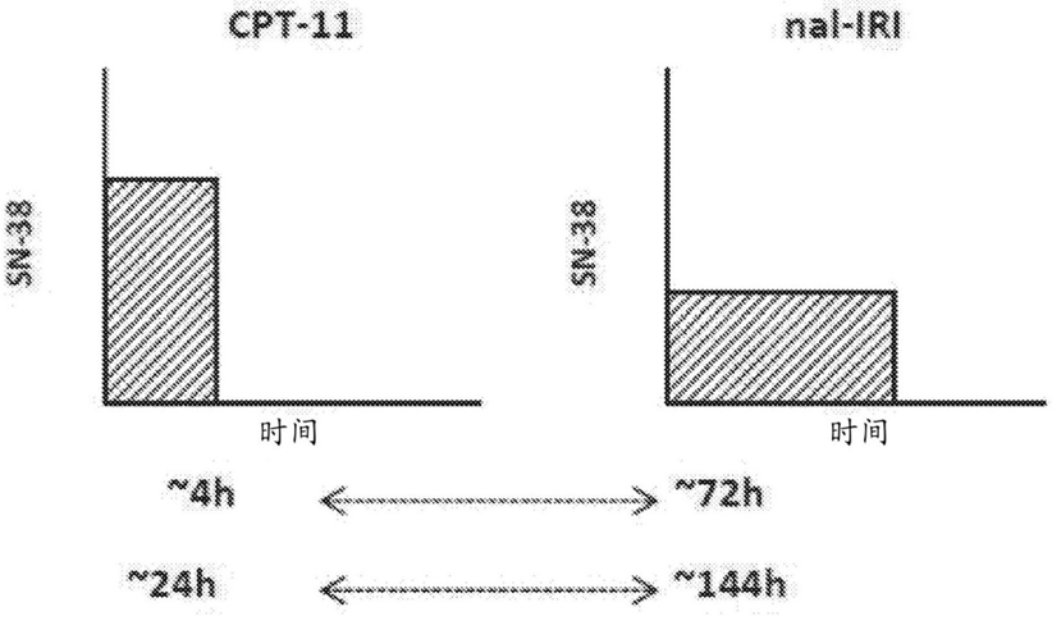
CPT-11
nal-IRI
SN-38
SN-38
时间
时间
~4h
~72h
~24h
~144h

图1B

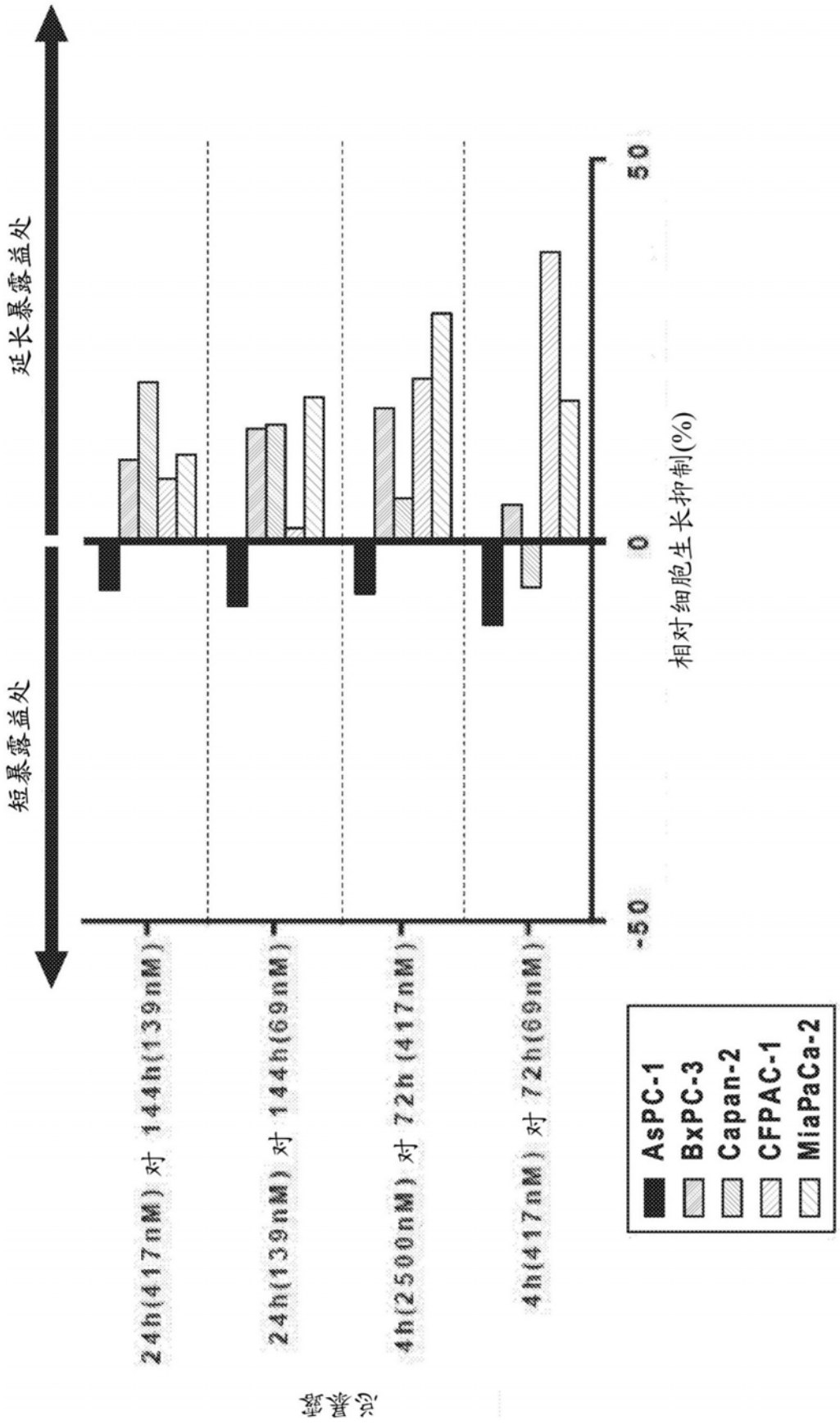
延长暴露益处
短暴露益处
相对细胞生长抑制(%)
50
0
-50
24h(417nM)对144h(139nM)
24h(139nM)对144h(69nM)
4h(2500nM)对72h(417nM)
4h(417nM)对72h(69nM)
AsPC-1
BxPC-3
Capan-2
CFPAC-1
MiaPaCa-2

图1C

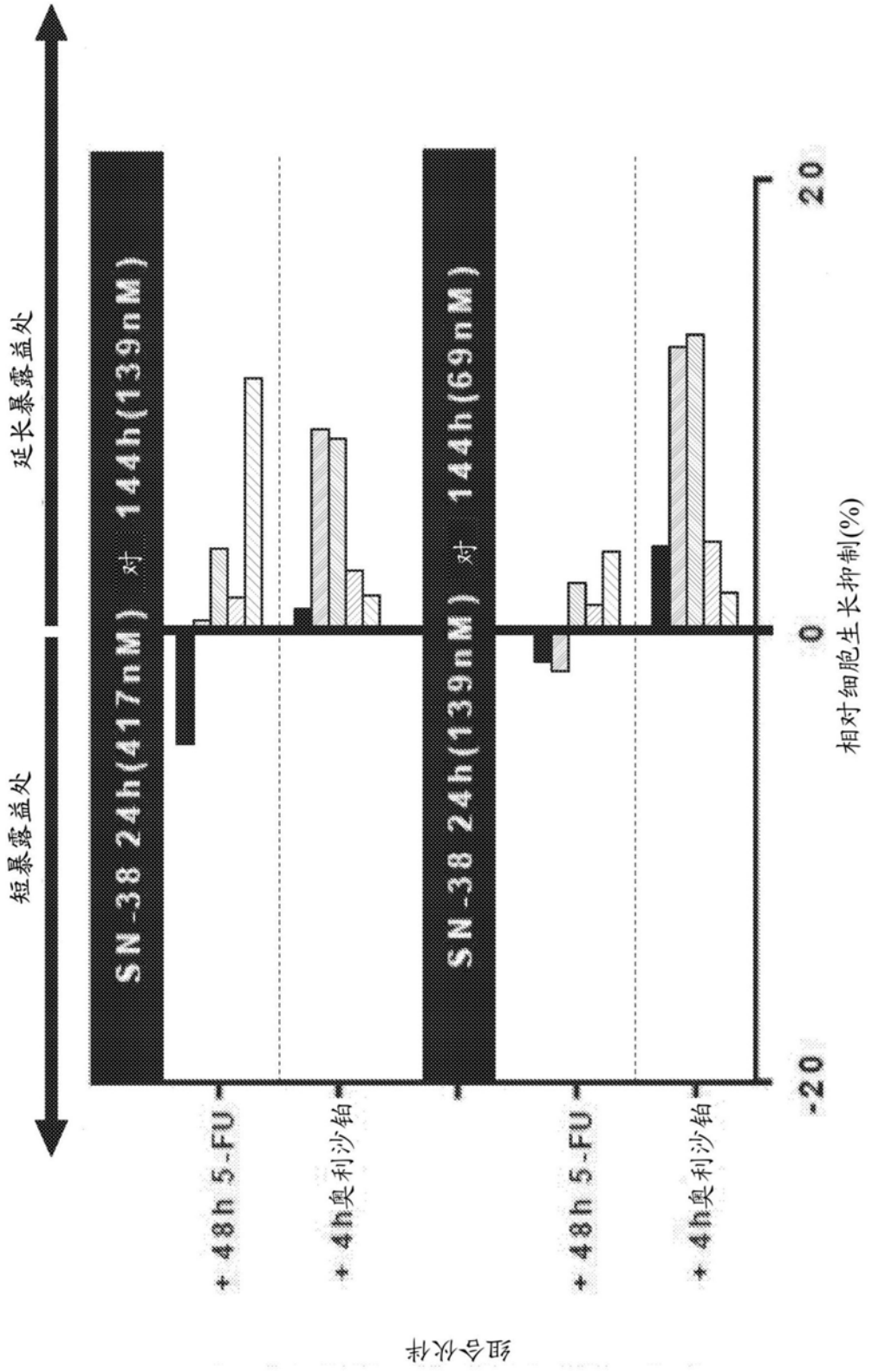
延长暴露益处
短暴露益处
SN-38 24h(417nM) 对 144h(139nM)
SN-38 24h(139nM) 对 144h(69nM)
+ 48h 5-FU
+ 4h奥利沙铂
+ 48h 5-FU
+ 4h奥利沙铂
20
0
-20
相对细胞生长抑制(%)
组合伙伴

图1D

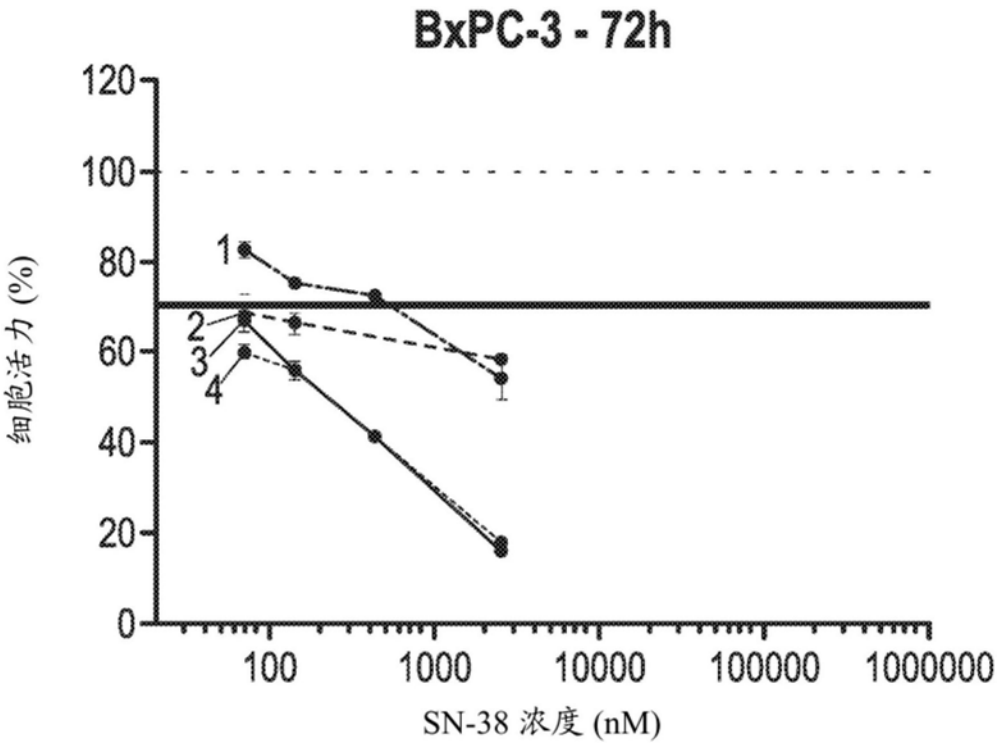
BxPC-3 - 72h
细胞活力 (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 浓度 (nM)

图2A

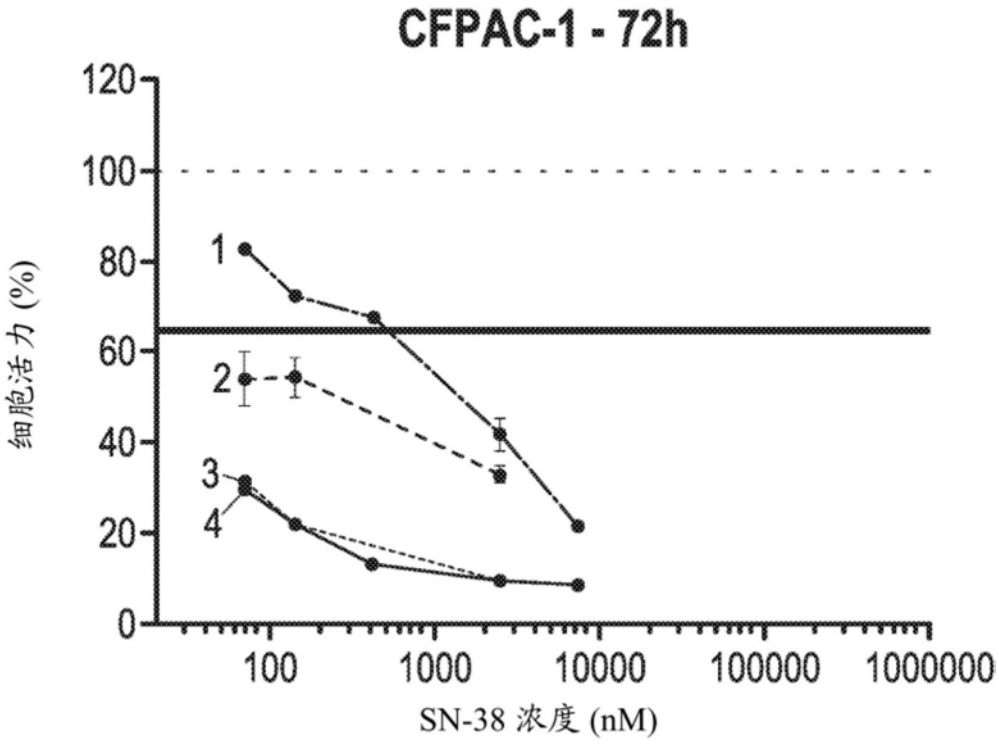
CFPAC-1 - 72h
细胞活力 (%)
120
100
80
60
40
20
0
1
2
3
4
100
1000
10000
100000
1000000
SN-38 浓度 (nM)

图2B

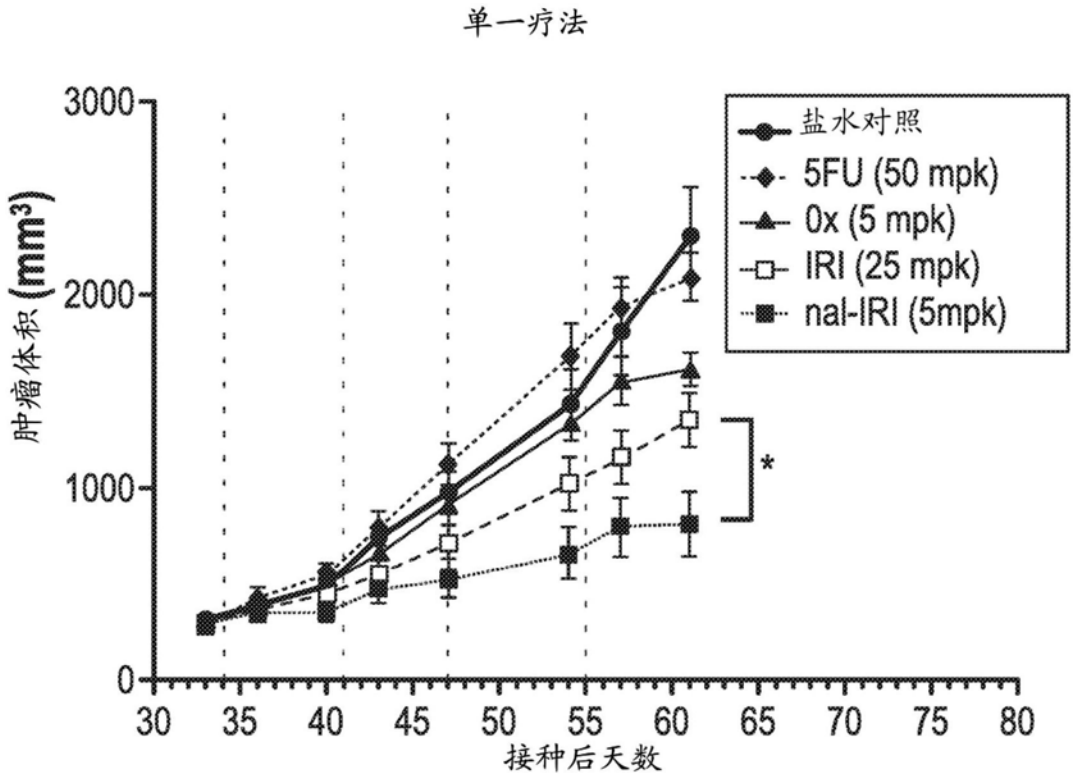
单一疗法
肿瘤体积 (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
接种后天数
盐水对照
5FU (50 mpk)
0x (5 mpk)
IRI (25 mpk)
nal-IRI (5mpk)
*

图3A

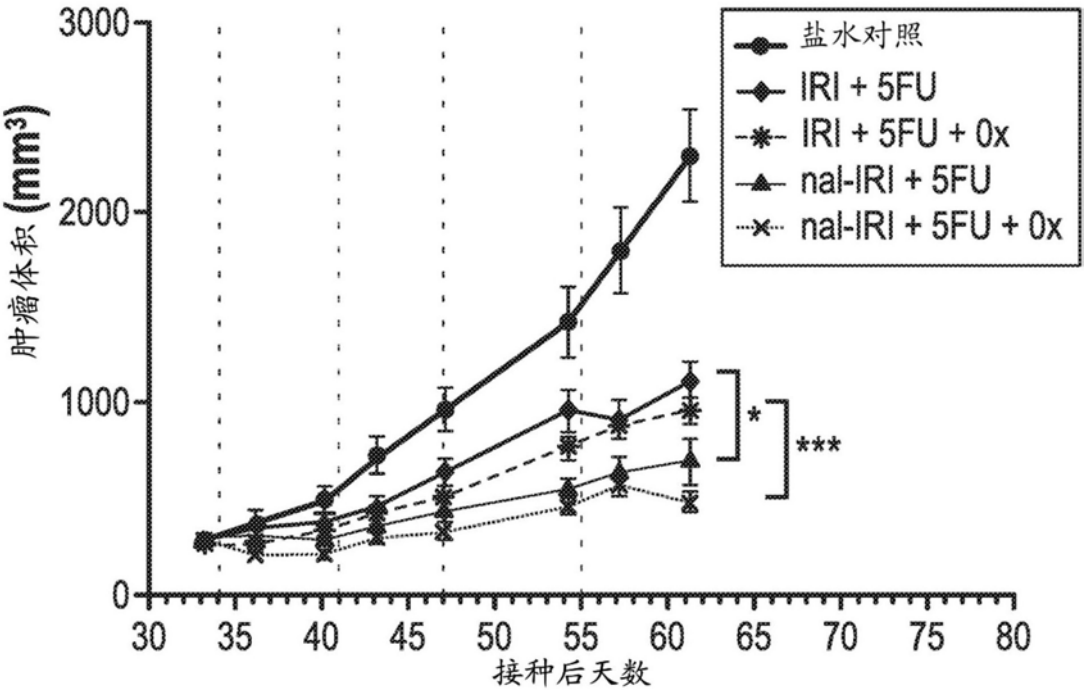
肿瘤体积 (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
接种后天数
盐水对照
IRI + 5FU
IRI + 5FU + 0x
nal-IRI + 5FU
nal-IRI + 5FU + 0x
*
***

图3B

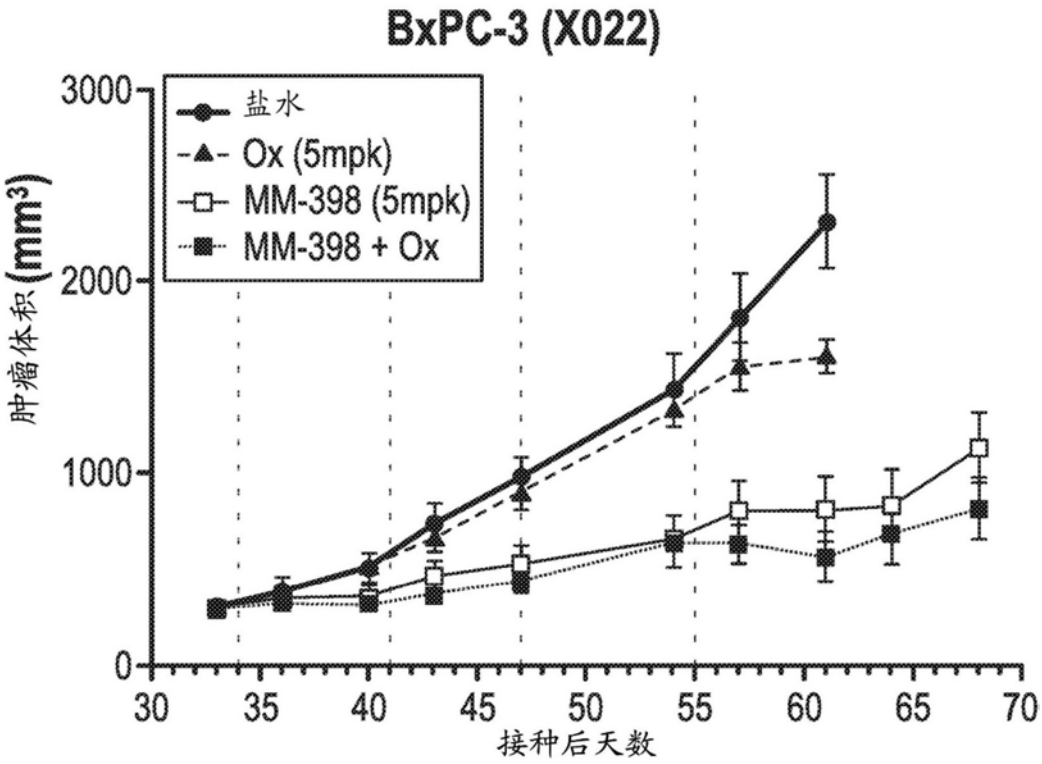
BxPC-3 (X022)
盐水
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
肿瘤体积 (mm³)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
接种后天数

图4A

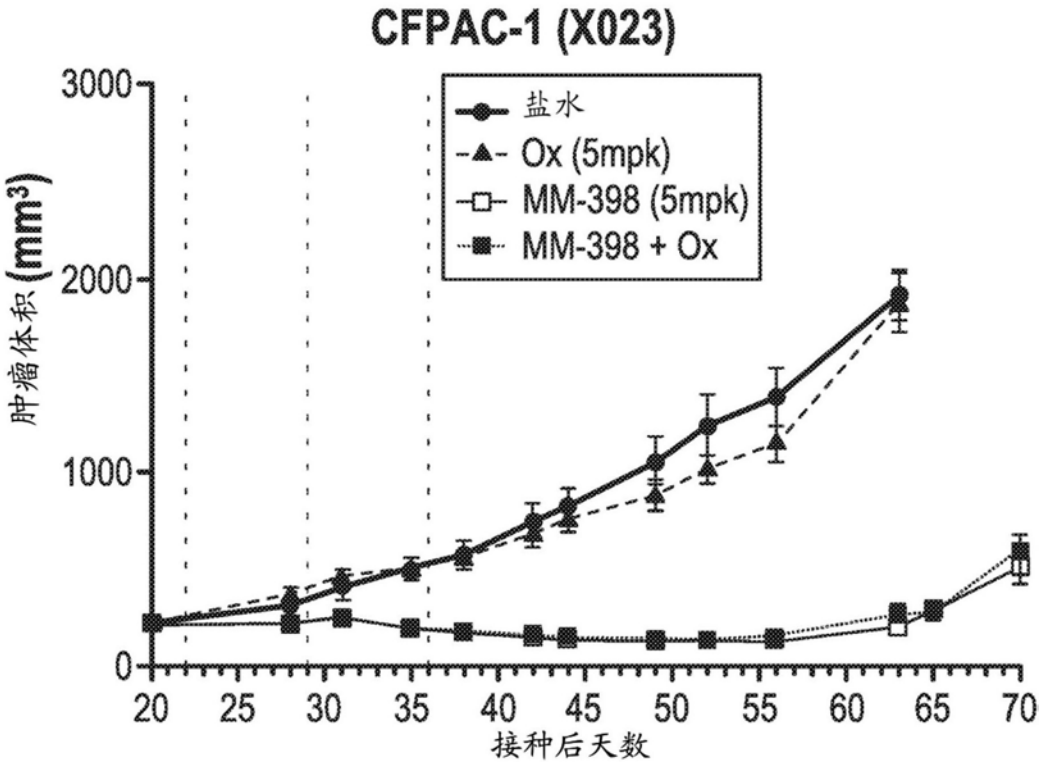
CFPAC-1 (X023)
盐水
Ox (5mpk)
MM-398 (5mpk)
MM-398 + Ox
肿瘤体积 (mm³)
3000
2000
1000
0
20
25
30
35
40
45
50
55
60
65
70
接种后天数

图4B

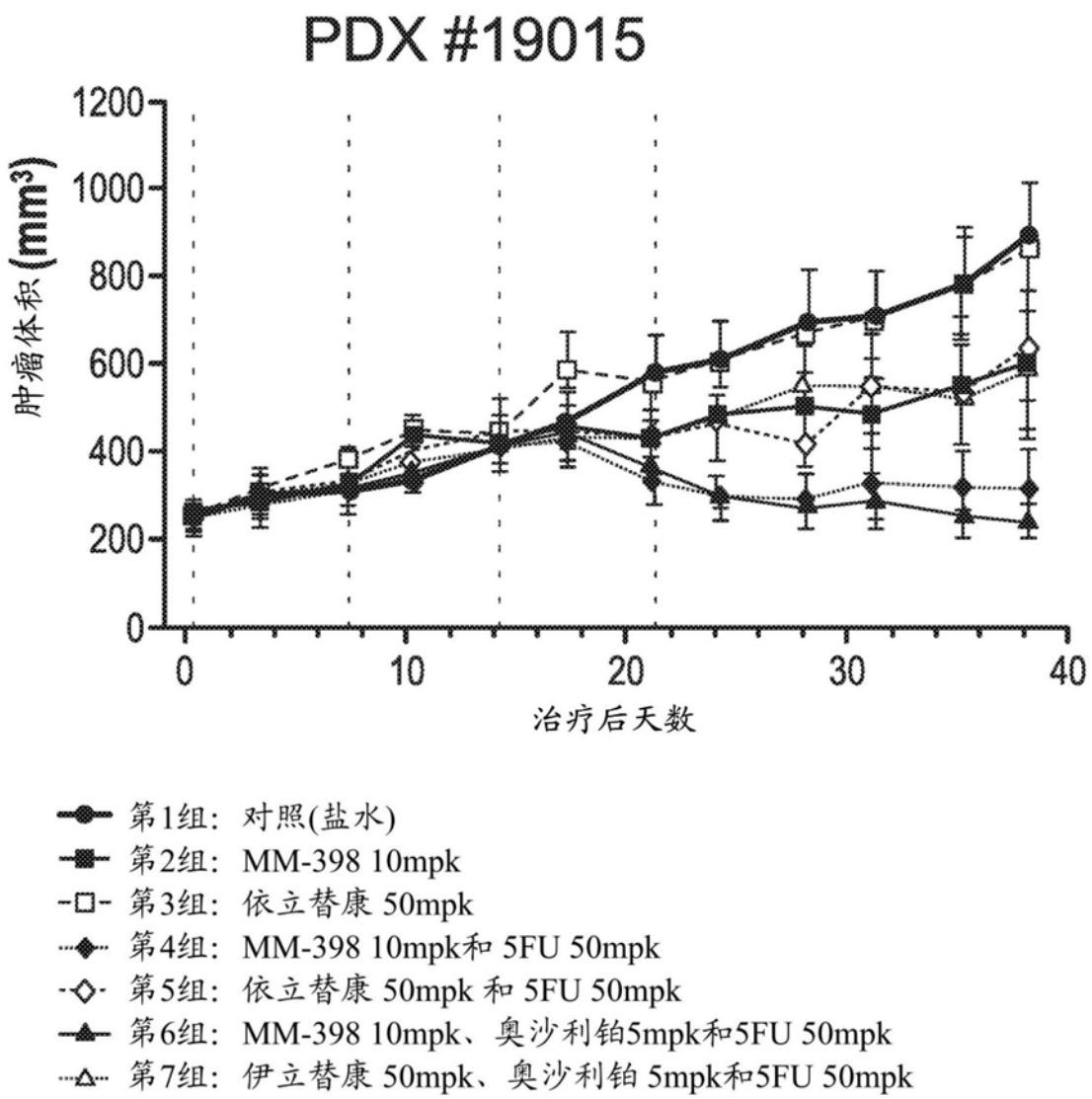
PDX #19015
肿瘤体积 (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
治疗后天数
第1组：对照(盐水)
第2组：MM-398 10mpk
第3组：依立替康 50mpk
第4组：MM-398 10mpk和 5FU 50mpk
第5组：依立替康 50mpk 和 5FU 50mpk
第6组：MM-398 10mpk、奥沙利铂5mpk和5FU 50mpk
第7组：伊立替康 50mpk、奥沙利铂 5mpk和5FU 50mpk

图5A

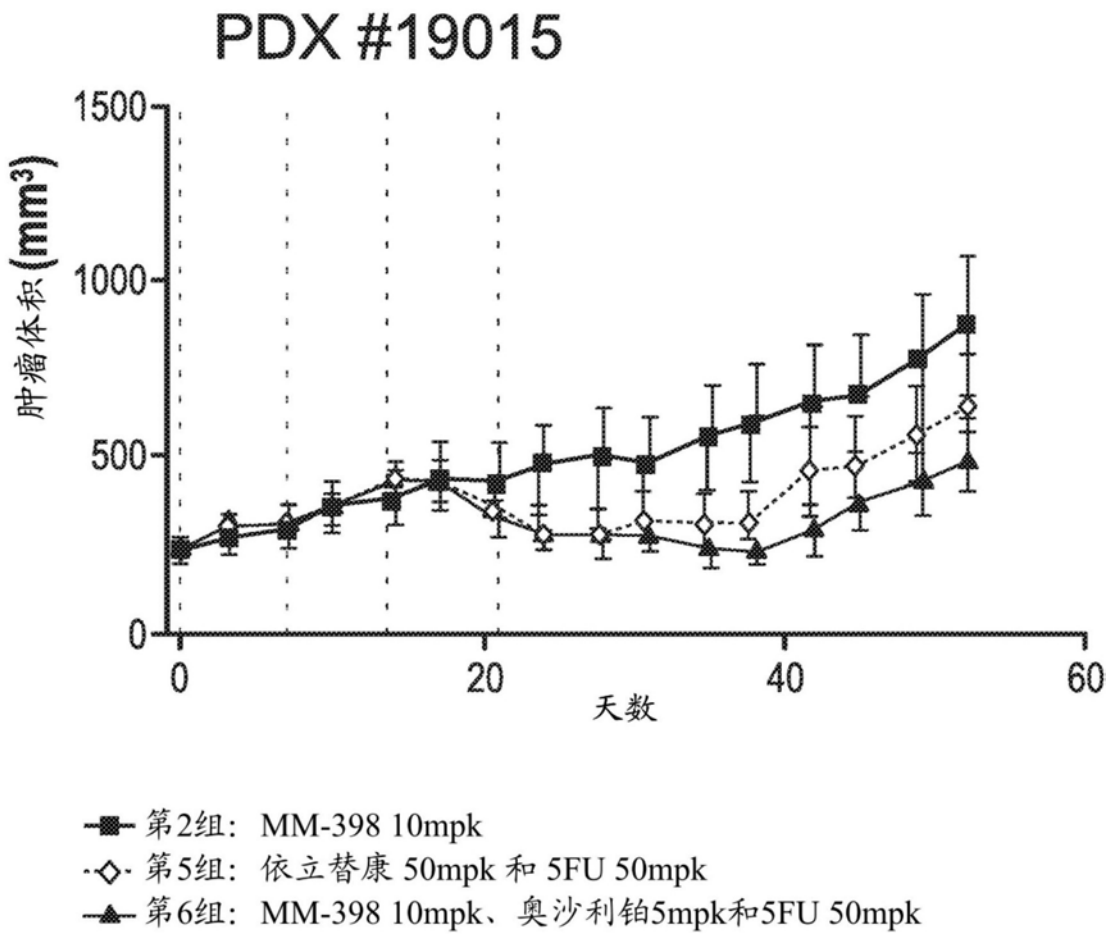
PDX #19015
肿瘤体积 (mm3)
1500
1000
500
0
0
20
40
60
天数
第2组: MM-398 10mpk
第5组: 依立替康 50mpk 和 5FU 50mpk
第6组: MM-398 10mpk、奥沙利铂5mpk和5FU 50mpk

图5B

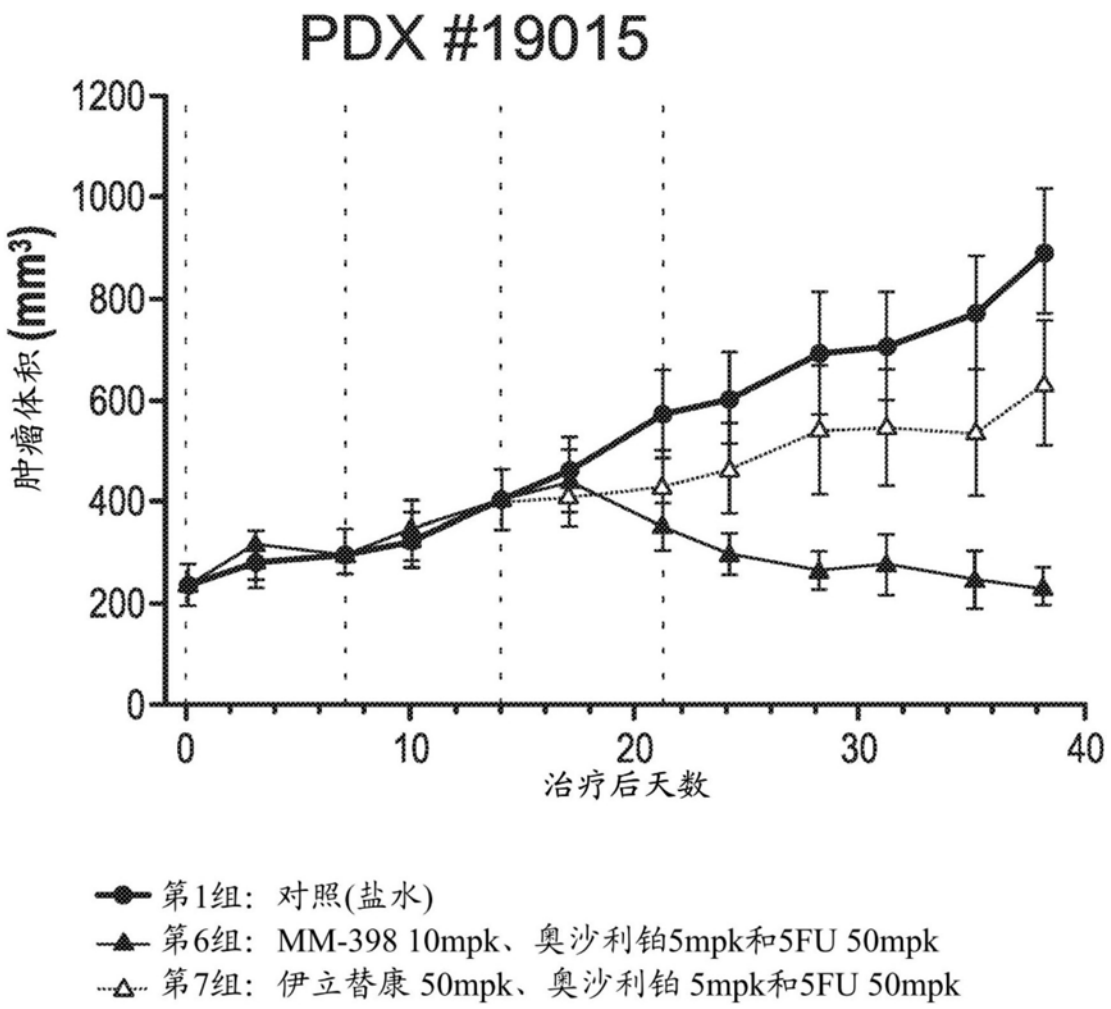
PDX #19015
肿瘤体积 (mm³)
1200
1000
800
600
400
200
0
0
10
20
30
40
治疗后天数
第1组：对照(盐水)
第6组：MM-398 10mpk、奥沙利铂5mpk和5FU 50mpk
第7组：伊立替康 50mpk、奥沙利铂 5mpk和5FU 50mpk

图5C

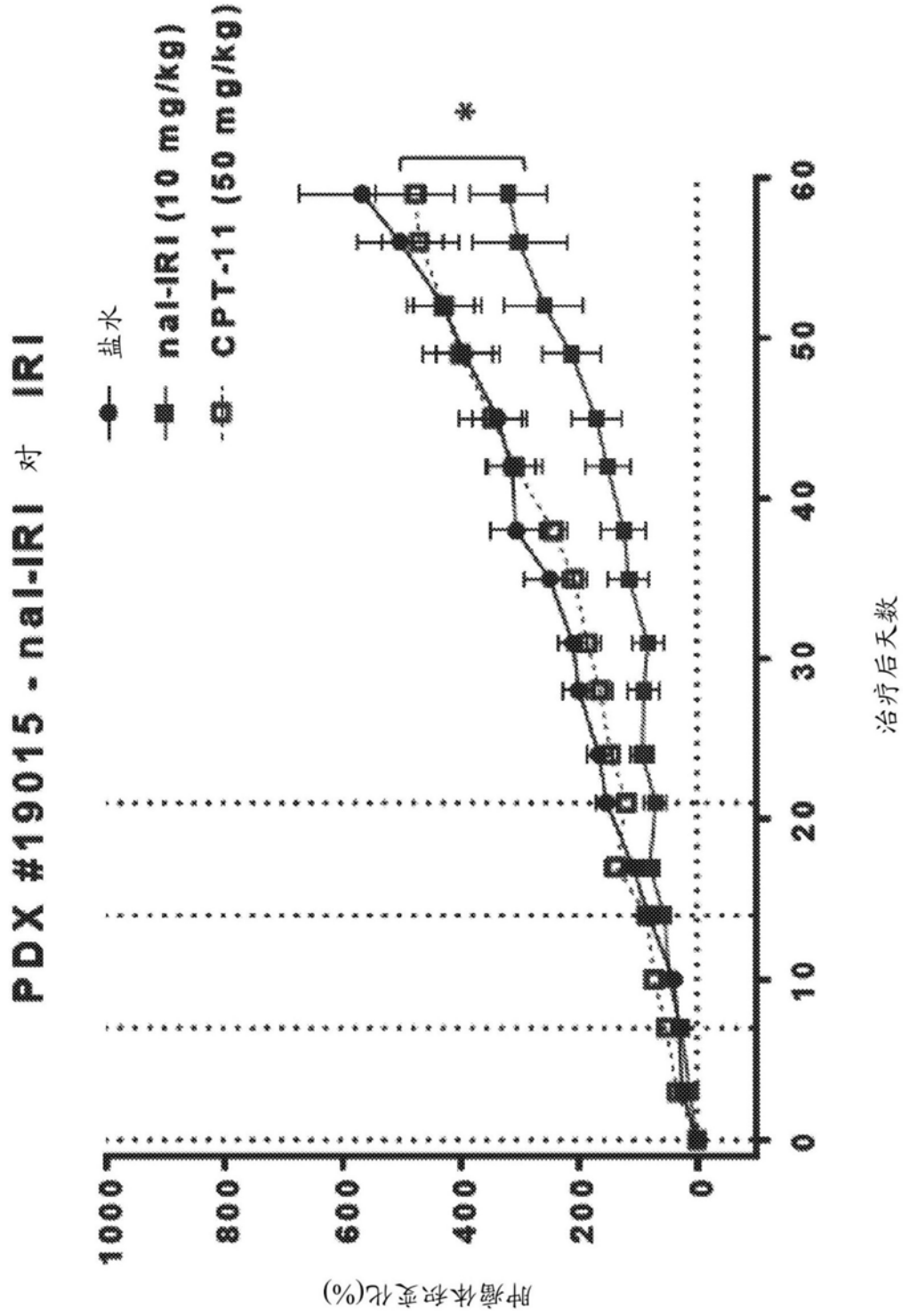
PDX #19015 - nal-IRI 对 IRI
盐水
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
*
肿瘤体积变化(%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
治疗后天数

图6A

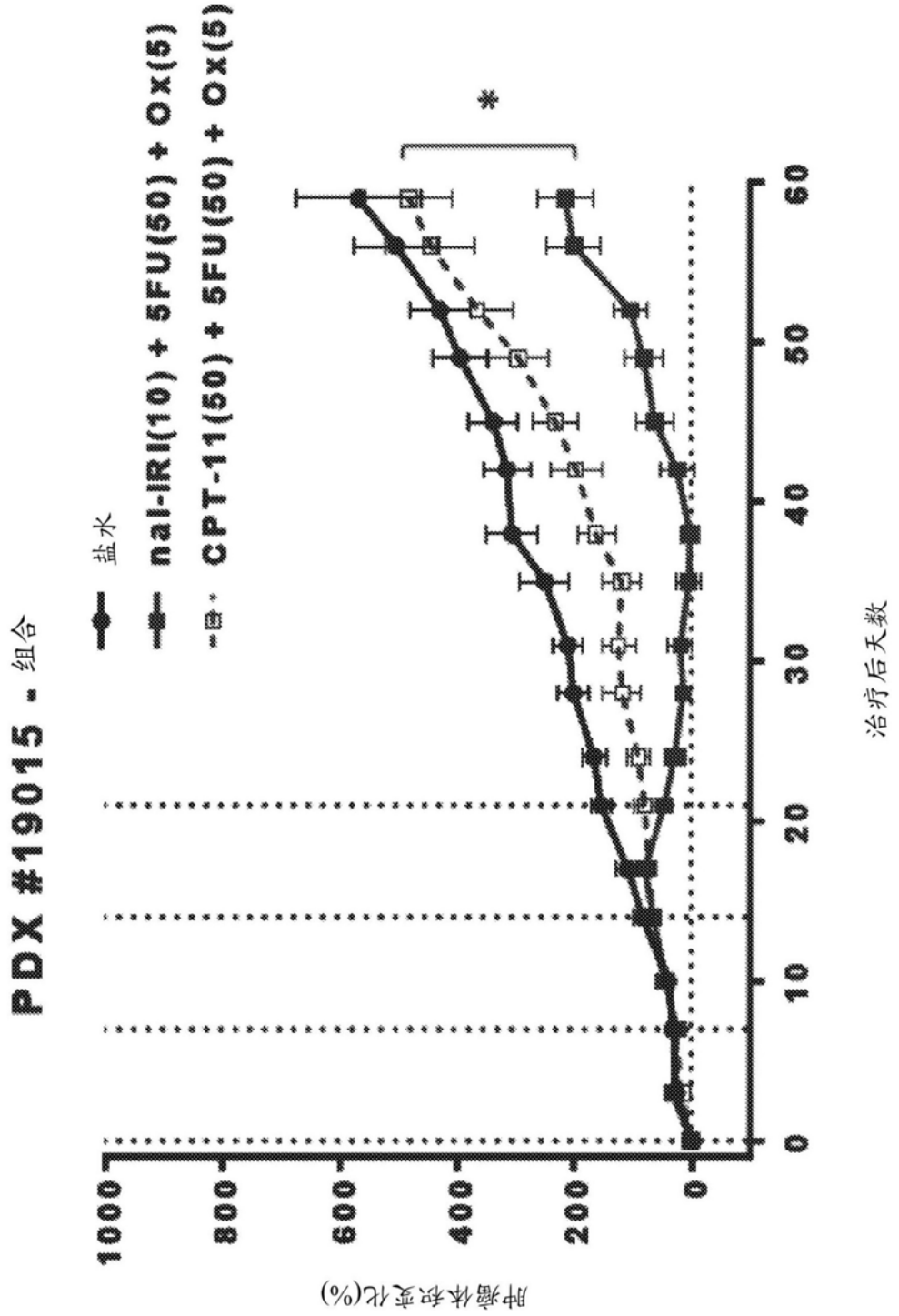
PDX #19015 - 组合
盐水
nal-IRI(10) + 5FU(50) + Ox(5)
CPT-11(50) + 5FU(50) + Ox(5)
*
肿瘤体积变化(%)
1000
800
600
400
200
0
0
10
20
30
40
50
60
治疗后天数

图6B

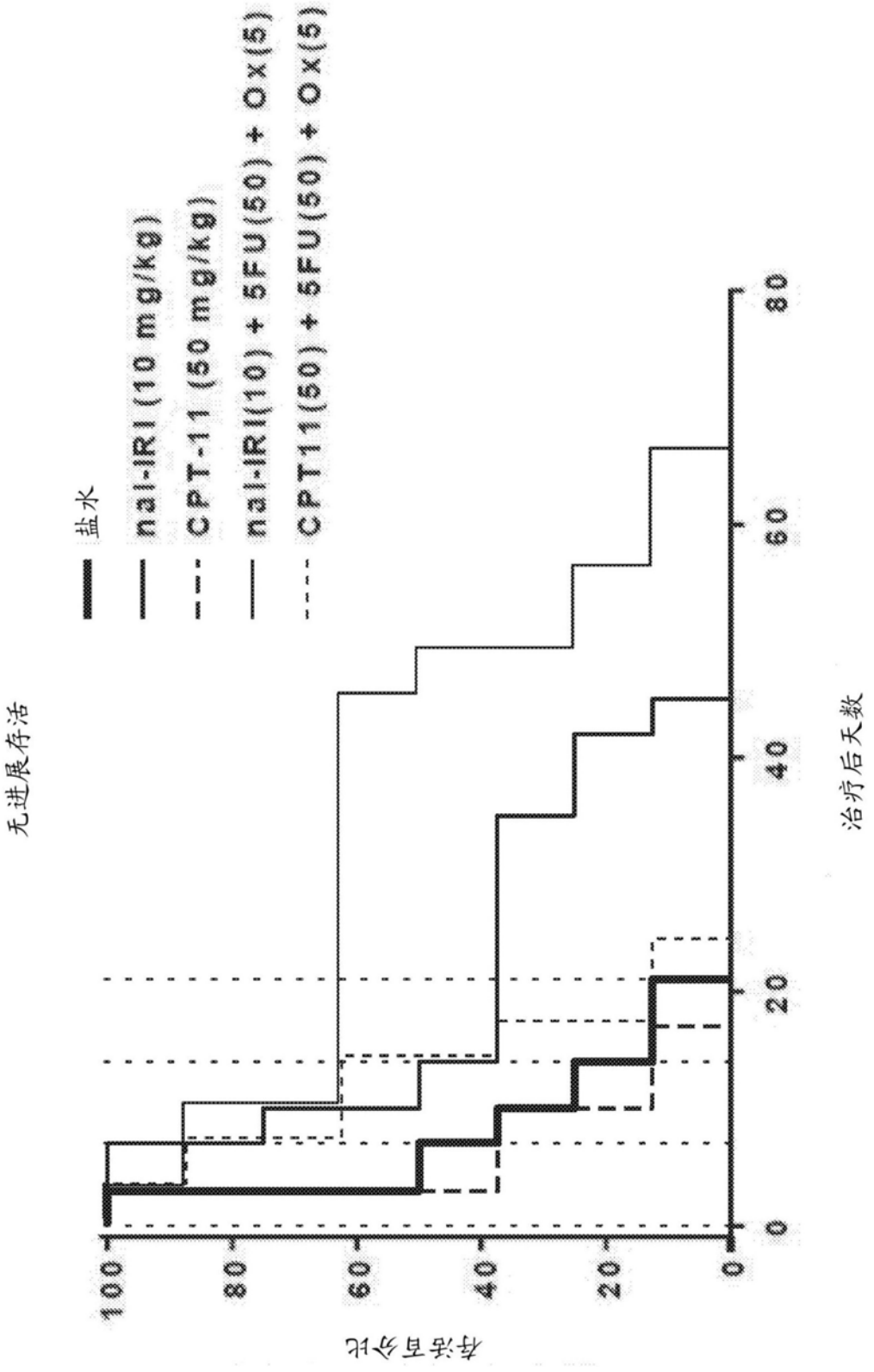
无进展存活
治疗后天数
存活百分比
盐水
nal-IRI(10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(50) + Ox(5)
0
20
40
60
80
100

图6C

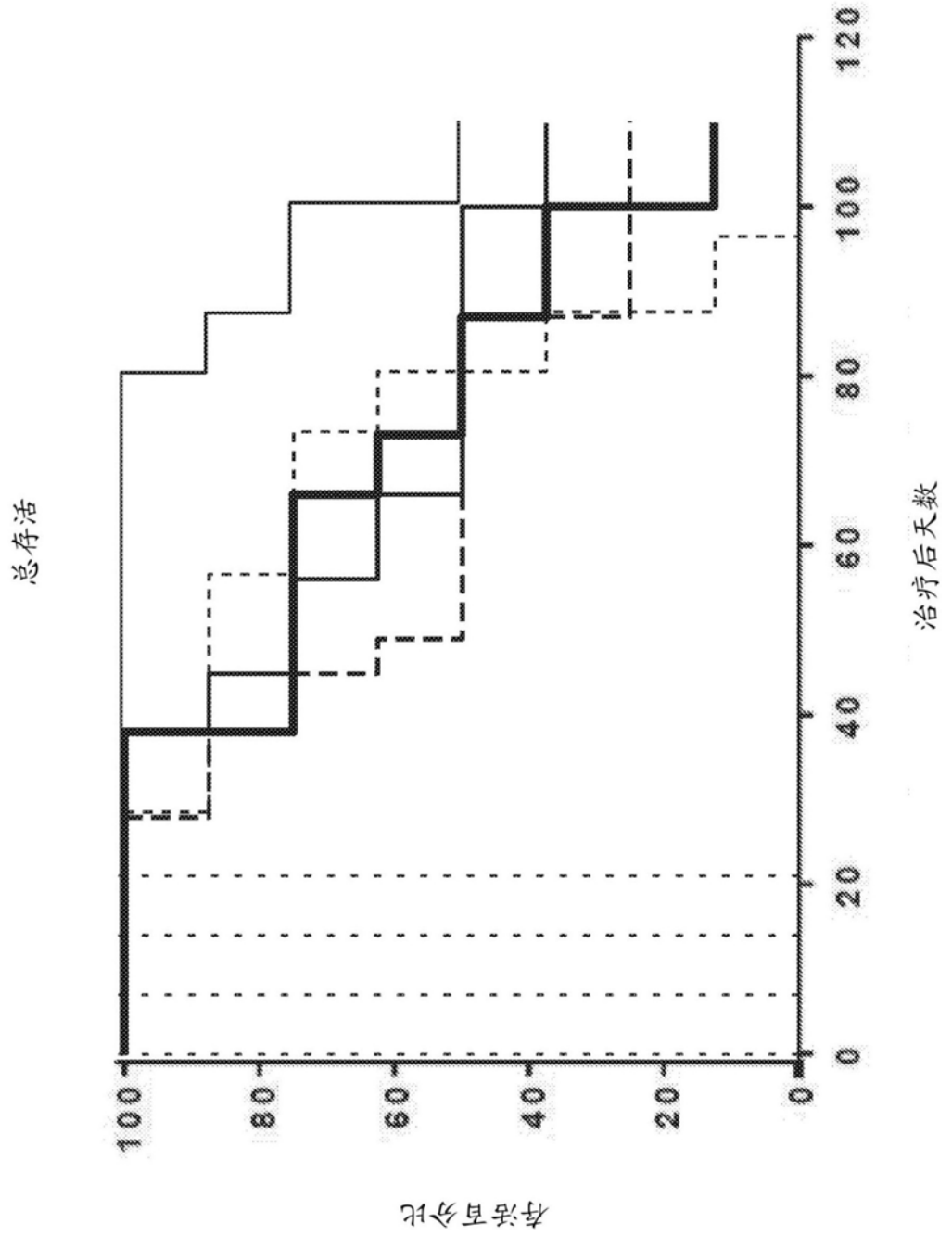

图6D

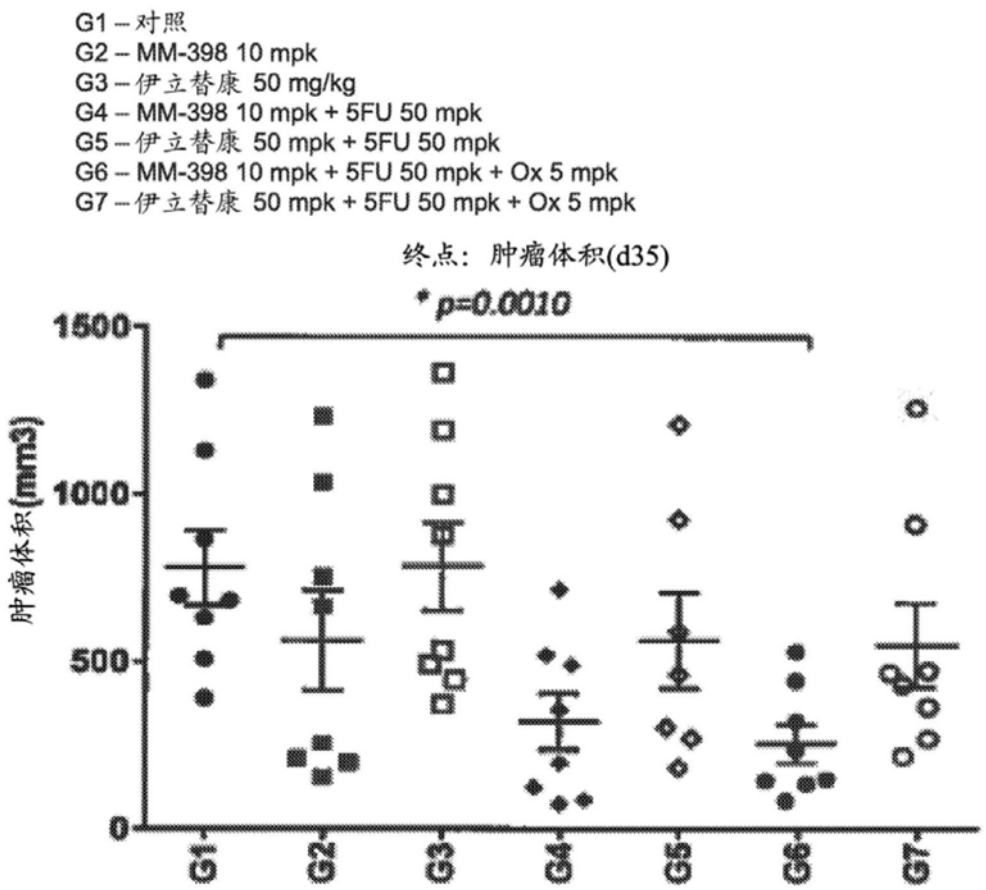
G1 – 对照
G2 – MM-398 10 mpk
G3 – 伊立替康 50 mg/kg
G4 – MM-398 10 mpk + 5FU 50 mpk
G5 – 伊立替康 50 mpk + 5FU 50 mpk
G6 – MM-398 10 mpk + 5FU 50 mpk + Ox 5 mpk
G7 – 伊立替康 50 mpk + 5FU 50 mpk + Ox 5 mpk
终点：肿瘤体积(d35)
* p=0.0010
肿瘤体积(mm3)
1500
1000
500
0
G1
G2
G3
G4
G5
G6
G7

图7

	对照	MM-398	IRI	NAPOLI	FOLFIRI	NAPOX	FOLFIRINOX
肿瘤体积（平均 mm^3,d35)	779	562	753	321	523	255	445
TGI(%，在d35)	n/a	27.9%	3.4%	58.8%	32.9%	67.3%	42.9%
中位天数至 1000mm^3	50.5 (n=8个中8个)	68 (8个中6个，2个估计)	43.5 (8个中8个)	70 (8个中6个，2个估计)	56 (7个中7个)	77 (8个中8个)	56 (8个中8个)
稳定疾病 (-30% - +30%)	0	3	1	2	3	2	4
PR (30%-95%减少)	0	0	0	3	0	4	0
CR (≥95% 减少)	0	0	0	0	0	0	0
响应率 (≥30%减少)	0%	0%	0%	38%	0%	50%	0%
疾病控制	0%	38%	13%	63%	38%	75%	50%
比率 (ORR + SD)							
中位无进展存活 (天数)	5	12	3	36.5	10	47	14
中位OS(天数)	80	83	68	100	80	105	80

图8

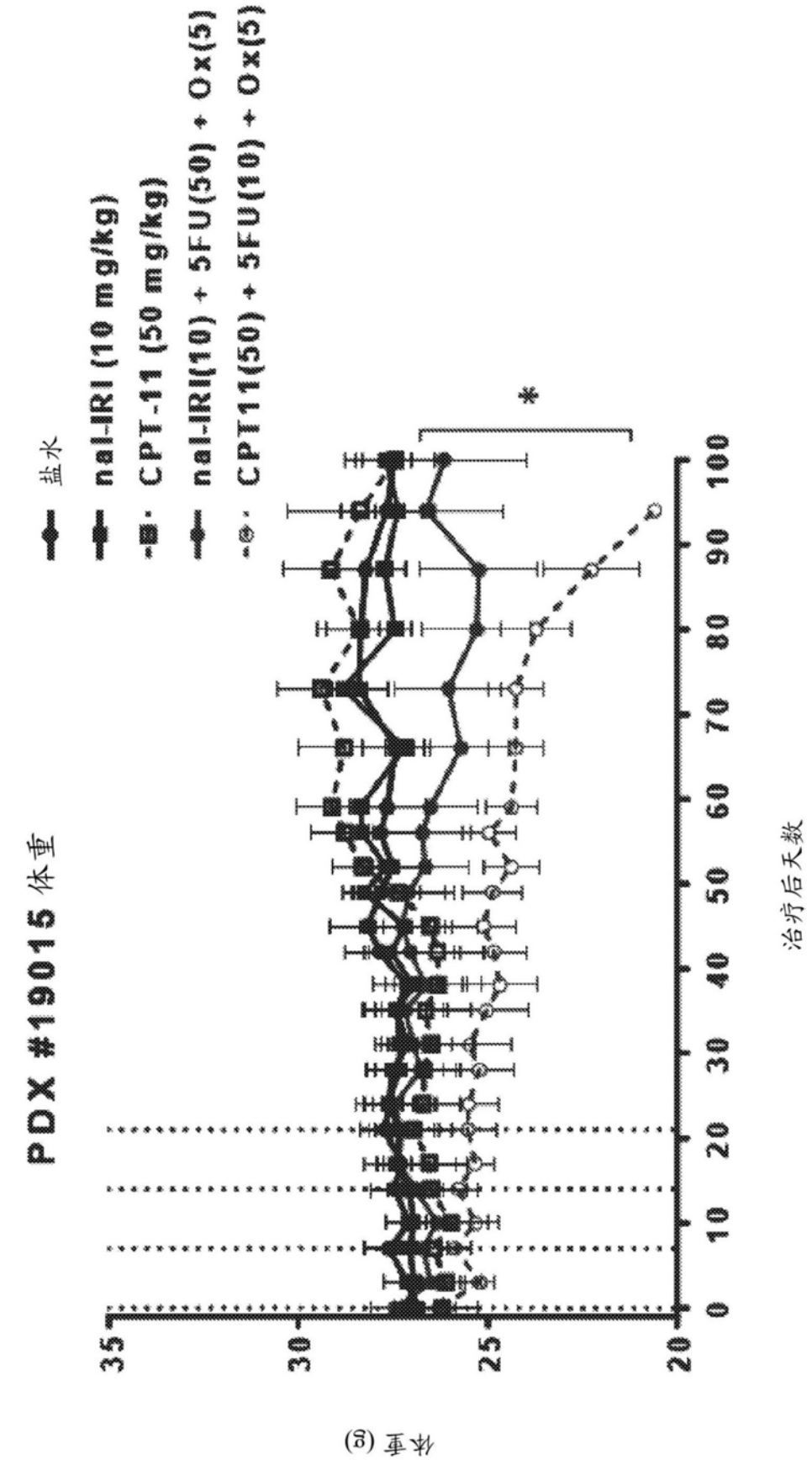
PDX #19015 体重
盐水
nal-IRI (10 mg/kg)
CPT-11 (50 mg/kg)
nal-IRI(10) + 5FU(50) + Ox(5)
CPT11(50) + 5FU(10) + Ox(5)
*
体重 (g)
治疗后天数
35
30
25
20
0
10
20
30
40
50
60
70
80
90
100

图9

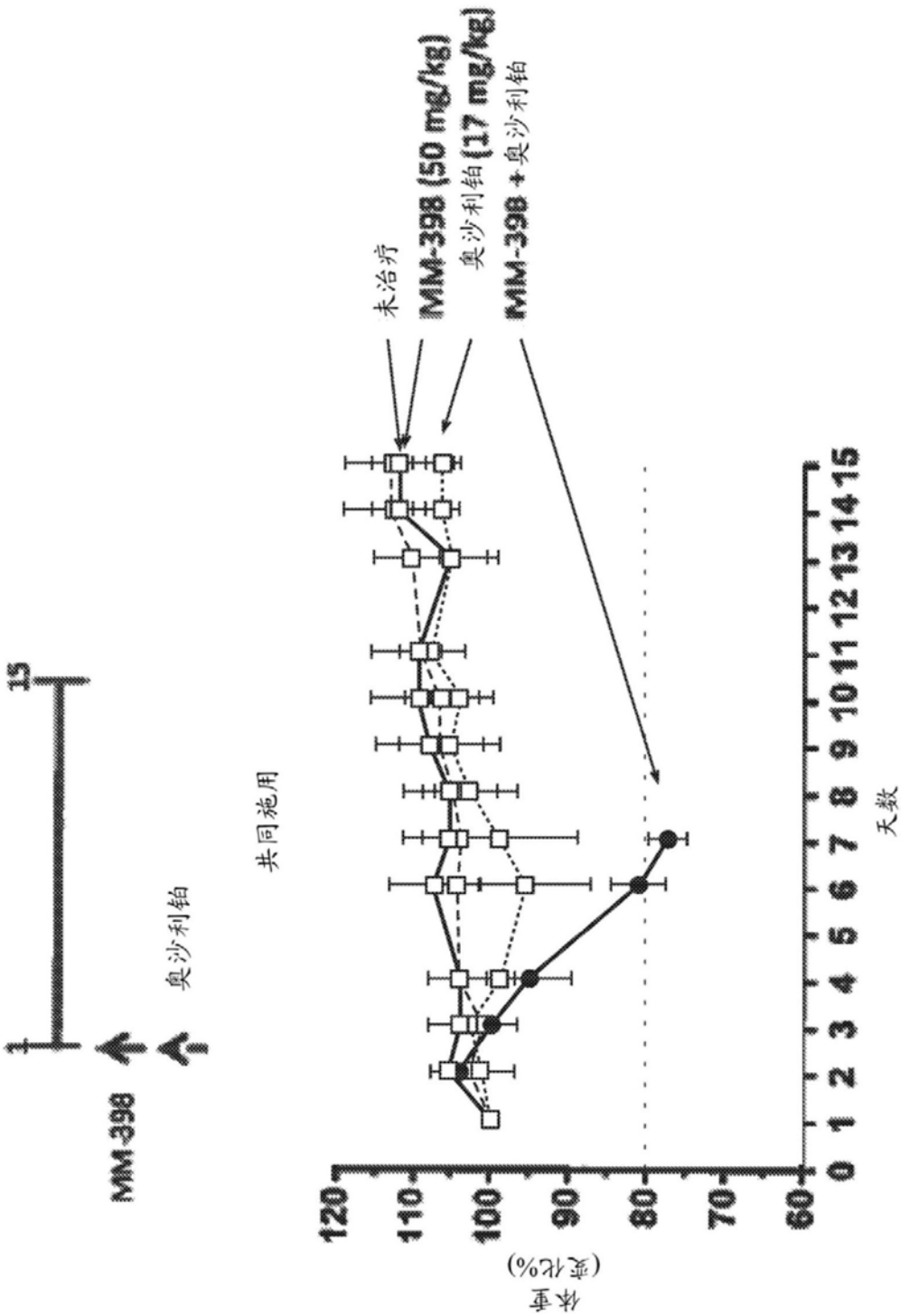
15
1
MM-398
奥沙利铂
共同施用
未治疗
MM-398 (50 mg/kg)
奥沙利铂 (17 mg/kg)
MM-398 + 奥沙利铂
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
天数
120
110
100
90
80
70
60
体重
(对比%)

图10A

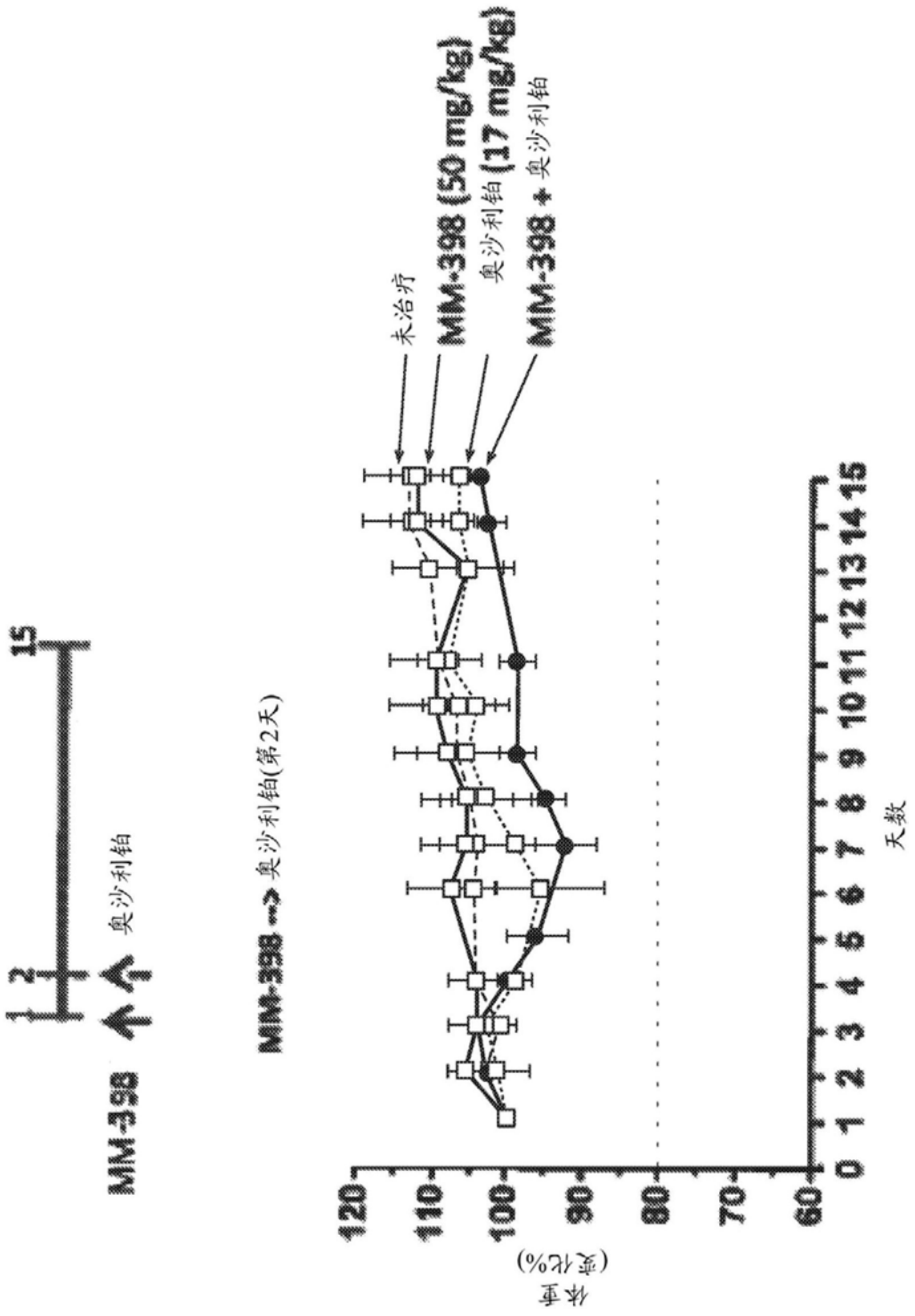
15
2
1
MM-398
奥沙利铂
MM-398 --> 奥沙利铂(第2天)
未治疗
MM-398 (50 mg/kg)
奥沙利铂 (17 mg/kg)
MM-398 + 奥沙利铂
120
110
100
90
80
70
60
体重
(变化%)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
天数

图10B

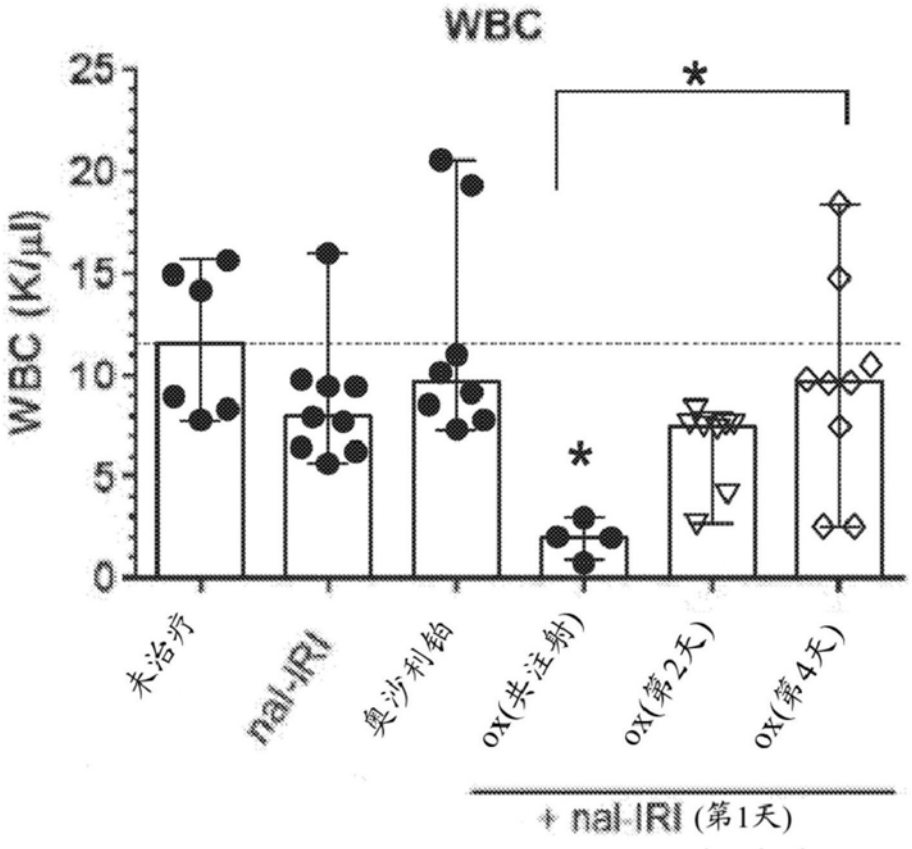
WBC
WBC (K/μl)
25
20
15
10
5
0
*
*
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+ nal-IRI (第1天)

图11A

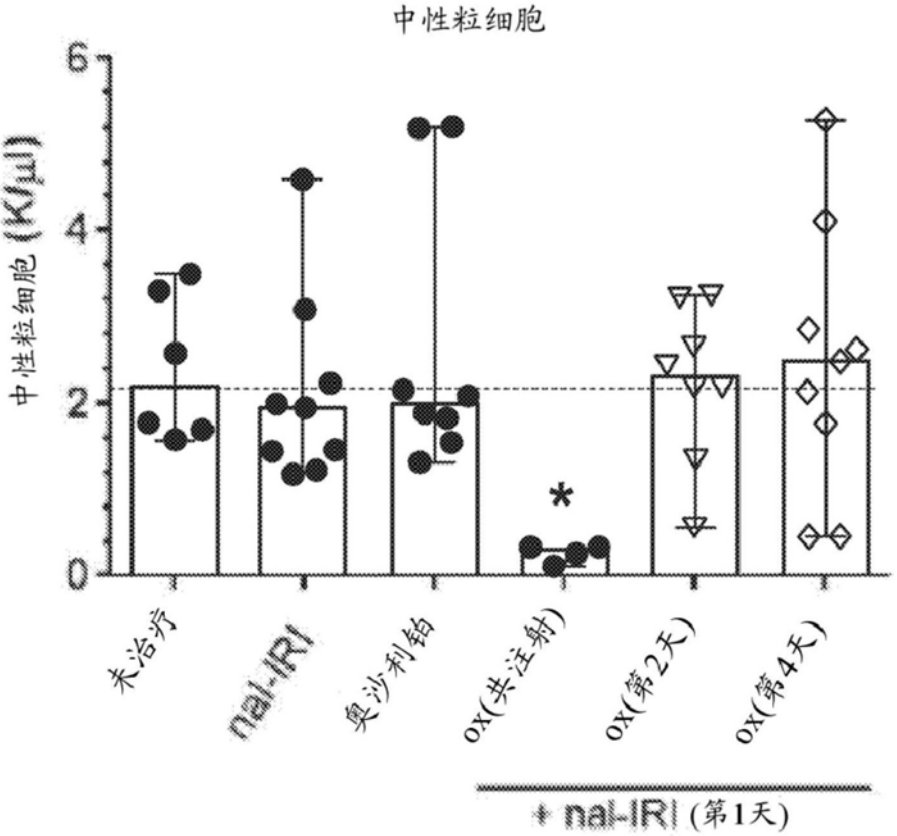
中性粒细胞
中性粒细胞 (K/μl)
6
4
2
0
*
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+ nal-IRI (第1天)

图11B

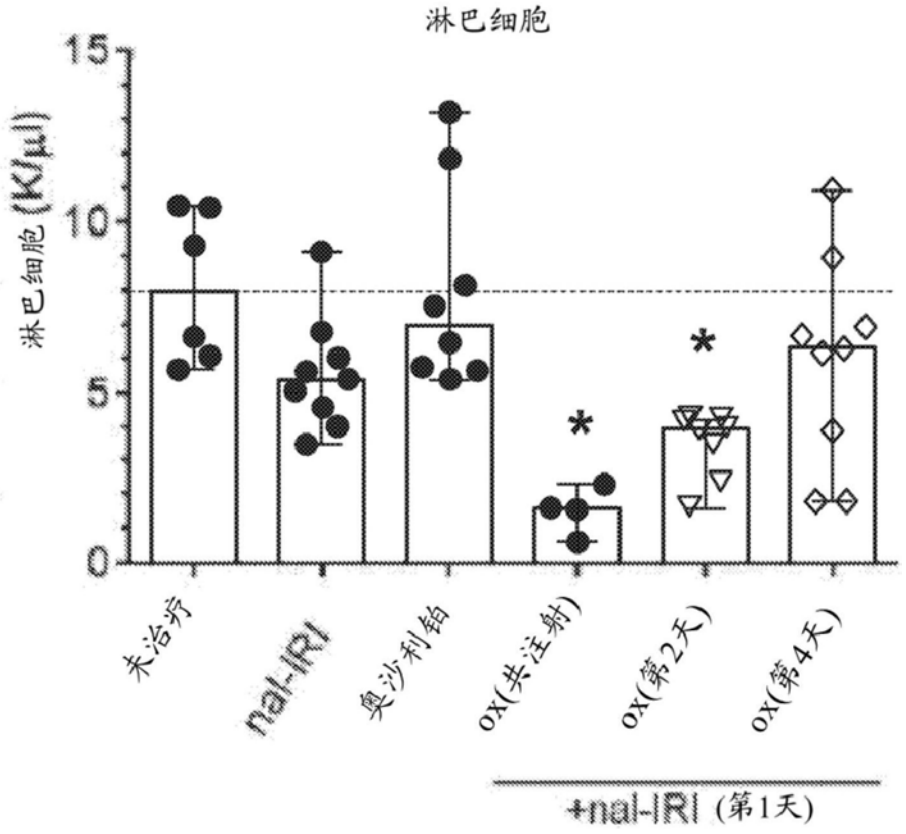
淋巴细胞
淋巴细胞 (K/μl)
15
10
5
0
*
*
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+nal-IRI (第1天)

图11C

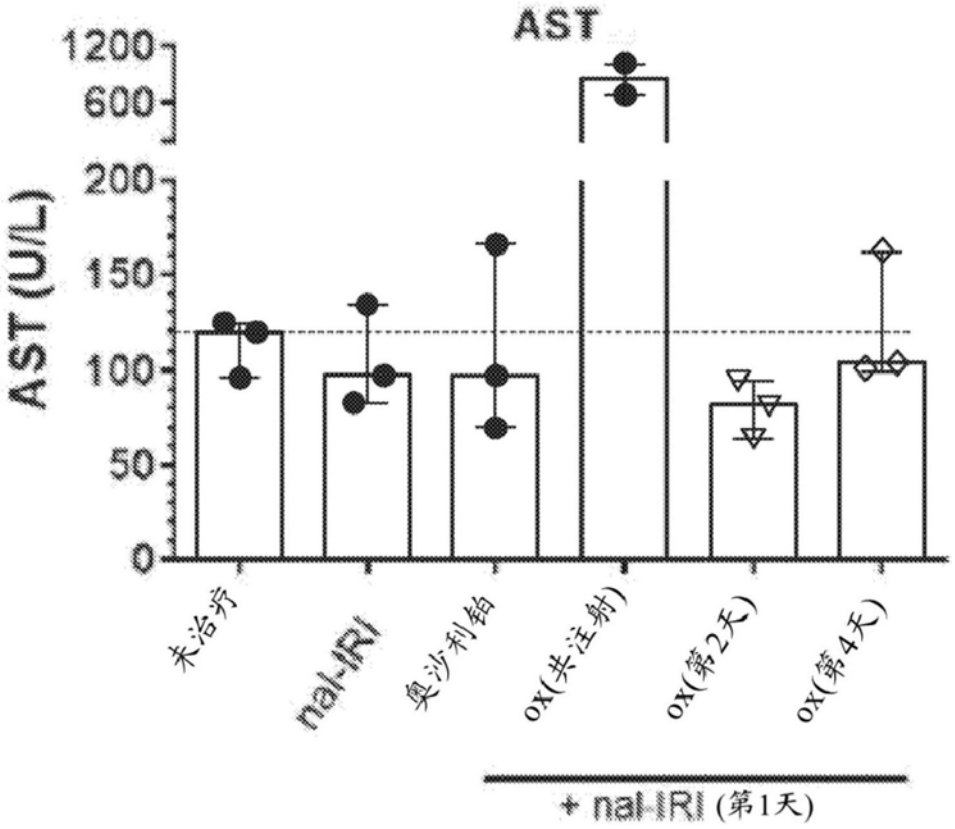
AST
1200
600
200
150
100
50
0
AST (U/L)
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+ nal-IRI (第1天)

图11D

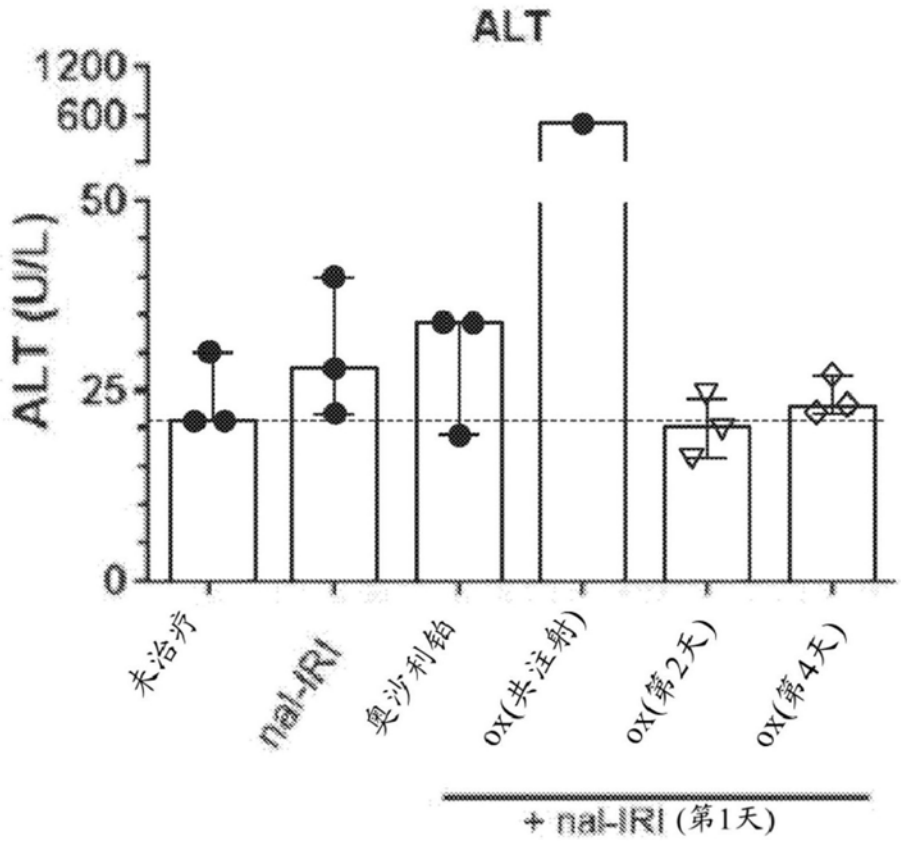
ALT
1200
600
50
25
0
ALT (U/L)
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+ nal-IRI (第1天)

图11E

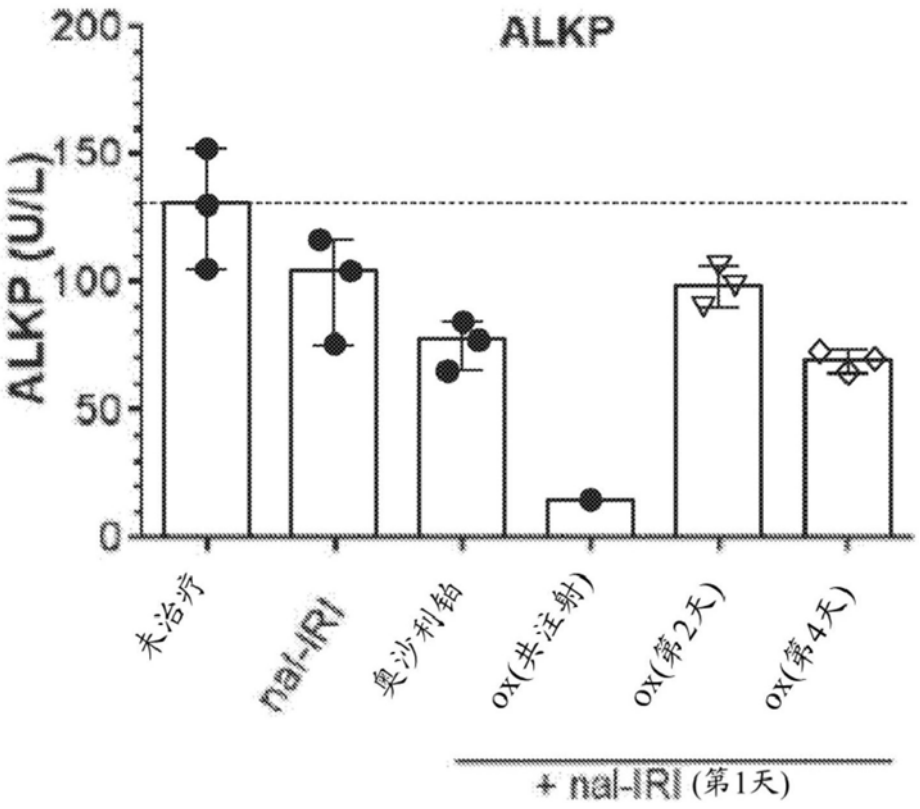
ALKP
ALKP (U/L)
200
150
100
50
0
未治疗
nal-IRI
奥沙利铂
ox(共注射)
ox(第2天)
ox(第4天)
+ nal-IRI (第1天)

图11F

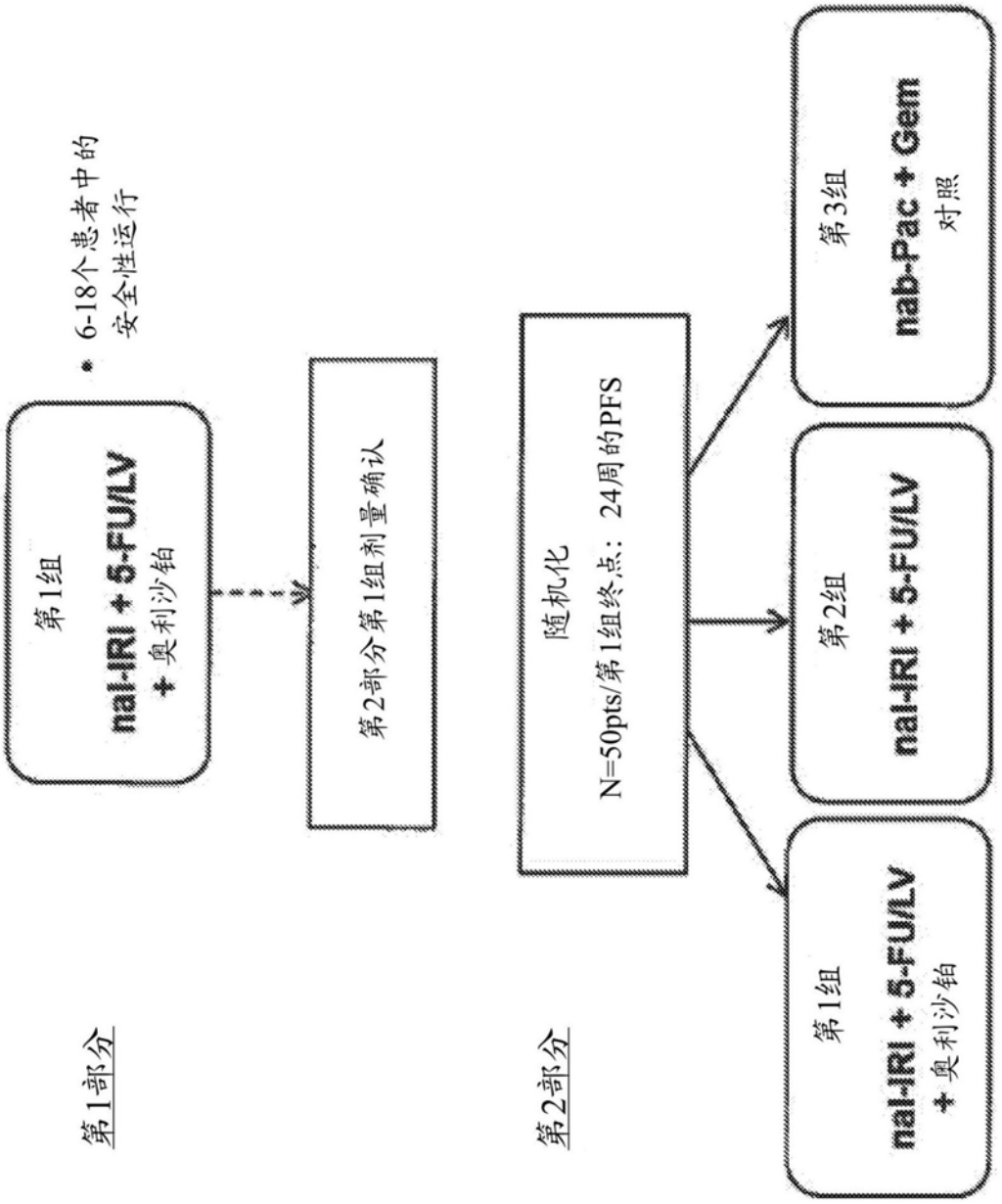
第1部分
第1组
nal-IRI + 5-FU/LV
+ 奥利沙铂
• 6-18个患者中的
安全性运行
第2部分第1组剂量确认
第2部分
随机化
N=50pts/第1组终点：24周的PFS
第1组
nal-IRI + 5-FU/LV
+ 奥利沙铂
第2组
nal-IRI + 5-FU/LV
第3组
nab-Pac + Gem
对照

图12