WIPO
WORLD
INTELLECTUAL PROPERTY
ORGANIZATION

DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/US2016/047727**
International filing date:		**19 August 2016 (19.08.2016)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**62/323,245**
	Filing date:	**15 April 2016 (15.04.2016)**
Date of receipt at the International Bureau:		**27 August 2016 (27.08.2016)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

34, chemin des Colombettes
1211 Geneva 20, Switzerland
www.wipo.int

801909

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 26, 2016

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *62/323,245*
FILING DATE: *April 15, 2016*
RELATED PCT APPLICATION NUMBER: *PCT/US16/47727*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US62/323,245*

Certified by

Michelle K. Lee

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
ELIEL		BAYEVER	CAMBRIDGE	MA	US

Inventor 2 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
NAVREET		DHINDSA	BOSTON	MA	US

Inventor 3 — Remove

Given Name	Middle Name	Family Name	City	State	Country i
JONATHAN	BASIL	FITZGERALD	ARLINGTON	MA	US

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add**button. — Add

Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND
Attorney Docket Number (if applicable)	239669-393537

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	133156

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ◉ No.
- ○ Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
- ○ Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 05/31/2015. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

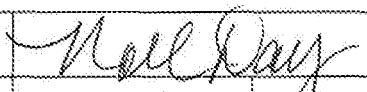
- ○ Applicant asserts small entity status under 37 CFR 1.27
- ○ Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ◉ No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature				Date (YYYY-MM-DD)	2016-04-15
First Name	Noel	Last Name	Day	Registration Number (If appropriate)	57597

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ELIEL		BAYEVER	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	NEW YORK	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	225 WEST 60TH STREET #PH1D		
Address 2			
City	NEW YORK	State/Province	NY
Postal Code	10023	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	NAVREET		DHINDSA	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	BOSTON	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	190 BOLTEN STREET		
Address 2			
City	BOSTON	State/Province	MA
Postal Code	02127	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	JONATHAN	BASIL	FITZGERALD	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

City	CAMBRIDGE	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	104 THORNDIKE STREET, #3		
Address 2			
City	CAMBRIDGE	State/Province	MA
Postal Code	02141	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	133156		
Email Address	PATENTS@HONIGMAN.COM	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN		
Attorney Docket Number	239669-393537	Small Entity Status Claimed	☐
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	20	Suggested Figure for Publication (if any)	

Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	133156		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add**button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add**button.

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.
In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	MERRIMACK PHARMACEUTICALS, INC.		
Mailing Address Information For Applicant:			
Address 1	ONE KENDALL SQUARE, SUITE B7201		
Address 2			
City	CAMBRIDGE	**State/Province**	MA
Country	US	Postal Code	02139
Phone Number		Fax Number	
Email Address	PATENTS@HONIGMAN.COM		

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	239669-393537
	Application Number	
Title of Invention	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature				Date (YYYY-MM-DD)	2016-04-15
First Name	Noel	Last Name	Day	Registration Number	57597

Additional Signature may be generated within this form by selecting the Add button.

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	TBD
Filing Date	April 15, 2016
First Named Inventor	Eliel Bayever
Title	METHODS FOR TREATING METASTATIC PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN AND OXALIPLATIN
Art Unit	N/A
Examiner Name	N/A
Attorney Docket Number	239669-393537/100.1085US00P6

SIGNATURE of Applicant or Patent Practitioner

Signature	Noel Day	Date (Optional)	April 15, 2016
Name	Noel E. Day	Registration Number	57,597
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	Merrimack Pharmaceuticals, Inc.		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U S DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with Customer Number: 133156

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒ The address associated with Customer Number: 133156

OR

☐	Firm or Individual Name		
	Address		
	City	State	Zip
	Country		
	Telephone	Email	

Assignee Name and Address: MERRIMACK PHARMACEUTICALS, INC.
ONE KENDALL SQUARE, SUITE B7201
CAMBRIDGE, MA 02139-1670

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Nicholas M Boivin	Date	22 JUNE 2015
Name	NICHOLAS BOIVIN	Telephone	(774) 776-1422
Title	HEAD OF INTELLECTUAL PROPERTY		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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

FIELD OF THE INVENTION

[0001] The present invention relates to a method of treating metastatic pancreatic cancer using a combination therapy comprising liposomal irinotecan, in patients not previously treated with a chemotherapeutic agent.

BACKGROUND

[0002] Pancreatic cancer is chemotherapy-resistant, with an extremely poor prognosis. It is the fourth leading cause of cancer death in the United States and the 5-year survival rate is about 6%. (R. Siegel, J. Ma, Z. Zou, and A. Jemal, "Cancer statistics, 2014.," *CA. Cancer J. Clin.*, vol. 64, no. 1, pp. 9–29, 2014). 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.

[0003] Irinotecan is 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycampothecin, IUPAC name (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. 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. Also known as CPT-11, irinotecan is currently marketed formulated as an aqueous solution as CAMPTOSAR® (irinotecan hydrochloride injection). Topoisomerase I inhibitors such as irinotecan work to arrest uncontrolled cell growth by inhibiting the unwinding of DNA and thereby preventing DNA replication.

[0004] Irinotecan hydrochloride injection is approved in the United States for treatment of metastatic colon or renal cancer and is also used to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

[0005] Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong overall survival. Attempts to improve on gemcitabine single agent activity by

combining it with other available chemotherapies have been largely unsuccessful. During the last 5 years, two combination chemotherapy regimens emerged as new standards of care for first-line treatment of metastatic pancreatic cancer: 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and nab-paclitaxel + gemcitabine. These demonstrate median overall survivals (OS) of 11.1 months and 8.5 months, respectively in separate Phase 3 studies. Given the poor prognosis and the low median survival rates of less than one year for patients with metastatic pancreatic cancer, new treatment options are still needed.

SUMMARY

[0006] Provided are methods for treating pancreatic cancer in a patient (i.e., a human patient) not previously treated with a chemotherapeutic agent in the metastatic setting, the method comprising administering to the patient liposomal irinotecan (e.g., irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398) in combination with oxaliplatin, leucovorin and 5-fluorouracil (5-FU), according to a particular clinical dosage regimen. Compositions adapted for use in such methods are also provided.

[0007] In one aspect, a method for treatment (e.g., effective treatment) of metastatic pancreatic cancer in a patient is provided, the method comprising: administering to the patient, an effective amount of liposomal irinotecan, in combination with oxaliplatin, leucovorin and 5-fluorouracil (5-FU), wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2. In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 80 mg/m^2. In addition, a corticosteroid and an anti-emetic can be administered 30 minutes prior to administration of the liposomal irinotecan infusion.

[0008] In some aspects, the anti-neoplastic agent gemcitabine is not administered to the patient. In some aspects, the anti-neoplastic agent cisplatin is not administered to the patient.

[0009] In another aspect, a method for treatment of pancreatic cancer in a patient is provided, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at

least one cycle of administration, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2, and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m^2 to 80 mg/m^2 (e.g., 60 mg/m^2 or 70 mg/m^2 or 80 mg/m^2); (b) oxaliplatin is administered at a dose of 60, 75 or 85 mg/m^2; (c) leucovorin is administered at a dose of 200 mg/m^2 (*l*) form, or 400 mg/m^2 (*l* + *d* racemic form) and (d) 5-FU is administered at a dose of 2400 mg/m^2.

[0010] In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2. In one embodiment, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

[0011] In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes. In another embodiment, the oxaliplatin is administered intravenously over 120 minutes. In one embodiment, the oxaliplatin is administered from about 6 hours to about 72 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered from about 12 to about 48 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered from about 18 to about 24 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 6 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 12 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 18 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 24 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 36 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 48 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 60 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 72 hours after administration of the liposomal irinotecan. In another embodiment, the 5-FU is administered intravenously over 46 hours. In another embodiment, leucovorin is administered intravenously over 30 minutes.

[0012] In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

[0013] In another embodiment, 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. In some embodiments, the metastatic pancreatic cancer is metastatic adenocarcinoma of the pancreas.

[0014] In another embodiment, the patient, for example, a human patient has not previously been treated with a chemotherapeutic in the metastatic cancer setting. In another embodiment, the patient is a human patient with advanced pancreatic adenocarcinoma who has not received prior chemotherapy, or a human patient with previously untreated, metastatic pancreatic adenocarcinoma.

[0015] In one embodiment, treating the patient results in a positive outcome, wherein the positive outcome is pathologic complete response (pCR), complete response (CR), partial response (PR) or stable disease (SD). In another embodiment, the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy.

[0016] In another embodiment, the liposomal irinotecan is formulated as irinotecan sucrose octasulfate salt liposome injection (MM-398). Irinotecan sucrose octasulfate salt liposome injection may also be referred to as irinotecan HCl liposome injection because irinotecan HCl is the active pharmaceutical ingredient that is used to load irinotecan into liposomes containing triethylammonium sucrose octasulfate to prepare MM-398 liposomes. This nomenclature may be used even though the hydrochloride ion of the irinotecan HCl reacts with the triethylammonium ion of the triethylammonium sucrose octasulfate to yield triethylammonium chloride (triethylamine hydrochloride), leaving irinotecan sucrose octasulfate salt as the entrapped pharmaceutical agent within the MM-398 liposomes.

[0017] In another aspect, kits for treating pancreatic cancer in a patient are provided, the kit

comprising a dose of each liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin as described herein.

[0018] In one embodiment, the kit encompasses treating an exocrine metastatic pancreatic cancer selected from the group consisting of Duct cell carcinoma, Acinar cell carcinoma, Adenosquamous carcinoma, Cystadenocarcinoma (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 in a patient not previously treated with a chemotherapeutic agent in the metastatic cancer setting.

[0019] In one embodiment, the liposomal irinotecan is liposomal irinotecan sucrose octasulfate salt injection (MM-398).

[0020] In another aspect, a method for treating metastatic adenocarcinoma of the pancreas in a human patient, wherein the patient has metastatic pancreatic cancer that has not been previously treated with a chemotherapeutic agent in the metastatic setting prior to the administration of MM-398, the method comprising, intravenously administering to the patient, beginning on day 1 of a 2-week cycle,

(a) dexamethasone and a 5-HT3 antagonist or other anti-emetic; followed by

(b) 80 mg/m^2 of MM-398 liposomal irinotecan administered over 90 minutes; followed by

(c) 60-85 mg/m^2 oxaliplatin; followed by

(d) 400 mg/m^2 of the (*l+d*) racemic form of leucovorin; followed by

(e) 2,400 mg/m^2 5-fluorouracil.

wherein the patient is treated with multiple cycles.

[0021] In one embodiment, after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to from 60 mg/m^2 to 80 mg/m^2. In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes.

[0022] In another embodiment, oxaliplatin is administered intravenously over 120 minutes.

[0023] 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 from about 12 to about 48 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered from about 18 to about 24 hours after administration of the liposomal irinotecan.

[0024] In another embodiment, the oxaliplatin is administered 6 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 12 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 18 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 24 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 36 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 48 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 60 hours after administration of the liposomal irinotecan. In another embodiment, the oxaliplatin is administered 72 hours after administration of the liposomal irinotecan.

[0025] In another embodiment, the 5-FU is administered intravenously over 46 hours.

[0026] In another embodiment, leucovorin is administered intravenously over 30 minutes.

[0027] In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

[0028] In another embodiment, the metastatic pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of: Duct cell carcinoma, Acinar cell carcinoma, Adenosquamous carcinoma, Cystadenocarcinoma (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.

BRIEF DESCRIPTION OF THE FIGURES

[0029] FIG. 1 represents a line graph depicting levels of SN-38 in various tissues following a single nal-IRI (20 mg/kg) dose are shown. Prolonged accumulation of SN-38 (~168 h) seen in tumor compared to other organs (~48 h).

[0030] FIG. 2 represents line graphs depicting mean plasma concentrations of total irinotecan and SN-38 following the administration of either nal-IRI (MM-398) (120mg/m^2) or Camptosar® (300mg/m2) in Study PEP0206. Gastric cancer patients received either nal-IRI (MM-398) at a dose of 120 mg/m^2 (blue line) or free irinotecan (Camptosar®) at a dose of 300 mg/m^2 (red line) every 3 weeks. Total irinotecan (top) and its active metabolite, SN-38 (bottom) were measured during Cycle 1. Error bars indicate 95% confidence interval. Dotted lines indicate lower limit of quantification (LLOQ); total irinotecan measurements consists of two LLOQ values because of two different irinotecan assay was used to measure low and high range of concentrations. The concentrations less than LLOQ values were set to the corresponding LLOQ

[0031] FIG. 3 represents clinical evidence for local activation and accumulation of SN-38 in tumor tissue. In panel A, a line graph depicts the mechanistic tumor PK model of nal-IRI predicted higher SN-38 levels in tumor compared to plasma. The range of actual data, collected from a Phase I study of patients (n=12) with advanced solid tumors, is indicated by the gray (tumor) or green (plasma) vertical bars shown in panels B and C. Panel B depicts a bar graph of CPT-11 levels. Panel C depicts a bar graph of SN-38 levels, as measured from patient tumor (black) and plasma (green) samples collected 72h post-nal-IRI infusion.

[0032] FIG. 4A depicts a line graph representing tumor growth in various treatment agents. Efficacy of nal-IRI 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 free irinotecan (IRI), nal-IRI, 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. Single agent results of the individual treatments are shown in FIG. 4A, demonstrating that nal-IRI significantly inhibits tumor growth compared to free IRI.

[0033] FIG. 4B depicts a line graph representing tumor growth in various treatment agents. Efficacy of nal-IRI 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 nal-IRI 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 FIG. 4A, doublet or triplet regimens containing either IRI or nal-IRI in

combination with oxaliplatin and/or 5-FU demonstrate that the nal-IRI-containing doublet and triplet inhibit tumor growth significantly better than the IRI-containing regimens.

[0034] FIG. 5 depicts a graphical representation of the study design employing the combination of nal-IRI + 5-FU/LV + oxaliplatin in (Arm 1) and nal-IRI + 5-FU/LV (Arm 2), and nab-paclitaxel + gemcitabine (Arm 3) as described herein.

[0035] FIG. 6 is a representation of the nal-IRI design.

[0036] FIG. 7 shows the sustained circulation of nal-IRI.

[0037] FIG. 8 depicts the irinotecan and SN-38 levels 72 hours after nal-IRI treatment.

[0038] FIG. 9 depicts the Kaplan-Meier overall survival (OS) in the NAPOLI-1 trial.

[0039] FIG. 10 is a representation of the study design.

[0040] FIG. 11 shows the countries with participating sites.

[0041] FIG. 12 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 (A) or CFPAC-1 (B) 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.

[0042] FIG. 13 is 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 (A) or CFPAC-1 (B) 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.

[0043] FIG. 14 is three line graphs depicting 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 ~250mm^3, IV treatment with MM-398 or unencapsulated 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 unencapsulated 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. (A) 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). (B) is a line graph comprising data from the MM-398 combinations only (no irinotecan combinations or control line) for the purposes 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 was the better than MM-398 alone in inhibiting tumor growth. (C) is a subset of the same data that allows comparison of the oxaliplatin combinations to the saline control.

[0044] FIG. 15 shows graphs depicting 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 ~250mm^3, IV treatment with MM-398 or unencapsulated 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. A) 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. B) 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. C) 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 unencapsulated irinotecan.

[0045] FIG. 16 is a table showing results of tumor growth and survival 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 ~250mm^3, IV treatment with MM-398 or unencapsulated 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. However, NAPOX was not significantly different from NAPOLI.

[0046] FIG. 17 depicts 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 as delaying oxaliplatin administration by 24h after MM-398 does not lead to significant changes in body weight.

[0047] FIG. 18 is a set of bar graphs depicting hematological and liver toxicities following treatment with nal-IRI with or without oxaliplatin given either concurrently or sequentially with nal-IRI. Hematological toxicities (A-C) were improved by delayed administration of oxaliplatin. Liver enzymes (D-F) remained comparable to monotherapies when oxaliplatin administration was delayed.

[0048] FIG. 19 shows that prolonged exposure of SN-38 simulates nal-IRI treatment *in vitro*. (A) Nal-IRI treatment results in prolonged tumor exposure to the active metabolite, SN-38, compared to unencapsulated irinotecan (CPT-11). (B) Prolonged low-dose exposure of SN-38 mimics nal-IRI tumor delivery *in vitro*. (C) 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. (D) The benefit of prolonged exposure to low concentrations of SN-38 was also observed when combined with 5-FU (20.7mM for 48h) or oxaliplatin (12.3mM for 4h). Both combinations also increased sensitivity of resistance cell lines to prolonged low-dose SN-38.

DETAILED DESCRIPTION

I. Definitions

[0049] 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 80 mg/m^2 liposomal irinotecan refers an amount of the liposomal irinotecan providing the same amount of liposome encapsulated irinotecan that is present in 80 mg/m^2 of irinotecan hydrochloride trihydrate, and is equivalent to a dose of 70 mg/m^2 of liposomal irinotecan based on the amount of the irinotecan free base encapsulated in the liposomal irinotecan.

[0050] As used herein, the term "subject" or "patient" is a human metastatic pancreatic cancer patient, which also includes within this definition, a human with metastatic adenocarcinoma of the pancreas and pancreatic cancer patients at stages III and IV as defined in the "Exocrine and endocrine pancreas." In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 241-9.

[0051] As used herein, "effective treatment" refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer. Effective treatment may refer to alleviation of at least one symptom of a cancer. Such effective treatment may, e.g., reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.

[0052] The term "effective amount" or "therapeutically effective amount" refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective

amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

[0053] The terms "combination therapy," "co-administration," "co-administered" or "concurrent administration" (or minor variations of these terms) include simultaneous administration of at least two therapeutic agents to a patient or their sequential administration within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

[0054] The term "monotherapy" refers to administering a single drug to treat a disease or disorder in the absence of co-administration of any other therapeutic agent that is being administered to treat the same disease or disorder.

[0055] "Dosage" refers to parameters for administering a drug in defined quantities per unit time (e.g., per hour, per day, per week, per month, etc.) to a patient. Such parameters include, e.g., the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, e.g., taken at a single administration, e.g., orally (e.g., as one, two, three or more pills, capsules, etc.) or injected (e.g., as a bolus). Dosage sizes may also relate to doses that are administered continuously (e.g., as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

[0056] "Dose" refers to an amount of a drug given in a single administration.

[0057] The term "jointly therapeutically active" or "joint therapeutic effect" as used herein means that the therapeutic agents can be given separately (in a chronologically staggered manner, especially a sequence-specific manner) in such time intervals that they prefer, in the warm-blooded animal, especially human, to be treated, still show an interaction (joint therapeutic effect). Whether this is the case can, inter alia, be determined by following the blood levels, showing that the administered compounds are present in the blood of the human to be treated at least during certain time intervals.

[0058] The terms "comprising" and "including" are used herein in their open-ended and non-

limiting sense unless otherwise noted.

[0059] The terms "a" and "an" and "the" and similar references in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

[0060] The term "about" or "approximately" usually means within 20%, more preferably within 10%, and most preferably still within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (i.e., an order of magnitude) preferably within a factor of two of a given value.

[0061] The term "first-line" or "front line" treatment or therapyis the treatment regimen or regimens that are generally accepted by the medical establishment for initial treatment of a given type and stage of cancer.

II. Compositions

A. Irinotecan sucrose sulfate liposome injection (Nal-IRI, MM-398)

[0062] As provided herein, irinotecan is administered in a stable liposomal formulation as 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). MM-398 may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of MM-398 may be diluted, e.g., in 500mL 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.

[0063] An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which 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 200 phospholipid molecules.

[0064] This stable liposomal formulation of irinotecan has several attributes that may provide an

improved therapeutic index. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process. The long circulating pharmacokinetics and high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR allows for deposition of the liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor.

[0065] In some embodiments, a pharmaceutical composition comprising one or more dosages of each of the active agents, liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin are provided. In some examples, the pharmaceutical compositions can include one or more separate packages, each package containing sterile formulations of the active agents, for example, each active agent formulated in the presence of one or more pharmaceutically acceptable excipients. In another aspect, kits for treating metastatic pancreatic cancer in a patient are provided, the kit comprising one or more doses of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin and instructions for using the active agents as described herein.

[0066] In another aspect, kits for treating metastatic pancreatic cancer in a patient are provided, the kit comprising a dose of each liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin as described herein.

[0067] The many types of pancreatic cancer can be divided into two general groups. The vast majority of cases (about 99%) occur in the part of the pancreas which produces digestive enzymes, known as the exocrine component. There are several sub-types of exocrine pancreatic cancers, but their diagnosis and treatment have much in common. The small minority of cancers

that arise in the hormone-producing (endocrine) tissue of the pancreas have different clinical characteristics. Both groups occur mainly (but not exclusively) in people over 40, and are slightly more common in men, but some rare sub-types mainly occur in women or children.

[0068] The exocrine group is dominated by pancreatic adenocarcinoma (variations of this name may add "invasive" and "ductal"), which is by far the most common type, representing about 85% of all pancreatic cancers. This is despite the fact that the tissue from which it arises - the pancreatic ductal epithelium - represents less than 10% of the pancreas by cell volume. This cancer originates in the ducts that carry secretions (such as enzymes and bicarbonate) away from the pancreas.

[0069] The next most common type, acinar cell carcinoma of the pancreas, arises in the clusters of cells that produce these enzymes, and represents 5% of exocrine pancreas cancers. Like the 'functioning' endocrine cancers described below, acinar cell carcinomas may cause over-production of certain molecules, in this case digestive enzymes, which may cause symptoms such as skin rashes and joint pain.

[0070]

[0071] In one embodiment, the kit encompasses treating metastatic pancreatic cancer selected from the group consisting ductal cell carcinoma, acinar cell carcinoma, adenosquamous carcinoma, cystadenocarcinoma (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.

Pharmacogenetics of Irinotecan Glucuronidation

[0072] The enzyme produced by the UGT1A1 gene, UDP-glucuronosyltransferase 1, is responsible for bilirubin metabolism and also mediates SN-38 glucuronidation, which is the initial step in the predominant metabolic clearance pathway of this active metabolite of irinotecan. Besides its anti-tumor activity, SN-38 is also responsible for the severe toxicity sometimes associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form, SN-38 glucuronide, is an important step in the modulation of irinotecan toxicity.

[0073] Mutational polymorphisms in the promoter of the UGT1A1 gene have been described in which there is a variable number of thymine adenine (ta) repeats. Promoters containing seven thymine adenine (ta) repeats (found in the UGT1A1*28 allele) have been found to be less active than the wild-type six repeats, resulting in reduced expression of UDP-glucuronosyltransferase 1. Patients who carry two deficient alleles of UGT1A1 exhibit reduced glucuronidation of SN-38. Some case reports have suggested that individuals who are homozygous for UGT1A1*28 alleles (referred to as having the UGT1A1 7/7 genotype, because both alleles are UGT1A1*28 alleles that contain 7 ta repeats, as opposed to the wild-type UGT1A1 6/6 genotype in which both alleles contain 6 ta repeats) and who have fluctuating elevation in serum bilirubin, (e.g., Gilbert's Syndrome patients), may be at greater risk of toxicity upon receiving standard doses of irinotecan. This suggests that there is a link between homozygosity of the UGT1A1*28 allele, bilirubin levels and irinotecan toxicity.

[0074] The metabolic transformation of MM-398 to SN-38 (e.g., in plasma) includes two critical steps: (1) the release of irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. While not intending to be limited by theory, it is believed that once irinotecan leaves the liposomes, it is catabolized by the same metabolic pathways as conventional (free) irinotecan. Therefore the genetic polymorphisms in humans predictive for the toxicity and efficacy of irinotecan and those of MM-398 can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance, higher systemic exposure and longer elimination half-life of SN-38 of the MM-398 formulation compared to free irinotecan, the deficient genetic polymorphisms may show more association with severe adverse events and/or efficacy.

Patients with Reduced UGT1A1 Activity

[0075] Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) have been shown to be at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan (Camptosar®), in a study of 66 patients who received single-agent irinotecan (350 mg/m2 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 allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of life threatening

neutropenia is described. For this reason, patients who are enrolled in the phase 3 study described in the Examples herein and are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) will have MM-398 treatment initiated at a lower dose than patients with one (e.g., UGT1A1 6/7) or two (UGT1A1 6/6) wild-type alleles.

Additional genotypic modifiers of irinotecan metabolism:

[0076] Although the UGT1A1*28 allele is relatively common in Caucasians (estimates 10%), the prevalence is varied in other ethnic groups. Furthermore, additional UGT1A1 genotypes are found with higher prevalence for example in Asian populations and these could be important for the metabolism of irinotecan in these populations. For example, the UGT1A1*6 allele is more prevalent in Asians. This allele is not associated with a TA repeat, but with a Gly71Arg mutation that reduces enzyme activity. In previous and ongoing studies of MM-398, pharmacogenetic information has been collected on patients being enrolled. In a study referred to as the PEP0203 study, the relationship of genetic polymorphism of UGT1A family and of DPYD (dihydropyrimidine dehydrogenase, an enzyme associated with catabolism of 5-FU) with pharmacokinetic parameters of MM-398 and toxicity did not provide a clear correlation with the small sample size of subjects evaluated. However, it was observed that patients with UGT1A1*6/*28 combined polymorphism had higher dose-normalized AUCs of SN-38 and experienced DLT.

B. Oxaliplatin, 5-Fluorouracil (5-FU) and Leucovorin (LV)

[0077] The combination treatment described herein encompasses administration of MM-398 liposomal irinotecan in combination with three 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. 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 can be used in combination with infusional 5-FU/LV, and is approved for use in advanced colorectal cancer.

[0078] 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.

[0079] Leucovorin (also called folinic acid) 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.

[0080] Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levoleucovorin") 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.

[0081] FU and leucovorin will be stored and handled according to the country specific package inserts.

III. Administration

[0082] Liposomal irinotecan is 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 over followed by administration of the oxaliplatin, followed by administration of the leucovorin, 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.

A. Patient Populations

[0083] In one embodiment, a patient treated using the methods and compositions disclosed herein exhibits evidence of metastatic pancreatic cancer not previously treated with a chemotherapeutic agent in the metastatic setting. In related embodiments, patients with metastatic pancreatic cancer can include those patients with metastatic adenocarcinoma of the pancreas, for example, those patients having a pancreatic adenocarcinoma tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor not previously treated with a chemotherapeutic agent in the metastatic setting.

[0084] In other embodiments, patients with metastatic pancreatic cancer can include those patients with advanced pancreatic adenocarcinoma, or those pancreatic cancer patients, with Stage III or Stage IV metastatic pancreatic cancer as defined by the National Institutes of Health National Cancer Institute (NIH-NCI), each of which not previously treated with a chemotherapeutic agent in the metastatic setting.

B. Combination Therapy

[0085] In one embodiment, liposomal irinotecan is co-administered to patients having pancreatic cancer in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen, such as those described herein. In one embodiment, the liposomal irinotecan is MM-398. In some embodiments, the present disclosure provides a method for treating pancreatic cancer in a human subject, the method comprising: administering to the subject a therapeutically effective amount of MM-398 liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil to treat the pancreatic cancer in the human subject not previously treated with a chemotherapeutic agent in the metastatic setting. In various embodiments, the oxaliplatin, leucovorin, and 5-fluorouracil are also administered in effective

amounts.

[0086] As used herein, adjunctive or combined administration (coadministration) includes simultaneous administration of the compounds in the same or different dosage forms, or separate administration of the active agents or compounds (e.g., sequential administration). For example, liposomal irinotecan can be simultaneously administered with oxaliplatin, 5-FU and leucovorin. Alternatively, liposomal irinotecan can be administered in combination with oxaliplatin, 5-FU and leucovorin, wherein liposomal irinotecan, oxaliplatin, 5-FU and leucovorin are formulated for separate administration and are administered concurrently or sequentially. For example, liposomal irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the oxaliplatin, followed by administration of leucovorin, followed by administration of the 5-FU. Such concurrent or sequential administration preferably results in liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin being simultaneously present in treated patients. In a particular embodiment, liposomal irinotecan is administered prior to oxaliplatin, 5-FU and leucovorin. In another particular embodiment, leucovorin is administered prior to 5-FU. In some embodiments, the combination regimen includes a dosing schedule comprising: administration to a human patient having metastatic pancreatic cancer, not previously treated with a chemotherapeutic in the metastatic setting, with therapeutically effective amount of MM-398 liposomal irinotecan, 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-fluorouracil 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 various embodiments as described herein, the human patient is pre-medicated by administering to the human patient dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan. In various embodiments, the leucovorin can be administered to the human patient in the (l)-form or in the (*l*+*d*) racemic form. In some embodiments, leucovorin is administered in the (*l*+*d*) racemic form. In other embodiments, the combination comprising MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil is administered to the human subject in therapeutically effective amounts once per day, every seven days, every 14 days or every 28 days. In various embodiments, the MM-398

liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil are administered to the patient with metastatic cancer not previously treated with a chemotherapeutic agent in the metastatic setting beginning on day 1 of a 2-week cycle wherein the method may include one or multiple cycles. In some of these embodiments, the leucovorin is administered as the (*l*+*d*) racemic form of leucovorin.

[0087] In various embodiments, liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin are each formulated for intravenous administration. In other embodiments, therapeutically effective amounts of liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin are administered to a human patient with metastatic pancreatic cancer, not previously treated with a chemotherapeutic agent in the metastatic setting.

[0088] In a related embodiment, 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.

[0089] In some embodiments, 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.

[0090] In some embodiments, 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.

[0091] In some embodiments, 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.

[0092] In a particular embodiment, a patient with metastatic pancreatic cancer, for example, metastatic adenocarcinoma of the pancreas, is administered an effective amount of liposomal irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a)

liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2; (b) oxaliplatin is administered at a dose of 60, 75 or 85 mg/m^2; (c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form); and (d) 5-FU is administered at a dose of 2400 mg/m^2. In a particular embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2. In some embodiments, the human patient is pre-medicated by administering to the human patient dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan.

[0093] In some embodiments, 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, 80 mg/m^2 of MM-398 liposomal irinotecan in combination with 60-85 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.

[0094] 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-fluorouracil, wherein the human patient is treated with one or multiple cycles. In the above embodiments, oxaliplatin is administered over 120 minutes, leucovorin is administered over 30 minutes, and 5-fluorouracil is administered 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 related embodiments, the human patient is pre-medicated by administering to the human patient dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan.

[0095] 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, (a) dexamethasone and a 5-HT3 antagonist or other anti-emetic; followed by (b) 80 mg/m^2 of MM-398 liposomal irinotecan administered over 90 minutes; followed by (c) 60-85 mg/m^2 oxaliplatin; followed by (d) 400 mg/m^2 of the *(l+d)* racemic form of leucovorin; followed by (e) 2,400 mg/m^2 5-fluorouracil. In some of these embodiments, the oxaliplatin is intravenously administered over 120 minutes; the leucovorin is intravenously administered over 30 minutes; the 5-fluorouracil is administered 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 various embodiments, the dosing regimen includes multiple cycles.

[0096] In one embodiment, liposomal irinotecan may be initially administered at a high dose and may be lowered over time. In another embodiment, liposomal irinotecan is initially administered at a low dose and increased over time.

[0097] In another embodiment, the dose of oxaliplatin is varied over time. For example, oxaliplatin may be initially administered at a high dose and may be lowered over time. In another embodiment, oxaliplatin is initially administered at a low dose and increased over time.

[0098] In another embodiment, the dose of 5-FU is varied over time. For example, 5-FU may be initially administered at a high dose and may be lowered over time. In another embodiment, 5-FU is initially administered at a low dose and increased over time.

[0099] In another embodiment, the dose of leucovorin is varied over time. For example, leucovorin may be initially administered at a high dose and may be lowered over time. In another embodiment, leucovorin is initially administered at a low dose and increased over time.

C. Outcomes

[00100] Provided herein are methods for treating metastatic pancreatic cancer in a patient, not previously treated with a chemotherapeutic agent in the metastatic setting comprising administering to the patient, an effective amount of liposomal irinotecan (MM-398),

in combination with effective amounts of oxaliplatin, 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen. In some embodiments, administering an effective amount of liposomal irinotecan (MM-398) to a metastatic pancreatic cancer in a patient, not previously treated with a chemotherapeutic agent in the metastatic setting, results in the dosing of at least one of oxaliplatin, 5-fluorouracil (5-FU) and leucovorin in amounts that are below their effective therapeutic concentrations when compared to their use in other combination therapies or when used as a monotherapy.

[00101] Preferably, the combination therapy with liposomal irinotecan with oxaliplatin, 5-FU and leucovorin exhibits therapeutic synergy. In some embodiments, the combination therapy comprising liposomal irinotecan with oxaliplatin, 5-FU and leucovorin exhibits superadditive effects. In some embodiments, the combination therapy with liposomal irinotecan with oxaliplatin, 5-FU and leucovorin exhibits additive effects.

[00102] "Therapeutic synergy" refers to a phenomenon where treatment of patients with a combination of therapeutic agents manifests a therapeutically superior outcome to the outcome achieved by each individual constituent of the combination used at its optimum dose (T. H. Corbett et al., 1982, Cancer Treatment Reports, 66, 1187). In this context a therapeutically superior outcome is one in which the patients either a) exhibit fewer incidences of adverse events while receiving a therapeutic benefit that is equal to or greater than that where individual constituents of the combination are each administered as monotherapy at the same dose as in the combination, or b) do not exhibit dose-limiting toxicities while receiving a therapeutic benefit that is greater than that of treatment with each individual constituent of the combination when each constituent is administered in at the same doses in the combination(s) as is administered as individual components. In xenograft models, a combination, used at its maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its individual maximum tolerated dose, manifests therapeutic synergy when decrease in tumor growth achieved by administration of the combination is greater than the value of the decrease in tumor growth of the best constituent when the constituent is administered alone.

[00103] Thus, in combination, the components of such combinations have an additive or superadditive effect on suppressing metastatic pancreatic tumor growth, as compared to monotherapy with liposome-encapsulated irinotecan alone or treatment with the chemotherapeutic(s) in the absence of liposomal irinotecan therapy. By "additive" is meant a

result that is greater in extent (e.g., in the degree of reduction of tumor mitotic index or of tumor growth or in the degree of tumor shrinkage or the frequency and/or duration of symptom-free or symptom-reduced periods) than the best separate result achieved by monotherapy with each individual component, while "superadditive" is used to indicate a result that exceeds in extent the sum of such separate results. In one embodiment, the additive effect is measured as slowing or stopping of pancreatic tumor growth. The additive effect can also be measured as, e.g., reduction in size of a pancreatic tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, increase in overall response rate, or increase in median or overall survival.

[00104] One non-limiting example of a measure by which effectiveness of a therapeutic treatment can be quantified is by calculating the log10 cell kill, which is determined according to the following equation:

$\log_{10}$ cell kill = T C (days)/3.32 × Td

in which T C represents the delay in growth of the cells, which is the average time, in days, for the tumors of the treated group (T) and the tumors of the control group (C) to have reached a predetermined value (1 g, or 10 mL, for example), and Td represents the time, in days necessary for the volume of the tumor to double in the control animals. When applying this measure, a product is considered to be active if $\log_{10}$ cell kill is greater than or equal to 0.7 and a product is considered to be very active if $\log_{10}$ cell kill is greater than 2.8. Using this measure, a combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose generally less than or equal to its maximum tolerated dose, exhibits therapeutic synergy when the $\log_{10}$ cell kill is greater than the value of the $\log_{10}$ cell kill of the best constituent when it is administered alone. In an exemplary case, the $\log_{10}$ cell kill of the combination exceeds the value of the $\log_{10}$ cell kill of the best constituent of the combination by at least 0.1 log cell kill, at least 0.5 log cell kill, or at least 1.0 log cell kill.

[00105] Responses to therapy may include:

[00106] Pathologic complete response (pCR): absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

[00107] Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

[00108] Partial Response (PR): At least a 30% decrease in the sum of

dimensions of target lesions, taking as reference the baseline sum diameters;

[00109] Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

[00110] Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

[00111] Progressive Disease (PD) denotes at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression.

[00112] In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of pancreatic cancer.

[00113] In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

[00114] In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

[00115] In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as >10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target lesions, e.g., pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

[00116] In other embodiments, cytology or histology can be used to evaluate

responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

[00117] In some embodiments, administration of effective amounts of liposomal irinotecan, oxaliplatin, 5-FU and leucovorin according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a metastatic tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate (CBR = CR+ PR+ SD $\geq$ 6 months) better than that achieved by the same combinations of anti-cancer agents administered without concomitant MM-398 administration. In other embodiments, the improvement of clinical benefit rate is about 20% 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to the same combinations of anti-cancer agents administered without concomitant MM-398 administration.

[00118] The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

Examples

[00119] List of Abbreviations

5-FU	5-Fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
ASCO	American Society of Clinical Oncology
BOR	Best overall response
BUN	Blood urea nitrogen

CA19-9	Carbohydrate antigen 19-9
CBC	Complete blood count
Cmax	Maximum concentration
CR	Complete response
CRF	Case report forms
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPR	Enhanced permeability and retention
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factors
HIV	Human immunodeficiency virus
ICH	International Conference on harmonization
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase

LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
nal-IRI	Nanoliposomal irinotecan; MM-398
NCI	National Cancer Institute
ng	Nanogram
nm	Nanometer
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PI	Principal investigator
PFS	Progression free survival
PR	Partial response
PS	Performance Status
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
t1/2	Half-life
TOP-1	Topoisomerase-1
TAM	Tumor associated macrophages
ULN	Upper limit of normal
Vss	Volume at steady state
WBC	White blood count

Example 1. Phase 2 Study of Nanoliposomal Irinotecan (Nal-IRI)-Containing Regimens in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma

A. Study Overview

[00120] Two combination chemotherapy regimens have emerged as standard of care options for first-line treatment of metastatic pancreatic cancer: 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and nab-paclitaxel + gemcitabine, demonstrating a median overall survival (OS) of 11.1 months and 8.5 months, respectively, in separate Phase 3 studies. Nal-IRI (also known as MM-398) is a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation. In a randomized phase 3 study, patients with metastatic pancreatic cancer who had received and progressed on gemcitabine (the NAPOLI-1 study), nal-IRI in combination with 5-FU/LV demonstrated significant clinical activity, increasing OS and PFS relative to 5-FU/LV.

[00121] The purpose of this study is an open-label, phase 2 comparative study to assess the safety, tolerability, and efficacy of nal-IRI in combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with advanced pancreatic adenocarcinoma who have not received prior chemotherapy. This study will assess the following regimens:

i. nal-IRI + 5-FU/LV + oxaliplatin;

ii. nal-IRI + 5-FU/LV; and

iii. nab-paclitaxel + gemcitabine.

[00114] The condition is Pancreatic Cancer. The title of this study is: A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (Nal-IRI)-Containing Regimens Versus Nab-Paclitaxel Plus Gemcitabine in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma.

The study will be conducted in two parts:

1. a safety run-in of the nal-IRI + 5-FU/LV + oxaliplatin regimen, and

2. a randomized, efficacy study of nal-IRI + 5-FU/LV + oxaliplatin, and nal-IRI + 5-FU/LV, versus nab-paclitaxel + gemcitabine, as will be described below in greater detail.

[00115] Primary Outcome Measure:

i. To evaluate the safety and tolerability of nal-IRI + 5FU/LV + oxaliplatin; and

ii. To assess the efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine

Estimated Enrollment: 168. There will be three arms:

Experimental: **Arm 1**: nal-IRI + 5-FU/LV + oxaliplatin. Assigned Interventions: Drug: nal-IRI Other Names: MM-398; Drug: 5-fluorouracil, Other Names: 5-FU; Drug: Leucovorin; and Drug: Oxaliplatin.

Experimental: **Arm 2**: nal-IRI + 5-FU/LV; Assigned Interventions: Drug: nal-IRI, Other Names: MM-398; Drug: 5-fluorouracil, Other Names: 5-FU; and Drug: Leucovorin

Active Comparitor: **Arm 3**: nab-paclitaxel + gemcitabine; Assigned Interventions: Drug: nab-paclitaxel; and Drug: Gemcitabine.

[00116] Primary Objectives: Part 1:

i. To evaluate the safety and tolerability of nal-IRI + 5FU/LV + oxaliplatin

ii. To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5FU/LV + oxaliplatin and determine the Part 2 dose of the triplet combination

[00117] Primary Objectives: Part 2:

i. To assess the efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using the progression free survival (PFS) rate at 24 weeks

[00118] Secondary Objectives:

[00119] Part 1:

i. To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin

[00120] Part 2:

i. To assess efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using overall survival (OS), PFS, and objective response rate (ORR; CR + PR, per RECIST v1.1)

ii. To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine

iii. To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire

(EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) in each arm

iv. To compare the safety and adverse event profile between the treatment arms

[00121] Exploratory Objectives:

[00122] To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI PK, toxicity, and/or response nal-IRI.

[00123] Study Design:

[00124] This is an open-label, Phase 2 study of nanoliposomal irinotecan (Nal-IRI)-containing regimens in patients with previously untreated, metastatic pancreatic adenocarcinoma, compared to nab-paclitaxel + gemcitabine. This study will assess the following regimens:

i. nal-IRI + 5-FU/LV + oxaliplatin (Arm 1)

ii. nal-IRI + 5-FU/LV (Arm 2)

iii. nab-paclitaxel + gemcitabine (Arm 3)

[00125] The study will be conducted in two parts, as illustrated in the schematic below:

1) a safety run-in of the nal-IRI + 5-FU/LV + oxaliplatin regimen, and

2) a randomized, efficacy study of the nal-IRI + 5-FU/LV + oxaliplatin regimen, the nal-IRI + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), versus a nab-paclitaxel + gemcitabine control arm.

[00126] Part 1:

[00127] Part 1 will consist of an open-label safety run-in of the combination regimen in Arm 1: nal-IRI + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and nal-IRI + 5-FU/LV has been demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore will not be included in this part of the study. The safety run-in will enroll 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) will be evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2nd 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 oxaliplatin dose of the FOLFIRINOX regimen, as published by Conroy et al.). If there are no DLTs within the safety evaluation period,

then the subsequent cohort will be initiated following agreement between the Investigators, the Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort will be expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose will be considered to exceed the optimal safety and tolerability criteria of the combination, and the dose will not be escalated further; however, lower doses may be explored. The Part 2 dose will then be defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a DLT.

[00128] Since the individual chemotherapies included in the proposed combinations have been studied in previous clinical trials, it is important that the safety assessment takes into account the expected safety profile of the standard dose regimen (e.g. FOLFIRINOX). Any toxicity that is related to disease progression will not be considered a DLT. The following adverse events will be considered as DLTs if they occur during the first cycle of treatment and are deemed related to the study treatment regimen:

[00129] 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)

i. Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection

ii. Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity

iii. Any grade 4 non-hematologic toxicity with the specific exclusion of:

1. Fatigue/asthenia < 2 weeks in duration
2. Increases in alkaline phosphatase levels
3. Nausea and vomiting ≤ 3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen)
4. Diarrhea ≤ 3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

[00130] The final determination of DLTs will be made following discussion between the DLT review committee (i.e. the Part 1 Investigators, the Medical Monitor, and the Sponsor). As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status. If a patient in any cohort experiences a DLT, and is found to be homozygous for the UGT1A1*28 allele, the Investigators, Medical Monitor, and Sponsor

will assess if the adverse event was attributable to the patient's UGT1A1*28 homozygous status prior to being assigned the category of DLT. Additionally, adverse events meeting the criteria above which are also known adverse reactions of either 5-FU or oxaliplatin based on reported safety data, and unexpected of nal-IRI, will be discussed between the Investigators, Medical Monitor and Sponsor before being assigned the category of DLT in the first cycle of treatment.

[00131] Following the Cycle 1 safety evaluation period, dose escalation for the next cohort may occur. Patients will continue to be monitored for safety beyond Cycle 1 in order to determine if multiple cycles of treatment are tolerable.

[00132] Part 2:

[00133] Part 2 will consist of an open-label, randomized, Phase 2 study in which patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV, or gemcitabine + nab-paclitaxel (control regimen). The randomization will be stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1). An independent Data and Safety Monitoring Board (DSMB) will be utilized to monitor emerging safety data. Full details will be listed in a DSMB charter.

[00134] Translational Research:

[00135] Translational research components will include collection of blood samples (Parts 1 and 2) and archived tumor (during screening, if available) to look for potential biomarkers. Analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).

[00136] Number of Patients:

[00137] Approximately 6-18 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. Therefore, the total enrollment for the study will be approximately 156-168 patients.

[00138] The ages eligible for the present study are 18 years and older. Genders eligible for the study include male and female. The study does not accept healthy volunteers.

[00139] Inclusion Criteria:

i. Pathologically confirmed adenocarcinoma of the pancreas not previously treated in the metastatic setting

ii. Part 1: Unresectable, locally advanced or metastatic disease; diagnosed within 6 weeks prior to enrollment; Part 2: Metastatic disease; diagnosed within 6 weeks prior to randomization

iii. Measurable or non-measurable disease as defined by RECIST v1.1

iv. ECOG performance of 0 or 1

v. Adequate hematological, hepatic, renal and cardiac function

[00140] Exclusion Criteria:

i. Prior treatment of pancreatic cancer in the metastatic setting with surgery (placement of stent is allowed), radiotherapy, chemotherapy or investigational therapy

ii. Prior treatment of pancreatic cancer with chemotherapy (radiation sensitizer allowed if ≥ 6 months has elapsed from completion)

iii. Known metastasis to the central nervous system

iv. Clinically significant gastrointestinal disorder

v. 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

vi. Presence of any contraindications for nal-IRI, irinotecan, 5-FU, leucovorin, oxaliplatin, nab-paclitaxel (part 2 only) or gemcitabine (part 2 only)

vii. Use of strong CYP3A4 or CYP2C8 inhibitors or inducers (part 2 only)

viii. Pregnant or breast feeding

Length of Study:

[00141] Patients will be treated until disease progression (radiologic or clinical deterioration), intolerable toxicity, or at the discretion of the treating physician. A follow up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, patients will be followed for survival once every 2 months via telephone, email, or clinic visit until death or study closure, whichever occurs first.

[00142] Investigational Product:

[00143] Nal-IRI (irinotecan liposome injection; also known as MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL or 9.5 mL of nal-IRI at a

concentration of 5 mg/mL. Nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light.

[00144] Additional Anti-cancer Therapies:

[00145] Depending on the assigned treatment arm, patients may be treated with one or more of the following approved therapies: 5-FU/LV; oxaliplatin; nab-paclitaxel; gemcitabine.

[00146] Dosing regimens:

[00147] All regimens below will be tested in 28-day cycles. Planned cohorts for the Arm 1 safety assessment are described below (Part 1). Dosing will begin at dose level 1, with planned escalation to dose level 2, the target dose of oxaliplatin based on the established FOLFIRINOX regimen. One drug in the triplet combination will be escalated, while the other two drugs are held constant, as indicated in the table below. The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

Arm 1: nal-IRI + 5-FU/LV + oxaliplatin:

[00148] In Part 1, oxaliplatin will be administered at increasing dose levels as indicated in Table 5 (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

[00149] In Part 2, oxaliplatin will be 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).

[00150] nal-IRI 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle.

[00151] 5-FU 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each cycle.

[00152] leucovorin l + d racemic form 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each cycle.

[00153] Note: The order of infusions on Arm 1 will be as follows: nal-IRI will be administered first, followed by oxaliplatin, then LV, followed by 5-FU. Patients dosed in Part 1 will receive oxaliplatin infusion 2 hours after the completion of the MM-398 infusion.

[00154] Table 1. Dose of Combination Active Agents For Arm 1:

Dose Level*	Oxaliplatin (mg/m^2)	5-FU/LV (mg/m^2)	nal-IRI(mg/m^2)
1	60 (starting dose)	2400/400	80
2**	85	2400/400	80

[00155] Additional dose levels and dose de-escalation plans are presented herein.

[00156] **Dose level 2 is the target dose of oxaliplatin, based on the established FOLFIRINOX regimen published by Conroy et al., and will be used in Part 2 of the study following dose confirmation.

Arm 2: nal-IRI + 5-FU/LV:

[00157] The dose and regimen that is planned for Arm 2 has been previously studied in 117 patients who participated in the NAPOLI-1 trial, therefore a safety cohort in Part 1 is not needed. The following doses will be administered in Part 2 of the study:

i. nal-IRI 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle.

ii. 5-FU 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each cycle.

iii. leucovorin (*l* + *d*) racemic form 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each cycle.

Arm 3: nab-paclitaxel + gemcitabine

[00158] nab-paclitaxel 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle, and gemcitabine 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle

Criteria For Evaluation:

[00159] Part 1: Assessments for safety will include all treated patients and will be based on adverse events, laboratory data, and study treatment related dose-limiting toxicities. Patients who discontinue prior to completion of Cycle 1 due to events that are not related to study treatment toxicity will not be considered in the assessment for DLT, and will be replaced for the purposes of DLT evaluation. Plasma samples will be analyzed for the concentration of nal-IRI (irinotecan) and its metabolites (SN-38 and SN-38G) in order to derive PK parameters of nal-IRI when given in combination with other anticancer therapies. PK parameters of the combination therapies (5-FU and oxaliplatin) will also be analyzed to evaluate

any drug interactions with nal-IRI.

[00160] Part 2: The primary endpoint is progression free survival achievement rate at 24 weeks, which will be assessed in all 3 study arms. The secondary endpoints related to efficacy will include overall survival, PFS time, and objective response (CR or PR, per RECIST, v 1.1). Achievement of a 20%/50%/90% or greater decrease in CA19-9 levels compared to baseline (at 8, 16, and 24 weeks post-treatment and overall) will also be assessed, along with a quality of life assessment (EORTC-QLQ-C30 and EQ-5D-5L).

[00161] Translational / Exploratory:

[00162] Archived tumor tissue (if available) and blood samples will be collected and analyzed for biomarkers (Parts 1 and 2). Samples will be used to explore potential markers of sensitivity and resistance to irinotecan, including, but not limited to, the following: DNA damage repair pathways (e.g. Topo1, BRCA1/2, and SLFN11), growth factor pathways (IGF1 and EGFR family receptors and ligands), and factors involved in CPT-11 conversion to SN-38 (e.g. macrophage content and CES activity).

Statistical Analyses:

[00163] The safety population will include all patients receiving any part of at least one dose of study drug.

[00164] Efficacy and safety analyses will be presented separately for Part 1 and Part 2 of the study. Efficacy comparisons to the control arm, i.e. nab-paclitaxel + gemcitabine, will include only patients enrolled in Part 2.

[00165] Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum).

[00166] Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from randomization (for part 1 patients, the reference time will be date of first study drug) to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, 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 will be censored at the time of the last non-PD tumor assessment.

[00167] In the assessments of efficacy, each nal-IRI-containing arm will be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will use 0.10 level one-sided testing to evaluate whether the nal-IRI-containing arm improves the efficacy parameter. Confidence intervals will be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons. The primary efficacy comparisons will be based on the ITT population, which will included all randomized patients.

[00168] A primary analysis will be 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 will be performed when PFS events have occurred in at least 120 patients (i.e. 80% of randomized patients).

Primary Efficacy Analysis

[00169] In the intention-to-treat (ITT) analysis, a patient will be 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 will be considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.

[00170] For each arm, the progression-free survival achievement rate at 24 weeks will be 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 will be presented with corresponding 95% confidence intervals. Each nal-IRI containing arm will be 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

[00171] Progression-free survival (PFS) will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided

stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.

[00172] 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 will be 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 will be calculated for each treatment arm. For each nal-IRI-containing arm, ORR will be compared to the control arm. Differences in objective response rate between each nal-IRI-containing arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare objective response rates.

[00173] The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses at time points (up to Week 8, 16 and 24 visits) and overall. Summaries of CA19-9 response will be computed based on three thresholds for magnitude of the maximum reduction: ≥20%, ≥50%, ≥ 90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. The proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, for each arm.

[00174] 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 will be descriptively summarized for each arm using Kaplan-Meier methodology. For each nal-IRI-containing arm, OS will be compared to the control arm. Hypothesis tests will be conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models

Quality of Life Analyses

[00175] Analyses of quality of life will be carried out on treated patients

who provide baseline and at least 1 post-baseline assessment for the assessment (i.e. there will be an EORTC-QLQ-C30 analysis population and an EQ-5D-5L analysis population). EORTC-QLQ-C30 and EQ-5D-5L results will be summarized at each visit by treatment group

[00176] Subscale scoring will be carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations will be applied to the raw scores so that the reported score will have range 0 100 for all scales. Summary statistics will be presented for each subscale.

[00177] A summary health state index value will be computed for each EQ-5D-5L assessment. Summary statistics will be presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses will be tabulated.

Safety Analyses

[00178] Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA version 17.1 or higher. Toxicity will be graded according to the NCI CTCAE version 4.03.

[00179] Safety analysis of patients in Part 1 will include a summary of dose-limiting toxicity events.

[00180] The period for treatment-emergent adverse events and safety findings will be 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 will be considered as treatment-emergent.

[00181] Tabular summaries will 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 will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

[00182] Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so.

[00183] Laboratory, vital signs, and ECG data will be summarized according to parameter type.

Pharmacokinetic Analyses

[00184] Plasma concentrations of nal-IRI in the combination therapies will be used to characterize PK parameters. PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously published parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), will be compared in order to examine any possible interactions between nal-IRI and the combination therapies. The total number of patients enrolled in Part 1 of the study will depend on the number of dose cohorts required to confirm the optimal dose. Escalation to the next dose cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to 6 subjects, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.

[00185] Table 2. Probability of escalation with various toxicity rates.

Background Toxicity Rate	**1%**	**5%**	**10%**	**20%**	**30%**	**40%**	**50%**
Probability of Dose Escalation	0.999	0.973	0.906	0.709	0.494	0.309	0.172

[00186] Part 2 of this study will include a comparison of the progression-free survival achievement rate at 24 weeks for each nal-IRI-containing arm versus the control arm. In the phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab-paclitaxel with the median PFS of 5.5 months (compared with 3.7 months, i.e. 16 weeks, in the gemcitabine alone arm). The median PFS of 5.5 months corresponds to a PFS rate at 24 weeks of approximately 50%.

[00187] The table below illustrates the power to detect differences in PFS achievement rate at 24 weeks between an experimental arm and the control arm using a one-

sided comparison at an unadjusted 0.10 level of significance. If the true rate for the control arm is 50%, the study would have 78% power to detect an improvement in an experimental arm that has a true rate of 70%.

Reference %	Experimental %	Delta % pts	Power N=50/arm
50	60	10	39%
50	65	15	59%
50	70	20	78%
50	71	21	80%
50	75	25	91%

Introduction

Pancreatic Cancer

[00188] 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.

Pancreatic Cancer Treatment

[00189] Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong overall survival. Attempts to improve on gemcitabine single agent activity by combining it with other available chemotherapies have been largely unsuccessful . During the last 5 years, two combination chemotherapy regimens emerged

as new standards of care for first-line treatment of metastatic pancreatic cancer:

i. 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and

ii. nab-paclitaxel + gemcitabine,

[00190] These demonstrate median overall survivals (OS) of 11.1 months and 8.5 months, respectively in separate Phase 3 studies.

[00191] 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. In addition, research into novel and predictive biomarkers is important to manage this disease.

[00192] Nal-IRI, a liposomal formulation of irinotecan, has recently been studied in a randomized, Phase 3, international study (NAPOLI-1), in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy, in which the combination of nal-IRI and 5-FU/LV significantly prolonged OS compared to 5-FU/LV treatment alone, in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy.

[00193] The goal of the present study is to assess the efficacy and safety of nal-IRI, in combination with other anticancer therapies (i.e. 5-FU/LV and/or oxaliplatin) in previously untreated metastatic pancreatic cancer patients, compared to a nab-paclitaxel + gemcitabine control arm. Descriptions of the approved anticancer therapies to be used in combination regimens on this study are briefly described below.

Description of 5-FU and Leucovorin

[00194] 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, and is used in the treatment of carcinoma of the colon, rectum, breast, stomach and pancreas.

[00195] 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.

Description of Oxaliplatin

[00196] 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).

Description of Gemcitabine

[00197] Gemcitabine (trade name Gemzar®) is a nucleoside metabolic inhibitor that exhibits antitumor activity and is approved for treatment of ovarian cancer in combination with carboplatin, breast cancer in combination with paclitaxel, non-small cell lung cancer in combination with cisplatin, and for pancreatic cancer as a single-agent or in combination with nab-paclitaxel (refer to package insert for more details). Gemcitabine acts on cells
undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary, which ultimately results in the initiation of apoptotic cell death.

Description of nab-Paclitaxel

[00198] Nab-paclitaxel (trade name Abraxane®) is an albumin-bound form of paclitaxel, a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. The inhibition of normal microtubule network interferes with essential interphase and cellular functions. It is approved for the treatment of metastatic breast cancer, non-small cell lung cancer in combination with carboplatin, and adenocarcinoma of the pancreas in combination with gemcitabine (refer to package insert for more details).

Nal-IRI (MM-398)

[00199] Nal-IRI is irinotecan (also known as CPT-11) encapsulated in a nanoliposome drug delivery system (nanoliposomal irinotecan; nal-IRI). The active ingredient of the nal-IRI 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.

[00200] Drug carrier technologies represent a rational strategy to improve the pharmacokinetics and biodistribution of irinotecan while protecting it from premature metabolism. nal-IRI employs a novel intraliposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high in vivo stability. The stable nanoliposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle. The improved pharmacokinetics, high intravascular drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may potentially result in site-specific drug delivery to solid tumors. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in tumor associated macrophages (TAMs) release the active drug and convert it locally to the substantially more cytotoxic SN-38. The preferentially local bioactivation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor.

Nal-IRI Pre-Clinical Experience

[00201] Nal-IRI has been shown in pre-clinical settings to have a broad

spectrum of activity in a wide range of solid tumors including colon, pancreatic, gastric, cervical, non-small cell lung, small cell lung, ovarian, thyroid, and breast cancers, as well as glioma, Ewing's sarcoma, and neuroblastoma, often with a high degree of anti-tumor activity against resistant or difficult to treat cancer models. Nal-IRI has also shown potent antitumor activity, including durable tumor regressions, and was markedly superior to the equivalent dose of free drug in a bioluminescent-based orthotopic xenograft pancreatic model.

Nal-IRI Pre-Clinical Pharmacokinetics

[00202] The pharmacokinetic (PK) properties of nal-IRI were evaluated in an HT-29 colon cancer subcutaneous xenograft model, as reported by Kalra et al. Both irinotecan and SN-38 were cleared very rapidly (within 8 hours) from the plasma following free irinotecan administration; however, nal-IRI clearance was demonstrated to be considerably slower and remained in circulation for over 50 hours. SN-38 plasma exposure was also greater though C_{max} levels were reduced following nal-IRI administration, suggesting the advantage of the irinotecan liposomal formulation in prolonging exposure and half-life via the ability of the lipid bilayer to protect the conversion of prodrug CPT-11 to SN-38. Further, both irinotecan and SN-38 accumulated in tissues for extended time (at least 1 week after nal-IRI administration), yet there were relatively higher levels of prolonged accumulation in the tumor compared to normal tissue, where the metabolites are at very low levels after 48 hours. (See Figure 1).

[00203] Activation of irinotecan to SN-38 by the liver is the primary path for SN-38 tumoral accumulation when free irinotecan is administered. In contrast, these data suggest that accumulation of nal-IRI in the tumor and subsequent liposome breakdown and local conversion of irinotecan to SN-38 is responsible for the enhanced tumor exposure of SN-38 when nal-IRI is administered. These preclinical data demonstrating longer retention time in tumor lesions with nal-IRI administration compared to free irinotecan administration formed the basis for clinical development.

Nal-IRI Clinical Experience

[00204] Nal-IRI has been studied in patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer. Disease areas currently being studied include glioma (intravenous and convection-enhanced local delivery), breast

cancer and several pediatric solid tumors, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteosarcoma. Nine clinical studies of nal-IRI have been completed to date, with over 400 patients across multiple tumor types exposed to various dosing regimens, with an additional three studies actively recruiting patients across multiple tumor types (see Table 3).

Table 3. Summary of Clinical Studies with Nal-IRI

Study	**PEP0201**	**PEP0202**	**PEP0203**	**PEP0206**	**PEP0208**	**NAPOLI-1**
Tumor Type	Solid tumors	Cervical	Solid Tumors	Gastric	Pancreas	Pancreas
Phase	1	1	1	2	2	3
Study design	Open label, dose escalation	Open label, dose escalation	Open label, dose escalation	Open label, 3 arm study comparing nal-IRI, docetaxel and irinotecan (44 patients/arm)	Open label, single arm	Randomized comparison of nal-IRI and nal-IRI+ 5-FU/LV *vs.* a common control of 5-FU/LV
Number of Patients treated with nal-IRI	11	6	16	44	40	151 (monotherapy) 117 (combination)
Dosing Frequency	Q3W	Q3W	Q3W	Q3W	Q3W	Q3W (monotherapy) Q2W (combination)
Dose Level (mg/m^2)	60 (n = 1) 120 (n = 6) 180 (n = 4)	60 (n = 3) 80 (n = 3)	60 (n = 3) 80 (n = 6) 100 (n = 5) 120 (n = 2)	120	120	120 (monotherapy) 80 (combination)
Combination	No	Cisplatin	5FU/LV	No	No	5FU/LV

Combination dose	---	60 mg	2000/500 mg/m^2	---	---	2000/200 mg/m^2
Key result	MTD identified as 120 mg/m^2	Study terminated due to protocol violation	MTD identified as 80 mg/m^2	Similar safety profile across irinotecan and nal-IRI arms; 6 responses in nal-IRI arm met primary endpoint	Median survival of 5.2 months	Combination arm achieved median OS 6.1 months, 1.9 month improvement over control arm (HR=0.57; p-value=0.0009)

Table 3. Summary of Clinical Studies with Nal-IRI

Study	**UCSF 8603**	**PIST-CRC-01**	**PEPCOL**	**MM-398-01-01-02**	**UCSF 13-12025**	**SPOC 2012-001**
Tumor Type	Glioma	Colorectal	Colorectal	Solid Tumors	Glioma	Pediatric Solid Tumors
Phase	1	1	2	1	1	1
Study design	Open label, dose escalation	Open label, dose escalation	Comparison of nal-IRI + 5FU/LV + Avastin versus FOLFIRI + Avastin	Open label, ferumoxytol MRI prior to first dose	Open label, dose escalation using convection-enhanced delivery for direct tumoral injection	Open label, dose escalation

Study	UCSF 8603		PIST-CRC-01	PEPCOL	MM-398-01-01-02	UCSF 13-12025		SPOC 2012-001
Dosing Frequency	Q3W		Q2W	Q2W	Q2W	Single dose		Q3W
Dose Level (mg/m^2)	HTZ[1] 60 (n = 3) 90 (n = 6) 120 (n = 3) 150 (n = 6)	WT[2] 120 (n = 6) 180 (n = 7) 240 (n = 3)	80 (n = 6) 90 (n = 6) 100 (n = 6)	80	80	Dose 20 mg 40 mg 60 mg 80 mg	Tumor Volume 1-4 cm^3 1-4 cm^3 2-5 cm^3 2-6 cm^3	60 (n = 3) 90 (n = 3) 120 (n = 3) 150 180 210
Combination	No		No	5FU/LV + Avastin	No	No		Cyclophosphamide
Combination dose	---		---	2400/400 mg/m^2 (5FU/LV) 5 mg/kg (Avastin)	---	---		250 mg/m^2
Current status	Enrollment completed; MTD identified for HTZ of 150 mg/m^2 and MTD identified		Enrollment completed	Enrollment completed	Enrollment ongoing	Enrollment ongoing		Enrollment ongoing

Study	UCSF 8603	PIST-CRC-01	PEPCOL	MM-398-01-01-02	UCSF 13-12025	SPOC 2012-001
	for WT of 120 mg/m^2					

Nal-IRI PK in Humans

[00205] The pharmacokinetic profile of single agent nal-IRI has been investigated in several studies, in which plasma levels of total irinotecan, SN-38 and encapsulated irinotecan were measured. In a single phase II clinical study (study PEP0206), direct comparison of the pharmacokinetics of irinotecan and SN-38 in patients administered nal-IRI or conventional (i.e. free) irinotecan (Camptosar®) was evaluated. Compared to the administration of conventional irinotecan 300 mg/m^2 q3w, administration of nal-IRI 120 mg/m^2 q3w resulted in higher exposure of total irinotecan (C_{max}: 13.4 fold, $AUC_{0-\infty}$: 46.2 fold, $t_{1/2}$: 2.0 fold), and higher SN-38 $t_{1/2}$ (3 fold) and marginally higher $AUC_{0-\infty}$ (1.4 fold), however, SN-38 C_{max} was reduced by 5.3 fold (Figure 2). In other PK studies of single agent nal-IRI, similar findings were observed when compared to standard doses of conventional irinotecan. Based on population pharmacokinetic analysis, no significant association was observed between the PK parameters of total irinotecan and SN-38 following nal-IRI monotherapy and when co-administered with 5-FU/LV. This result is consistent with the lack of drug interaction noted between irinotecan and 5-FU (Camptosar® US label). A summary table of PK parameters from 95 patients who received 60-180 mg/m^2 nal-IRI is found below (see Table 4).

[00206] Table 4: Summary Statistics of nal-IRI PK Parameters across Multiple PK Studies

PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max} [µg/ml or ng/ml]‡	60	4	28.8	86	4	3.8	226
	80	25	38.0	36	25	4.7	89
	90	6	53.6	37	6	7.5	89
	100	11	41.9	25	11	6.2	79
	120	45	59.4	41	45	7.2	57
	180	4	102.4	32	4	11.8	89
$t_{1/2}$ [h]	60	4	22.0	87	3†	145.1	233
	80	23†	26.8	110	13†	49.3	103

	90	6	14.8	97	6	35.7	53
	100	11	21.6	192	10†	62.3	37
	120	45	15.6	198	40†	57.4	67
	180	4	22.8	86	4	50.2	122
$AUC_{0-\infty}$ [h·µg/ml or h·ng/ml]‡	60	4	352	489	3†	813	249
	80	23†	1030	169	13†	587	69
	90	6	1481	112	6	506	102
	100	11	919	256	10†	453	99
	120	45	1258	192	40†	574	64
	180	4	2076	90	4	1069	183
V_d [L/m²]	60	4	3.0	87	NA	NA	NA
	80	23†	2.2	55	NA	NA	NA
	90	6	1.5	40	NA	NA	NA
	100	11	2.2	24	NA	NA	NA
	120	45	1.9	52	NA	NA	NA
	180	4	2.1	30	NA	NA	NA

[00207] †t1/2 and AUC0-∞ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available. Cmax are in µg/ml for total irinotecan and ng/ml for SN-38; AUC are in h µg/ml for total irinotecan and h ng/ml for SN-38.

[00208] The above PK results obtained from patients treated with either nal-IRI or free irinotecan confirmed the pre-clinical observation that nal-IRI extended plasma PK of both CPT-11 and SN-38 compared to treatment with free irinotecan. Further, a Phase I clinical study of nal-IRI monotherapy (protocol nal-IRI-01-01-02; NCT# 01770353) investigated tumor levels of both CPT-11 and SN-38 following treatment with nal-IRI using post-treatment biopsies. Based on model predictions, SN-38 levels in tumor were expected to be higher than in plasma, suggesting local conversion of CPT-11 to SN-38 in the tumor microenvironment with nal-IRI (Figure 3A). Predictions were confirmed by measuring levels of CPT-11 and SN-38 in tumor biopsy samples collected from patients 72 hours post-dose, demonstrating 5-fold higher levels of SN-38 in the tumor than the plasma (Figure 3B-C). Collectively the evidence suggests that the prolonged systemic exposure to CPT-11 and SN-38 leads to prolonged levels of SN-38 in tumor

tissue, which in turn leads to prolonged DNA damage to tumor cells, suggesting an advantage of nal-IRI compared to conventional irinotecan.

Nal-IRI Safety in Humans

[00209] It has been shown in animal and human PK studies that once irinotecan is released from the nal-IRI liposomes, the conversion of irinotecan to SN-38 is similar to that of the unencapsulated irinotecan. The safety of nal-IRI, therefore, may be indirectly compared with the safety of irinotecan, primarily based on a qualitative comparison of adverse reactions, as reported in the Camptosar US label for irinotecan. The comparison is qualitative, as both irinotecan and nal-IRI have been used in different doses and schedules as monotherapy and combination therapy with other chemotherapeutic agents; therefore, quantitative comparisons are difficult. The most common adverse reactions of irinotecan and nal-IRI are similar and are mainly gastrointestinal events and myelosuppression.

[00210] The common adverse reactions (>30%) observed in clinical studies with irinotecan in combination with other agents are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia. The common adverse reactions (>30%) observed in single agent irinotecan therapy in clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia (Camptosar US label).

[00211] With respect to liposomal irinotecan, nal-IRI, when used in combination with 5-FU and leucovorin, the most common adverse reactions (≥20 %) observed in clinical trials considered to be related are: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia. The overall safety profile of nal-IRI is presented in detail in the related Investigator Brochure. Additionally, Table 5 summarizes ≥ Grade 3 safety data from the NAPOLI-1 trial comparing nal-IRI + 5-FU/LV (at a dose of 80 mg/m2 given on an every 2 week schedule), or nal-IRI monotherapy (at a dose of 120 mg/m2 given on an every 3 week schedule), with 5-FU/LV alone (given weekly for 4 weeks followed by 2 weeks of rest) in the same population of patients who had received prior gemcitabine therapy.

[00212] Table 5: Summary of Grade 3 or Higher Adverse Events in NAPOLI-1 Study

	nal-IRI + 5-FU/LV (N=117)	**nal-IRI (N=147)**	**5-FU/LV (N=134)**
GRADE ≥3 NON-HEMATOLOGIC AEs IN >5% PATIENTS, %[1]			
Fatigue	14	6	4
Diarrhea	13	21	5
Vomiting	11	14	3
Nausea	8	5	3
Asthenia	8	7	7
Abdominal pain	7	8	6
Decreased appetite	4	9	2
Hypokalemia	3	12	2
Hypernatremia	3	6	2
GRADE ≥3 HEMATOLOGIC AES BASED ON LABORATORY VALUES, %[1,2]			
Neutrophil count decreased	20	16	2
Hemoglobin decreased	6	7	5
Platelet count decreased	2	1	0

1. Per CTCAE Version 4

2. Includes only patients who had at least one post-baseline assessment

Nal-IRI Clinical Efficacy in Pancreatic Cancer

[00213] Clinical efficacy of nal-IRI has been demonstrated in gemcitabine-

refractory metastatic pancreatic cancer patients: in a randomized, Phase 3, international study (NAPOLI-1), nal-IRI was given as a monotherapy, or in combination with 5-FU/LV, compared to the control arm of 5-FU/LV alone. The majority of patients enrolled in this study had received prior chemotherapy in the metastatic setting (others received gemcitabine as neoadjuvant or adjuvant therapy). Approximately 1/2 of patients were categorized as second-line, and approximately 1/3 of patients were post-second line in the metastatic setting. The nal-IRI + 5-FU/LV combination significantly prolonged OS compared to 5-FU/LV treatment alone. The median OS for the nal-IRI + 5-FU/LV combination arm was 6.1 months compared to 4.2 months for the 5-FU/LV alone control arm with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.41-0.80; p = 0.0009). The nal-IRI monotherapy arm demonstrated a median OS of 4.9 months (compared to 4.2 months in the control arm); although this was not a statistically significant difference, there was numerical improvement in ORR and CA19-9 response, suggesting activity of nal-IRI alone. Further, in patients who received ≥80% of the protocol defined treatment during the first 6 weeks of treatment (the per protocol analysis), the nal-IRI + 5-FU/LV combination arm achieved a median OS of 8.9 months vs. 5.2 months for the control arm (HR 0.47 [95% CI 0.29-0.77]; p = 0.0018). The overall response rate in the nal-IRI + 5-FU/LV combination arm was 16% vs. 1% on the control arm (p <0.001). The results from this study are very promising and provide motivation for testing nal-IRI in pancreatic cancer patients not previously treated with gemcitabine.

Study Rationale

[00214] As mentioned previously, metastatic pancreatic cancer patients have a very poor prognosis and low median survival rates (< 1 year), necessitating the need for new treatment options. nal-IRI is a novel agent which has demonstrated efficacy in the Phase 3 NAPOLI-1 trial, in patients with metastatic pancreatic cancer previously treated with gemcitabine. This study will examine the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5-FU/LV and oxaliplatin, and nal-IRI + 5-FU/LV (the NAPOLI-1 regimen), compared with nab-paclitaxel and gemcitabine (a standard of care control) in previously untreated metastatic pancreatic cancer patients.

Rationale for Arm 1: Nal-IRI + 5-FU/LV + Oxaliplatin

[00215] The combination of 5-FU/LV + irinotecan + oxaliplatin (the FOLFIRINOX regimen) has been studied in multiple clinical trials. As mentioned previously, FOLFIRINOX has become a standard of care regimen for patients with good performance status based on the results of a single Phase 3 trial conducted in France of 342 patients showing mOS of 11.1 months vs. 6.8 months for the gemcitabine alone control arm (HR 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). The FOLFIRINOX regimen has been recommended by the NCCN as a preferred option for first-line metastatic disease since 2011. However, there are some concerns about the toxicity associated with FOLFIRINOX, as the reported incidence of grade 3 or 4 toxicity was significantly greater in the FOLFIRINOX group than in the gemcitabine control group, specifically neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), thrombocytopenia (9% vs. 4%), diarrhea (13% vs. 2%), and sensory neuropathy (9% vs. 0%).

[00216] In the current study, nal-IRI will be evaluated instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of the FOLFIRINOX regimen. By adding oxaliplatin to the NAPOLI-1 regimen that has proven efficacy in post-gemcitabine pancreatic cancer, the potential to increase DNA damage and potentiate efficacy exists.

[00217] Further, due to the nal-IRI prolonged PK properties and sustained tumor exposure, it is thought that using nal-IRI instead of conventional irinotecan would improve upon the efficacy of FOLFIRINOX. In order to test this hypothesis pre-clinically, the FOLFIRINOX regimen was tested against the nal-IRI + 5-FU/LV + oxaliplatin regimen in a pancreatic tumor xenograft mouse model (Figure 4). Results show that nal-IRI performs better than conventional irinotecan at equivalent exposure doses (5 mg/kg nal-IRI vs. 25 mg/kg free IRI) in the BxPC-3 pancreatic cancer model either alone (Figure 4A), or in combination with oxaliplatin and/or 5-FU (Figure 4B)

[00218] In the mouse model tested, the addition of oxaliplatin to the doublet combinations of FOLFIRI or nal-IRI+5-FU/LV causes a slight increase in tumor growth inhibition (Figure 4B: compare light green to pink for FOLFIRI vs. FOLFIRINOX; compare dark green to red for nal-IRI+5-FU/LV vs. nal-IRI+5-FU/LV+Ox). However, comparison of FOLFIRI versus the nal-IRI+5-FU/LV doublet (light green vs. dark green), and FOLFIRINOX vs. the nal-IRI+5-FU/LV+Ox triplet (pink vs. red), demonstrates significantly more tumor growth inhibition with the nal-IRI-containing regimens. Further, the nal-IRI-containing doublet

regimen performed better than the FOLFIRINOX triplet (dark green vs. pink), owing to the improved efficacy of nal-IRI compared to conventional irinotecan.

[00219] In humans, the standard dose regimen of FOLFIRINOX which demonstrated efficacy is 85 mg/m2 oxaliplatin, 180 mg/m2 irinotecan, and fluorouracil at a dose of 400 mg/m2 administered by IV bolus followed by a continuous infusion of 2400 mg/m2. 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. In the current study, a modified triplet regimen is proposed, whereby no bolus of 5-FU will be administered. The target dose of oxaliplatin (85 mg/m2) is proposed in the Arm 1 combination regimen with the standard continuous infusion dose of 5-FU (excluding the bolus), and the every 2 week dose of nal-IRI previously shown to be tolerable and efficacious in combination with 5-FU. Note that with nal-IRI dosing, the Cmax of SN-38 is predicted to be lower than would be expected for standard dosing with free irinotecan. Additionally, in a small Phase 2 study in colorectal cancer, data suggest that nal-IRI + 5-FU/LV may have less toxicity than FOLFIRI (Chibaudel et al, J Clin Oncol 33, 2015 (suppl 3; abstr 751). Therefore, toxicity of the nal-IRI-containing triplet regimen is not expected to be greater than that seen with FOLFIRINOX; nonetheless, a safety run-in of this combination will be tested in Part 1 of this study.

Rationale for Arm 2: Nal-IRI + 5-FU/LV

[00220] Tolerability of multi-drug regimens is important in advanced cancer. The longer the duration of manageable treatment should translate into improved outcome due to longer drug exposure. Triplet drug regimens such as FOLFIRINOX are 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 doublet regimens can be identified, patients may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit. Given the statistically significant improvement of OS of the nal-IRI + 5-FU/LV doublet in patients with metastatic pancreatic cancer previously treated with gemcitabine in the NAPOLI-1 trial, it is logical to test this combination in previously untreated metastatic pancreatic cancer. As suggested by the pre-clinical data (shown in Figure 4, above), it is possible that the advantages of the liposomal formulation of nal-IRI

result in a more effective doublet, such that the addition of oxaliplatin may not be necessary to significantly impact tumor response. In this case, patients may be spared additional toxicity that would be expected with the addition of oxaliplatin. Table 6 below summarizes the efficacy and safety results of the NAPOLI-1 trial compared with two standard of care options for first-line metastatic disease. Although this is a cross-study comparison, the nal-IRI + 5-FU/LV doublet regimen may have a safety advantage over either FOLFIRINOX or the combination of nab-paclitaxel + gemcitabine with respect to both neutropenia and neuropathy.

[00221] Table 6: Comparison of Efficacy and Safety Characteristics of nal-IRI + 5-FU/LV versus 2 Standard of Care Regimens

Regimens	**nal-IRI + 5FU-LV[1]**	**FOLFIRINOX[2]**	**nab-Paclitaxel + gemcitabine + [3]**
Setting	Post-gemcitabine	Front-line Metastatic Disease	
Efficacy			
Hazard Ratio	0.57	0.57	0.72
Median Overall Survival	6.1 months	11.1 months	8.5 months
Change vs. Control	1.9 months	4.3 months	1.8 months
Adverse Events ≥ Grade 3			
Neutropenia	20%	45%	38%
Febrile neutropenia	2%	5%	3%
Fatigue	14%	24%	17%
Vomiting	11%	15%	<5%
Diarrhea	13%	13%	6%
Neuropathy	None	9%	17%

- Data from Phase 3 trial of nal-IRI + 5-FU/LV vs. 5-FU/LV
- Data from Phase 3 trial of FOLFIRNOX vs. gemcitabine
- Data from Phase 3 trial of nab-paclitaxel + gemcitabine vs. gemcitabine

Rationale for Arm 3: nab-Paclitaxel + Gemcitabine Control Arm

[00222] While many gemcitabine-based combination regimens have been tested in clinical trials, nab-paclitaxel plus gemcitabine is the only approved standard of care regimen that offers significant benefit for first-line treatment of metastatic pancreatic cancer. The nab-paclitaxel + gemcitabine combination became a preferred first-line treatment option according to the NCCN recommendations in 2013. In a Phase 3, international study of 861 patients (MPACT trial), nab-paclitaxel + gemcitabine demonstrated a mOS of 8.5 months versus 6.7 months for gemcitabine alone (HR 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). While nab-paclitaxel + gemcitabine is generally thought to be more tolerable than FOLFIRINOX, this combination is associated with neuropathy and neutropenia, and has not been compared directly with FOLFIRINOX (see Table 6). In the current study, the nab-paclitaxel + gemcitabine regimen will be compared to nal-IRI-containing regimens, including the modified triplet regimen which substitutes nal-IRI instead of irinotecan.

Study Objectives

PART 1

[00223] **Primary Objectives**

i. To evaluate the safety and tolerability of nal-IRI + 5FU/LV + oxaliplatin

ii. To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5FU/LV + oxaliplatin and determine the Part 2 dose of the triplet combination

[00224] **Secondary Objectives**

i. To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin

[00225] **PART 2**

[00226] **Primary Objectives**

i. To assess efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using the progression-free survival (PFS) rate at 24 weeks

[00227] **Secondary Objectives**

i. To assess the efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using overall survival (OS), PFS, and objective response rate (ORR; CR + PR, per

RECIST v1.1)

ii. To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine

iii. To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) in each arm

iv. To compare the safety and adverse event profile between the treatment arms

[00228] **Exploratory Objectives**

i. To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI PK, toxicity, and/or response

Study Design

Study Design Overview

[00229] The present study is an open-label, phase 2 comparative study to assess the safety, tolerability, and efficacy of nal-IRI 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 will assess the following regimens:

i. nal-IRI + 5-FU/LV + oxaliplatin (Arm 1)

ii. nal-IRI + 5-FU/LV (Arm 2)

iii. nab-paclitaxel + gemcitabine (Arm 3)

[00230] The study will be conducted in two parts, as illustrated in the schematic below: 1) a safety run-in of the nal-IRI + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the nal-IRI + 5-FU/LV + oxaliplatin regimen, the nal-IRI + 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.

[00231] <u>Part 1:</u>

[00232] As schematically shown in Figure 5, Part 1 will consist of an open-label safety run-in of the combination regimen in Arm 1: nal-IRI + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and nal-IRI + 5-FU/LV has been

demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore will not be included in this part of the study. The safety run-in will enroll 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) will be evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2nd 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 will be initiated following agreement between the Investigators, Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort will be expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose will be considered to exceed the safety and tolerability criteria of the combination, and the dose will not be escalated further; however, lower doses may be explored. The Part 2 dose will then be defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a toxicity that qualifies as a DLT.

[00233] Additionally, UGT1A1*28 allele status will be 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/m2 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 nal-IRI have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study (UCSF 8603, as referenced in Table 1 above) 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 will not be required prior to the first dose of nal-IRI on this study and the starting dose for all patients will be 80 mg/m2. However, if patients are known to be homozygous for UGT1A1*28, the dose of nal-IRI may be reduced as described herein.

Part 2:

[00234] Part 2 will consist of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV, or nab-paclitaxel + gemcitabine. The randomization will be stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1).

[00235] During Part 2, a regular review of safety data will be conducted by an independent Data and Safety Monitoring Board (DSMB). The DSMB will consist of oncology and statistical experts, independent of the Sponsor. The timing of the safety reviews, and the workings of the DSMB, will be detailed in the DSMB charter. The DSMB is a precaution in the event of unanticipated toxicities, and the study will not be stopped early on the basis of differences in efficacy, therefore no prospective adjustment of the final significance levels is planned on the basis of this review.

Translational Research:

[00236] Translational research components will include collection of blood samples (Parts 1 and 2) and archived tumor (during screening, if available) to look for potential biomarkers. Analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).

Part 1 Safety Assessment

Toxicities with Oxaliplatin

[00237] Since the individual therapies included in the proposed combination have been studied in previous clinical trials, it is important that the safety assessment takes into account the expected safety profile of the standard dose regimen (e.g. FOLFIRINOX). The following adverse events are common ($\geq$ 40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the nal-IRI-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 will be evaluated for safety and tolerability in Part 1 of the study as described below.

DLT Definition for Arm 1 (nal-IRI + 5-FU/LV + oxaliplatin)

[00238] For nal-IRI administered in combination with 5-FU/LV and oxaliplatin, the following adverse events will be considered as dose limiting toxicities (DLTs) if they occur during the first cycle of treatment and are deemed related to the study treatment regimen. Any toxicity that is related to disease progression will not be considered a DLT.

i. 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)

ii. Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection

iii. Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity

iv. Any grade 4 non-hematologic toxicity with the specific exclusion of:

1. Fatigue/asthenia < 2 weeks in duration
2. Increases in alkaline phosphatase levels
3. Nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen)
4. Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

[00239] The final determination of DLTs will be made following discussion between the DLT review committee (i.e. the Part 1 Investigators, the Medical Monitor, and the Sponsor). As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status. If a patient in any cohort experiences a DLT, and is found to be homozygous for the UGT1A1*28 allele, the Investigators, Medical Monitor, and Sponsor

will assess if the adverse event was attributable to the patient's UGT1A1*28 homozygous status prior to being assigned the category of DLT. Additionally, adverse events meeting the criteria above which are also known adverse reactions of either 5-FU or oxaliplatin based on reported safety data, and unexpected of nal-IRI, will be discussed between the Investigators, Medical Monitor and Sponsor before being assigned the category of DLT in the first cycle of treatment.

Part 2 Dose Confirmation (Arm 1)

[00240] The standard dose of oxaliplatin in the FOLFIRINOX regimen is 85 mg/m2, based on the established FOLFIRINOX regimen published by Conroy et al., and is therefore the target dose for Part 2 of this study. The purpose of Part 1 is to confirm whether this dose is compatible when nal-IRI is used instead of conventional irinotecan. In case there are any unexpected toxicities, 3 to 6 patients will be initially treated at a lower dose of oxaliplatin (60 mg/m2, see Table 7) prior to administration of oxaliplatin at the highest proposed dose of 85 mg/m2. The dose of the triplet combination to be administered in Part 2 of the study will be 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 will be enrolled at that dose level, for no more than 6 total patients per cohort. If no additional DLTs are observed, the dose escalation will resume. If a second patient experiences a treatment-related toxicity that qualifies as a DLT at that dose, that dose will be considered to exceed the optimal safety and tolerability criteria of the combination. The dose to be used in Part 2 will then be defined as the next lower dose level in which 6 patients were treated and $\leq$ 1 patient experienced a toxicity that qualifies as a DLT.

Enrollment and Treatment

[00241] Approximately 6-18 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. The total enrollment for the study will be approximately 156-168 patients.

[00242] Patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of study drug), toxicity, or physician or patient's choice (see Patient Discontinuation).

Method of Assigning Patients to Treatment Groups

Part 1

[00243] It is expected that multiple sites will participate in Part 1 of this trial.

Enrollment will be based on the availability of patients at each site and the availability of slots in each cohort. Slots must be confirmed by the Sponsor, or designee, prior to consenting patients to Part 1. A reasonable attempt will be made to equally distribute patients between sites. Enrollment can proceed to the next cohort after the safety data from the first cycle in the previous cohort have been evaluated as described herein.

Part 2

[00244] Three arms are planned to enroll in parallel in Part 2, and enrollment into Part 2 will begin once the dose has been confirmed for Arm 1. After all screening assessments have been completed, patients will be randomized 1:1:1 using a computerized interactive web response system (IWRS). Randomization must occur within 7 days of planned dosing. The randomization will be stratified based on region (East Asia vs. rest of the world).

Part 1 Dose Levels

[00245] Dosing of patient cohorts will begin at dose level 1 with planned escalation to dose level 2 (target dose), in which the dose for one of the three drugs will be increased while the other two drugs will maintain a constant dose. In the event that any of the planned dose levels is not tolerable, de-escalation to the -1 or -2 dose levels may be tested as appropriate. If the -1 dose level is evaluated and deemed to be safe, escalation to the -2B dose level may be initiated. If dose level 2 is not tolerable, de-escalation to either dose level -2A and/or -2B may occur. 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 7 below; additional details on dose administration as described herein in the section "Study Treatment".

[00246] Table 7: Part 1 Dose Escalation Table (nal-IRI + 5-FU/LV + oxaliplatin)

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

2[e]	85	1, 15	2400/400	1, 15	80	1, 15
-2A[d]	75	1, 15	2400/400	1, 15	80	1, 15
-2B[d]	85	1, 15	2400/400	1, 15	60	1, 15

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

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

c Day indicated is part of a 28-day cycle

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

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

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

Decision Process for Dose Escalation

[00247] Decisions to escalate or de-escalate the dose to the next cohort will be made by mutual agreement of the DLT review committee (defined as Part 1 Investigators, the Medical Monitor, and the Sponsor) in accordance with the criteria described below. Regularly scheduled teleconferences of the Part 1 Investigators, Medical Monitor, and Sponsor will serve as a forum for ongoing review of safety and other relevant data. Decisions to escalate or de-escalate the dose must be agreed by the majority of the DLT review committee members, and will be documented along with a summary of the information supporting the decision.

Decision Criteria for Dose Escalation

[00248] The safety assessment period for purposes of DLT evaluation and dose escalation decisions will be 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 will 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) will be assessed for their potential relationship to cumulative nal-IRI or combination therapy doses and considered in the decision to escalate the dose. PK data may be available, but will not be required for decisions on dose escalation.

Patient Replacement

[00249] For Part 1, if a patient discontinues study treatment before completing one cycle, for reasons other than a DLT, or for adverse events that are clearly unrelated to study drug, then that patient may be replaced by a new patient at the same dose level. Patients must receive all doses of study drugs in Cycle 1 to contribute to the safety evaluation of the cohort.

Patient Selection and Discontinuation

Inclusion Criteria

[00250] In order for inclusion into the study, patients must have/be:

i. Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting

1. Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment
2. Part 2: must have metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed

ii. Measurable or non-measurable disease as defined by RECIST v1.1

iii. ECOG performance status of 0 or 1

iv. Adequate biological parameters as evidenced by the following blood counts:

1. ANC > 1,500 cells/μl without the use of hematopoietic growth factors,
2. Platelet count > 100,000 cells/μl, and
3. Hemoglobin > 9 g/dL

v. Adequate hepatic function as evidenced by:

1. Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and
2. AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present)

vi. 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 body weight should be used instead.

vii. Normal ECG or ECG without any clinically significant findings

viii. Recovered from the effects of any prior surgery or radiotherapy

ix. ≥ 18 years of age

x. Agreeable to submit unstained archived tumor tissue for analysis, if available

xi. Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Exclusion Criteria

[00251] Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

i. Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed)

ii. 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)

iii. Known metastasis to the central nervous system

iv. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction

v. 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.

vi. Known hypersensitivity to any of the components of nal-IRI, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin

vii. Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only)

viii. Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including:

1. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris,

stroke) less than 6 months before inclusion

2. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

3. Known historical or active infection with HIV, hepatitis B, or hepatitis C

ix. 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

x. Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan1

xi. Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin

xii. Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only)2

xiii. 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 interfere with the interpretation of the results

xiv. 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 drug3.

Patient Discontinuation

[00252] A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until Investigator-determined progressive disease per RECIST v1.1 or unacceptable toxicity. Some possible reasons for early discontinuation of study treatment include, but are not limited to the following:

i. Progressive neoplastic disease per RECIST v1.1

ii. The patient experiences an adverse event which:

1. in the opinion of the Investigator, precludes further participation in the trial

[1] See above text for examples of strong CYP3A4 inhibitors or inducers.
[2] See examples herein of strong CYP2C8 inhibitors or inducers.
[3] For a description of highly effective contraceptive measures, please see Appendix 2.

2. requires treatment to be withheld for more than 14 days, unless in the opinion of the investigator the patient is receiving benefit from the study treatment

3. requires more than 2 dose reductions

iii. Clinical and/or symptomatic deterioration

iv. Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial

v. Significant noncompliance with the protocol per PI assessment

vi. Withdrawal of consent

vii. The Investigator removes the patient from the trial in the best interests of the patient

viii. Study termination by the Sponsor

ix. Use of prohibited concomitant medications

x. Patient is lost to follow up

[00253] If a patient withdraws from the trial, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. Following treatment discontinuation for other reasons above, all procedures and evaluations required at the 30 day follow up visit should be completed. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records.

Study Treatment

Investigational Product

Description of Nal-IRI

[00254] Nal-IRI (irinotecan liposome injection, also known MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL or 9.5 mL of nal-IRI at a concentration of 5 mg/mL. Nal-IRI must be stored refrigerated at 2 to 8°C, with protection from

light. The appearance of MM-398 is white to slightly yellow opaque liquid.

Storage and Handling of Nal-IRI

[00255] Nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. Nal-IRI must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the Sponsor or its designee if they notice a problem with the study drug.

[00256] Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 6 hours if kept at room temperature (15-30°C).

Packaging and Labeling of Nal-IRI

[00257] Twenty vials of nal-IRI will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

Administration of Nal-IRI

[00258] See combination regimen administration instructions below for Arms 1 and 2.

Potential Toxicity of Nal-IRI

[00259] Data from previous nal-IRI studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the recommended treatment procedures for managing those toxicities are provided below. Certain known adverse reactions of irinotecan have not been observed with nal-IRI to date. This could be due to the limited cumulative patient exposure to date of nal-IRI, or the use of appropriate premedication and early recognition and treatment of expected adverse events. The adverse reactions not observed include anaphylaxis or anaphylactoid reaction, interstitial lung disease-like pulmonary toxicity and acute pancreatitis. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with nal-IRI.

Diarrhea

[00260] Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of nal-IRI, prophylactic administration of atropine will be given at the discretion of the investigator.

[00261] Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide, as described in Section (Therapy for Diarrhea). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

[00262] Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion, provided it is administered within parameters specified as described herein.

Hypersensitivity

[00263] Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed with irinotecan, however, have not been observed with nal-IRI to date. This could be due to the limited cumulative patient exposure to date of nal-IRI, or the use of appropriate premedication and early recognition and treatment of expected

adverse events. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with nal-IRI. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

[00264] **Colitis/Ileus**

[00265] Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

[00266] **Thromboembolism**

[00267] Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

[00268] **Pregnancy**

[00269] The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

[00270] **Care of Intravenous Site**

[00271] Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended, or as per institutional standard of care.

[00272] **Patients at Particular Risk**

[00273] In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

[00274] **Acute Infusion Associated Reactions**

[00275] Acute infusion-associated reactions characterized by flushing,

shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications. See guidelines on the management of infusion reactions.

[00276] **Other Potential Toxicities**

[00277] Nal-IRI, the liposomal formulation of irinotecan is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

[00278] **Additional Anticancer Therapies**

[00279] Depending on the assigned treatment arm, patients may be treated with one or more of the following approved therapies:

i. 5-FU/LV
ii. oxaliplatin
iii. nab-paclitaxel
iv. gemcitabine

[00280] **Description of Combination Therapies**

[00281] A description of each anticancer therapy to be used in combination with nal-IRI is described herein.

[00282] **Storage and Handling of Combination Therapies**

[00283] Refer to the country specific package inserts or SmPC for details on storage and handling for 5-FU and leucovorin, oxaliplatin, nab-paclitaxel, and gemcitabine.

[00284] **Packaging and Labeling of Combination Therapies**

[00285] Commercially available 5-FU and leucovorin (*l* + d racemic form, or the levoleucovorin *l* form), oxaliplatin, nab-paclitaxel, and gemcitabine will be provided to enrolled patients in accordance with the specific treatment regimen in the respective arms. All patients who are enrolled to Arms 1 and 2 will be provided with 5-FU, leucovorin, and oxaliplatin, if applicable. All patients who are enrolled to Arm 3 will be provided with nab-paclitaxel and gemcitabine, if applicable.

[00286] **Potential Toxicities of Combination Therapies**

[00287] **Potential Toxicities with 5-FU (Arms 1 and 2)**

[00288] Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea, emesis and leukopenia are commonly seen with treatment; alopecia and dermatitis, in the form of pruritic rash usually appearing on the extremities, may also be seen (see US package insert or SmPC). Common adverse events (≥20 %) that were observed with nal-IRI in combination with 5-FU/LV in clinical trials considered to be related were: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia.

[00289] **Potential Toxicities with Oxaliplatin (Arm 1)**

[00290] The following adverse events are relatively common (≥ 40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the nal-IRI-containing regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. In a phase 3 study of the FOLFIRINOX regimen (5-FU/LV + irinotecan + oxaliplatin), 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. Grade 3/4 hypersensitivity reactions, including anaphylactic reactions, have been observed in 2-3% of colon cancer patients receiving oxaliplatin; see package insert for more information. See guidelines on the management of infusion reactions. Additional adverse events may be anticipated, as described in the package insert or SmPC for oxaliplatin.

[00291] **Potential Toxicities with nab-Paclitaxel and Gemcitabine (Arm 3)**

[00292] The most common adverse reactions (≥20%) for single agent gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

[00293] The following adverse events are relatively common (≥ 20%) with nab-paclitaxel and gemcitabine combination treatment and are to be expected with the addition of nal-IRI: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema,

diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration.

[00294] Severe hypersensitivity reactions with fatal outcome have been reported with nab-paclitaxel treatment; see guidelines on the management of infusion reactions. Additional adverse events may be anticipated, as described in the package inserts for nab-paclitaxel and gemcitabine.

[00295] **Combination Regimen Dosage and Administration**

[00296] **Arm 1: Nal-IRI + 5-FU/LV + Oxaliplatin**

[00297] The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by oxaliplatin, then LV, followed by 5-FU.

[00298] In Part 1, patients will 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.

[00299] **Arm 1 Premedication**

[00300] All patients must be premedicated prior to nal-IRI 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.

[00301] **Arm 2: Nal-IRI + 5-FU/LV**

[00302] The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by LV, followed by 5-FU.

[00303] **Arm 2 Premedication**

[00304] All patients must be premedicated prior to nal-IRI 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.

[00305] **Doses and Administration of Nal-IRI (Arms 1 and 2)**

[00306] Nal-IRI will be 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.

[00307] Prior to administration, the appropriate dose of nal-IRI 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. Nal-IRI can be administered at a rate of up to 1 mL/sec (30 mg/sec).

[00308] The actual dose of nal-IRI 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 nal-IRI 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.

[00309] **Doses and Administration of 5-FU and Leucovorin (Arms 1 and 2)**

[00310] Leucovorin will be 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

[00311] 5-FU will be 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

[00312] Leucovorin should be reconstituted per the instructions on the package insert, SmPC or standard institutional guidelines for reconstitution of leucovorin.

[00313] 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 will be 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.

[00314] **Doses and Administration of Oxaliplatin (Arm 1 only)**

[00315] In Part 1, oxaliplatin will be administered at increasing dose levels as indicated in Table 7 (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

[00316] In Part 2, oxaliplatin will be 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)

[00317] Oxaliplatin should be prepared according to the instructions on the package insert, SmPC or per standard institutional guidelines for preparation and administration of oxaliplatin.

[00318] Oxaliplatin should be administered following nal-IRI infusion; in Part 1, the first 3 patients in Dose Level 1 will begin the oxaliplatin infusion two hours after the completion of the MM-398 infusion. Actual dose of oxaliplatin to be administered will be 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.

[00319] **Arm 3: nab-Paclitaxel + Gemcitabine**

[00320] The order of the infusions to be administered in the clinic will be as follows: nab-paclitaxel will be administered first, followed by gemcitabine.

[00321] **Arm 3 Premedication**

[00322] 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.

[00323] **Doses and Administration of nab-Paclitaxel and Gemcitabine (Arm 3)**

[00324] 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

[00325] 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

[00326] **Management of Infusion Reactions**

[00327] The guidelines described in this section can be followed in case of infusion reactions to any study treatment given per protocol (e.g. nal-IRI, oxaliplatin, nab-paclitaxel, etc.). Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03) definitions of an allergic reaction or anaphylaxis as defined below:

[00328] Allergic reaction (i.e., a disorder characterized by an adverse local or general response from exposure to an allergen):

[00329] Grade 1: Transient flushing or rash, drug fever <38° C (<100.4°F); intervention not indicated

[00330] Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=≤ 24 hrs.

[00331] Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)

[00332] Grade 4: Life-threatening consequences; urgent intervention indicated

[00333] Anaphylaxis (i.e., a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death):

[00334] Grade 1: Not applicable

[00335] Grade 2: Not applicable

[00336] Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension

[00337] Grade 4: Life-threatening consequences; urgent intervention indicated

[00338] Institutional policies or the following treatment guidelines shall be used for the management of infusion reactions.

[00339] Grade 1

[00340] Slow infusion rate by 50%

[00341] Monitor patient every 15 minutes for worsening of condition

[00342] Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator

[00343] Grade 2

[00344] Stop infusion

[00345] Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen

[00346] Resume infusion at 50% of the prior rate once infusion reaction has resolved

[00347] Monitor patient every 15 minutes for worsening of condition

[00348] For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

[00349] Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator

[00350] Grade 3

[00351] Stop infusion and disconnect infusion tubing from patient

[00352] Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary

[00353] No further treatment will be permitted

[00354] Grade 4

[00355] Stop the infusion and disconnect infusion tubing from patient

[00356] Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm

[00357] Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV and other medications as medically necessary

[00358] Consider hospital admission for observation

[00359] No further treatment will be permitted

[00360] For patients who experience a second grade 1 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 or as per institutional guidelines.

[00361] **Dose Modifications**

[00362] The toxicity of each cycle must be recorded prior to the

administration of a subsequent cycle and graded according to the NCI CTCAE (Version 4.03). All dose reductions for all arms should be based on the worst preceding toxicity.

[00363] 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 nal-IRI + 5-FU/LV at the discretion of the Investigator.

[00364] 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.

[00365] **Arm 1 and Arm 2 Dose Modifications**

[00366] Prior to each dosing, patients must have:

i. ANC $\geq$ 1500/mm^3
ii. WBC $\geq$ 3500/ mm^3
iii. Platelet count $\geq$ 100,000/ mm^3
iv. Diarrhea $\leq$ Grade 1

[00367] 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 $\geq$ 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 hematologic toxicities (Table 8), and for non-hematological toxicities (Table 9), and were based on published dose modifications for the established FOLFIRINOX regimen. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management should be followed.

[00368] For all tables below, patient should be withdrawn from study

treatment if more than 2 dose reductions are required or if nal-IRI reductions lower than 50 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.

[00369] Treatment discontinuation that is required due to nal-IRI 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 nal-IRI + 5-FU/LV only for all future dosing.

[00370] Table 8: Arm 1 and Arm 2 Dose Modifications for Hematologic Toxicities

Worst Toxicity by CTCAE Grade	**Nal-IRI**	**5-FU**	**Oxaliplatin[a]**
Grade 2 neutropenia (ANC <1500 - 1000 cells/ mm^3)	100 % of previous dose	100 % of previous dose	1st occurrence: 100% of previous dose 2nd occurrence: Reduce dose to 60 mg/m^2
Grade 3 or 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia[b]	1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	1st occurrence: 100% of previous dose 2nd occurrence: Reduce dose to 60 mg/m^2
≥ Grade 2 thrombocytopenia (Grade 2: platelets ≤ 75,000/mm^3 – 50,000/mm^3 OR	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 60 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	1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Maintenance of the reduced dose

Grade 3-4: platelets < 50,000/mm^3)	2nd occurrence: Reduce dose to 50 mg/m^2	dose another 25% (50% of original dose)	of 60 mg/m^2
Other hematologic toxicities not specifically listed above	If ≤ Grade 2: 100% of previous dose If ≥ Grade 3: 1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	If ≤ Grade 2: 100% of previous dose If ≥ Grade 3: 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	If ≤ Grade 2: 100% of previous dose If ≥ Grade 3: 1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Maintenance of the reduced dose of 60 mg/m^2

[a]Applies to Arm 1 only; disregard this column for Arm 2 patients

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

[00371] Table 9: Arm 1 and Arm 2 Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia [A,E]

Worst Toxicity by CTCAE Grade	**Nal-IRI**	**5-FU**	**Oxaliplatin[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 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)[e] *except for Grade 3 or 4 hand foot syndrome	1st occurrence[e]: 100% of previous dose 2nd occurrence: Reduce dose to 60 mg/m^2
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND reduce dose to 60 mg/m^2 ; if the patient is already receiving 60 mg/m^2, reduce dose to 50 mg/m^{2,f}	Optimize anti-emetic therapy AND reduce dose by 25% ; if the patient is already receiving a reduced dose, reduce dose an additional 25%[f]	1st occurrence[e]: 100% of previous dose 2nd occurrence: Reduce dose to 60 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% (50% of original dose)[e]	100 % of previous dose[e]
Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	Discontinue therapy	No dose modifications required[e]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	No dose modifications required[e]	Discontinue therapy	No dose modifications required[e]

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

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

[b] Applies to Arm 1 only; disregard this column for Arm 2 patients

[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

[e] Any toxicity $\geq$ Grade 2, except anemia and alopecia, can justify a dose reduction if medically indicated (e.g. reduction of oxaliplatin to 60 mg/m^2)

[f] Patients who require more than 2 dose reductions must be withdrawn from the study

[g] Patients who discontinue therapy due to oxaliplatin-related neuropathy may remain on study and continue to receive nal-IRI + 5-FU/LV

[00372] Nal-IRI Dose Modifications for UGT1A1*28 Positive Patients (Arms 1 and 2)

[00373] Patients will be tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of nal-IRI. All patients will begin dosing at 80 mg/m2, 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/m2 of nal-

IRI: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m2 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 will be replaced.

[00374] **Arm 3 Dose Modifications**

[00375] Dose level reductions required due to toxicities related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 10.

[00376] Table 10: 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

[00377] Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 11 and adjustments related to other toxicities are provided in Table 12.

[00378] Table 11: 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

Cycle Day	**ANC (cells/mm^3)**		**Platelet count (cells/mm^3)**	**Nab-paclitaxel / Gemcitabine**
	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

[00379] Table 12: 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	

[00380] **Other Toxicities Requiring Special Attention**

[00381] For all treatment arms, QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhea as described above.

[00382] **Rules for Dose Omissions and Modified Schedules**

[00383] The following guidance should be followed when all study drugs in any arm are held/missed:

i. If **Day 1** doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient

ii. If **Day 8** doses are held/missed (**applies to Arm 3 only**): the cycle will continue per

protocol and those doses will be considered missed.

iii. If **Day 15** doses are held/missed:

1. **Arms 1 and 2 only:** if toxicity recovers within 7 days, the day 15 doses may be delayed and subsequently given 1 week late. The next cycle would then continue 14 days following the administration of the delayed Day 15 dose. However, if the toxicity recovers between 7-14 days after scheduled Day 15 dose (i.e. dose is delayed for 2 weeks), that dose will be considered missed and Day 1 of the next cycle should occur as originally scheduled.

2. **Arm 3 only:** the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers (e.g. if toxicity recovers within 7 days, that week will be considered the rest week, and the next cycle can begin 1 week after the previously scheduled Day 15 dose; alternatively, if the toxicity recovers between 7-14 days from the scheduled Day 15 dose, the Day 1 dose of the next cycle should occur as originally scheduled).

[00384] **Drug Accountability**

[00385] The Investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of all study drugs provided by the Sponsor. A record of all vials of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor. The following information will be recorded:

i. Date and quantity of study drug received

ii. Date and quantity of study drug dispensed from the pharmacy per patient

iii. Date and quantity of study drug administered to each patient

iv. Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)

v. Date and quantity of study drug returned to sponsor

[00386] Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received, after which the Investigator or the Investigator's designee will place the invoice in the Investigator's file.

[00387] During monitoring, the Sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug

remaining at each site. At the conclusion of the study, the monitor will package and ship all unused vials of study drug back to Sponsor for destruction. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the Investigator's file.

[00388] **Concomitant Therapy**

[00389] All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions (see also Section "

[00390] Prohibited **Therapy**"). All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

[00391] Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

[00392] **Antiemetic Medications**

[00393] Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered as premedications to all patients assigned to Arm 1 and Arm 2 unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.

[00394] **Granulocyte Colony Stimulating Factors**

[00395] Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever. In Part 1, prophylactic use of G-CSF will be permitted only in those patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy. In Part 2, prophylactic use of G-CSF is recommended for patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy, however primary prophylaxis with G-CSF may be considered for high-risk patients.

[00396] **Therapy for Diarrhea**

[00397] Acute diarrhea and abdominal cramps, developing during or within 24 hours after nal-IRI administration, may occur as part of a cholinergic syndrome. The syndrome can be treated with atropine. Prophylactic or therapeutic administration of atropine, according to institutional standards, should be considered in patients experiencing cholinergic symptoms during the study.

[00398] Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Diarrhea should be managed according to institutional guidelines, or according to the guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea, abstracted below.

[00399] Table 13: Recommendations for Management of Chemotherapy Induced Diarrhea

Clinical Presentation	**Intervention**
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

[00400] **Prohibited Therapy**

[00401] The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any others that interact with irinotecan, 5-FU, oxaliplatin, or gemcitabine should be avoided wherever possible.

Additionally, nab-paclitaxel is catalyzed by CYP2C8 and CYP3A, therefore Part 2 patients randomized to Arm 3 should avoid concomitant treatment with strong inhibitors (ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir and nelfinavir) or inducers (rifampicin, carbamazepine, phenytoin, efavirenz, and nevgirapine) of CYP2C8 or CYP3A. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the country specific package inserts of 5-FU, leucovorin, oxaliplatin, nab-paclitaxel, or gemcitabine for any other drug interactions.

[00402] The following therapies are not permitted during the study treatment phase:

[00403] Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or antibodies

[00404] Potentially curative radiotherapy; palliative radiotherapy is permitted

[00405] Any other investigational therapy is not permitted

[00406] **Study Procedures**

[00407] **Protocol Visits**

[00408] **Screening Visit**

[00409] The screening phase will begin once the patient signs the informed consent form. All procedures for screening and baseline are outlined as described herein. For further descriptions of the clinical and laboratory assessments required, see methods described herein.

[00410] **On-study Visits**

[00411] Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in Part 1 and randomized via an IWRS in Part 2. The first dose (Cycle 1 Day 1) must be given within 7 days of enrollment/randomization. All study procedures and assessments are outlined as described herein. During the treatment period, a window of ±2 days will apply to all visits, unless otherwise stated.

[00412] **End of Treatment Visit**

[00413] All patients must complete an End of Treatment (EoT) assessment

at the time the Investigator removes the patient from treatment. This assessment should occur approximately 30 days (± 14 days) after the last dose of study treatment. All procedures and assessments are as described herein.

[00414] **Long-term Follow-up**

[00415] After the End of Treatment visit, patients should continue to be followed for survival status once every 2 months (± 14 days) via telephone, email, clinic visit, or medical record review until death, lost to follow-up, withdrawal of consent, or study closure, whichever occurs first. Additionally, data on subsequent anti-cancer treatments should be collected during these contacts and documented in the eCRF. In the case of patients who are discontinued for reasons other than progressive disease per RECIST v1.1, disease evaluations (including imaging studies) should continue into the follow-up period, as described herein below.

[00416] If a patient does not respond to the overall survival follow-up contacts, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient does not respond to these requests, the date of death may be captured from public records.

[00417] **Clinical Procedures**

[00418] **Medical History**

[00419] A medical history will include all pertinent prior medical conditions, surgeries or other medical procedures.

[00420] **Vital Signs**

[00421] Vital signs will include height (at screening only), weight, resting blood pressure, pulse, respiratory rate and temperature.

[00422] **Performance Status**

[00423] The Eastern cooperative oncology group (ECOG) Performance Status will be obtained by the PI or his/her designee by questioning the patient about their functional capabilities. See Appendix 4 for ECOG scale.

[00424] **Electrocardiogram (ECG)**

[00425] A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall impression. If ECG is abnormal, clinical significance should be indicated.

[00426] **Adverse Event and Hospitalization Assessment**

[00427] Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. For detailed information on adverse event reporting. In addition, information on patient hospitalizations and/or hospital visits should also be collected, whether or not associated with an adverse event.

[00428] **Disease Evaluation**

[00429] Tumor response will be 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, will be 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.

[00430] 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.

[00431] **EORTC-QLQ-C30 and EQ-5D-5L (Part 2 Only)**

[00432] Health-related quality of life (HRQL) will be 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.

[00433] Patients will be 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.

[00434] **Laboratory Procedures**

[00435] **Complete Blood Count**

[00436] A complete blood count (locally assessed) will include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

[00437] **Serum Chemistry**

[00438] Serum chemistry will be assessed centrally, and will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), uric acid, total protein, albumin, calcium, magnesium and phosphate. Chemistry may also be assessed locally, and local lab results may be used for enrollment and treatment decisions, if central lab results are not available.

[00439] **CA19-9**

[00440] CA19-9 biomarker levels will be measured centrally for all patients.

[00441] **UGT1A1*28**

[00442] A whole blood sample will be collected and assessed centrally at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of nal-IRI, but subsequent doses of nal-IRI may be reduced for patients positive for UGT1A1*28, as described herein.

[00443] **Biomarker Samples**

[00444] Whole blood and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK. Examples of potential analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), enzyme levels (e.g. MMP9).

[00445] **Urine or Serum Pregnancy Test**

[00446] A urine or serum pregnancy test will be obtained for all females of childbearing potential at screening, at the start of each cycle during study treatment, and at the EoT visit. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy or who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months).

[00447] **Pharmacokinetic Assessments (Arm 1 only)**

[00448] Since the combination of nal-IRI and oxaliplatin has not yet been tested in the clinic, plasma samples will be collected to determine the levels of nal-IRI and SN-38, as well as 5-FU and oxaliplatin, in Arm 1 patients. Additional analytes which may impact the pharmacokinetics of nal-IRI may also be measured from this sample. Directions for processing and shipping the PK plasma samples can be found in the study manual. The PK time points outlined in the Table 14 below will be drawn during Cycle 1 only. PK samples will be collected during Parts 1 and 2 of the study.

[00449] Table 14: Summary of PK Time points for Arm 1

Sample	Time-point	Window	Number of Draws*
1	Prior to nal-IRI infusion on Day 1 (pre-dose)	-24 hours	3
2	At the end of the nal-IRI infusion	+30 mins	1
3	At the end of the oxaliplatin infusion	+ 5 mins	2
4	Within 2 hours prior to the completion of the 5-FU infusion	-	3
5	+168 hours/7 days after the completion of the nal-IRI infusion	±24 hours	2
6	Prior to nal-IRI infusion on Day 15 (pre-dose)	-24 hours	2
7	End of Treatment visit (30 days post-last dose)	± 14 days	2

*The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the end of the oxaliplatin infusion will be used to measure nal-IRI and oxaliplatin.

Schedule of Assessments

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
		Cycle 1[21]				Additional Cycles[21]			Every 8w after 1st dose	End of Treatment Visit[22]	Every 2 months from EoT Follow-up visit
	-28d	D1	D3	D8	D15	D1	D8	D15			
Informed consent	X										
Medical history	X[1]										
Demographics	X[1]										
Vital signs	X[2]	X		X	X	X		X		X	
Performance Status	X[2]	X				X				X	
EORTC-QLQ-C30[9]	X[2]	X[3]				X[3]					
EQ-5D-5L[9]	X[2]	X[3]				X[3]				X	
CBC[4]	X[2]	X		X	X	X	X	X		X	
Serum chemistry[4]	X[2]	X		X	X	X		X		X	
CA19-9	X[2]								X[19]	X[20]	
UGT1A1*28	X[2,5]										

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
		Cycle 1[21]				Additional Cycles[21]			Every 8w after 1st dose	End of Treatment Visit[22]	Every 2 months from EoT Follow-up visit
	-28d	D1	D3	D8	D15	D1	D8	D15			
Pregnancy test	X[2]	X				X				X	
ECG[6]	X[1,7]									X	
Archived slides[8]	X										
Randomization[9]	X[2]										
Plasma for PK[10]		X[11]	X[12]	X[13]	X[14]					X	
Biomarker analysis[15, 14]		X[15]				X				X	
Concomitant meds and procedures	X[1]	X	X	X	X	X	X	X		X	
Arms 1 & 2 dosing[16]		X			X	X		X			
Arm 3 dosing[16]		X		X	X	X	X	X			
AE / Hospitalization assessment & reporting	X[17]	X	X	X	X	X	X	X		X	
Disease evaluation[18]	X[1]								X[19]	X[20]	X[23]

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
		Cycle 1[21]				Additional Cycles[21]			Every 8w after 1st dose	End of Treatment Visit[22]	Every 2 months from EoT Follow-up visit
	-28d	D1	D3	D8	D15	D1	D8	D15			
Overall Survival											X[24]

1. Procedures to be completed within 28 days of 1st dose of study drug
2. Procedures to be completed within 7 days of 1st dose of study drug
3. HRQL questionnaires must be completed before study treatment administration
4. After screening, samples should be obtained -2 days from scheduled date of collection
5. Result not required prior to enrollment in the study, but patients positive for UGT1A1*28 may have future doses reduced as described herein.
6. To be repeated as clinically indicated during the study
7. Two independent readings at least 1 minute apart
8. Collection of archived tumor block or paraffin embedded slides is required, if available
9. Part 2 only
10. PK sampling will only be collected from patients enrolled in Arm 1 (Part 1) or randomized to Arm 1 in Part 2

11. Samples collected at the following time points: pre-dose (within 24 hours prior to nal-IRI infusion); at the end of the nal-IRI infusion (+30 mins) and at the end of the oxaliplatin infusion (+5 mins)

12. Sample collected within 2 hours *prior* to the completion of the 5-FU infusion

13. Sample collected +168 hours/7 days after the completion of the nal-IRI infusion (±24 hours)

14. Sample collected just prior to dosing with nal-IRI (-24 hours)

15. Blood will be collected for biomarker analyses: plasma samples will be collected at all time points; additionally, a whole blood sample will be collected on Cycle 1 Day 1 only

16. Study drug administration should occur ±2 days from scheduled date of administration

17. Adverse events that occur during screening should be documented as pre-existing conditions; only SAEs that are felt by the Investigator to be directly related to a study procedure should be reported during screening.

18. Disease evaluation according to RECIST v. 1.1 (Disease evaluations and CA19-9 should be done every 8 weeks (± 7 days) after 1st dose

19. Unless completed in the prior 8 weeks

20. All cycles are 28-day cycles

21. The End of Treatment (EoT) Follow-Up visit should occur 30 days (± 14 days) after last dose

22. For patients who discontinue the study for reasons other than disease progression only (e.g. patients who are removed due to adverse events), imaging studies should be continued until documented progression of disease per RECIST v1.1.

23. Follow-up contacts should be made every 2 months (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.

[00450] **Adverse Event Reporting**

Definitions

Adverse Event

[00451] An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of a medical condition for which the efficacy of the study drug is being evaluated will not be considered an adverse event.

Unexpected Adverse Event

[00452] An unexpected adverse event is one for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure, or the package insert or SmPC for approved therapies.

Serious Adverse Event

[00453] A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

i. Results in death

ii. Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

iii. Requires in-patient hospitalization or prolongation of existing hospitalization

iv. Results in persistent or significant disability/incapacity

v. Is a congenital anomaly or birth defect

vi. Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

[00454] The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe

headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Documenting Adverse Events

[00455] SAE reporting will begin on the date the patient provides informed consent to participate in the study, however only those SAEs occurring prior to study drug administration, that the Investigator believes to be related to a protocol procedure, should be reported according to methods described herein below. All AEs that occur during the screening phase should be documented as pre-existing conditions. Treatment-emergent adverse event reporting will begin as of the administration of study drugs. The Investigator should elicit information regarding the occurrence of adverse events through open-ended questioning of the patient, physical examination, and review of laboratory results.

[00456] All adverse events, whether serious or not, will be recorded in the source documents and the adverse event page of the case report form (except as noted below). All new events, as well as those that worsen in intensity or frequency relative to baseline, must be recorded throughout the study, until the End of Treatment follow-up visit. Adverse events should be followed through resolution, where possible. However, new adverse events felt by the Investigator to be related to the study treatment, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

[00457] Laboratory or vital signs abnormalities are to be recorded as Adverse Events only if they are clinically significant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

[00458] Information to be reported in the description of each adverse event includes:

i. A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)

ii. The date of onset of the event

iii. The date of resolution of the event

iv. A determination of whether the event is serious or not

v. Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation

of hospitalization required (complete serious adverse event page); diagnostic procedure performed; patient discontinued from the study (complete Final Visit Section of the case report form)

vi. Outcome: resolved without sequelae; resolved with sequelae; event resolving; event ongoing; patient died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Final Visit section of the case report form)

Reporting Serious Adverse Events

[00459] All fatal or life-threatening adverse events must be reported to the medical monitor immediately by telephone, e-mail, or fax. Within 24 hours of knowledge of the event, the Serious Adverse Event Form must be faxed to the appropriate contact whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known. Source documentation of all examinations, diagnostic procedures, etc., which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

[00460] In case of accidental or intentional overdose of any of the study drugs, even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 1 working day) using the AE and SAE forms. Overdose will be defined as $\geq$133% of planned dose.

[00461] All other serious adverse events must be reported to the appropriate contact within 24 hours of becoming aware of the event by phone, e-mail or fax. The Serious Adverse Event Form must also be faxed to the appropriate contact within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known.

[00462] The medical monitor shall be contacted as deemed necessary by the site. Current contact information shall be maintained at the site within the regulatory binder.

[00463] All SAEs will be evaluated by the medical monitor. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other Investigators

involved in

clinical trials with the study drug. The Investigator is responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) or Ethics Committee (EC), as per local regulations.

Determining the Severity and Relatedness of Adverse Events

Grading the Severity of an Adverse Event

[00464] Each adverse event will be graded according to the NCI CTCAE Version 4.03, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

i. Mild: an event not resulting in disability or incapacity and which resolves without intervention;

ii. Moderate: an event not resulting in disability or incapacity but which requires intervention;

iii. Severe: an event resulting in temporary disability or incapacity and which requires intervention;

iv. Life-threatening: an event in which the patient was at risk of death at the time of the event

v. Fatal: an event that results in the death of the patient

Relatedness to Study Drug

i. The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

Reporting and Follow-Up of Pregnancy

[00465] Patients who become pregnant while on study must immediately discontinue study treatment, and the pregnancy must be immediately reported to the medical monitor. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the Sponsor.

[00466] The Investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should

continue until conclusion of the pregnancy.

[00467] In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, the possible effects on the fetus, and be followed until conclusion of the pregnancy.

[00468] **Data Management and Statistical Analysis**

Case Report Forms

[00469] All data for the patients recruited for the trial will be entered onto electronic case report forms (eCRFs) via an Electronic Data Capture (EDC) system provided by the Sponsor. The data for the patients who screen-failed from the study will not be entered into the database, unless the patient experienced an adverse event which was considered to be related to the study procedures. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Data Quality Assurance

[00470] Electronic CRFs will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the CRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines. Additional computer programs that identify selected protocol violations, out-of-range data and other data errors may be used to help monitor the study.

Statistical Analysis

[00471] Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. The SAP may modify the analysis outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

[00472] Categorical variables will be summarized by frequency distributions

(number and percentage of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Testing will be conducted using a one-sided 0.10 significance level unless stated otherwise.

Study Populations

[00473] Part 1 and Part 2 will be analyzed separately, according to safety and efficacy parameters.

[00474] Patient populations defined for this study are described below:

i. Intent-to-Treat (ITT) population (Part 2 only): This population includes all randomized patients. Patients will be analyzed according to the randomized arm.

ii. Safety (SAF) population:

1. Part 1: The Part 1 safety population includes patients receiving any part of at least one dose of study drug. This will be the study population for assessing Part 1.

2. Part 2: The Part 2 safety population includes patients receiving any part of at least one dose of study drug. The SAF population will be summarized according to arm actually received.

iii. EQ-5D-5L population (Part 2 only): Treated patients that have provided baseline and at least 1 post-baseline assessment for EQ-5D.

iv. EORTC-QLQ-30 population (Part 2 only): Treated patients that have provided baseline and at least 1 post-baseline assessment for EORTC-QLQ-30.

v. PK Population: The PK population will include all nal-IRI treated patients with at least one post-study drug PK assessment.

Disposition and Baseline Characteristics

[00475] Study populations (enrolled, safety, efficacy evaluable, PK) will be summarized and displayed as frequencies. Disposition of patients will be summarized including patients screened, randomized, treated, and discontinued. Reasons for discontinuation will be tabulated. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated.

Efficacy Analysis

[00476] In the assessments of efficacy, each nal-IRI-containing arm will be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will be use 0.10 level one-sided testing to evaluate whether the nal-IRI-containing arm improves the efficacy parameter. Confidence intervals will

be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons. The primary efficacy comparisons will be based on the ITT population, which will included all randomized patients.

[00477] Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be 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 will be censored at the time of the last non-PD tumor assessment.

[00478] A primary analysis will be 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 will be performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients.

[00479] **Primary Efficacy Analysis**

[00480] In the intention-to-treat (ITT) analysis, a patient will be 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 will be considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.

[00481] 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.

[00482] For each arm, the progression-free survival achievement rate at 24 weeks will be 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 will be presented with corresponding 95% confidence intervals. Each nal-IRI containing arm will be 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.

[00483] **Secondary Efficacy Analyses**

[00484] Progression-free Survival (PFS) will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.

[00485] 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 will be 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 will be calculated for each treatment arm. For each nal-IRI-containing arm, ORR will be compared to the control arm. Differences in objective response rate between each nal-IRI-containing arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare objective response rates.

[00486] The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses will be carried out using 3 thresholds for maximum reduction: $\geq$ 20%, $\geq$50%, $\geq$90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline will be included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, by treatment arm.

[00487] 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 will be descriptively summarized for each arm using

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

[00488] **Quality of Life Analyses**

[00489] Quality of life analyses will be 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

[00490] For each EORTC QLQ-C30 administered, scores will be computed for the following scales:

i. Global Health Status
ii. Physical Functioning
iii. Role Functioning
iv. Emotional Functioning
v. Cognitive Functioning
vi. Social Functioning
vii. Fatigue
viii. Nausea and vomiting
ix. Pain
x. Dyspnea
xi. Insomnia
xii. Appetite Loss
xiii. Constipation
xiv. Diarrhea
xv. Financial difficulties.

[00491] Scoring will be carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations will be applied to the raw scores so that the reported score will have range 0-100 for all scales. Summary statistics will be presented for each subscale. A summary health state index value will be computed for each EQ-5D-5L assessment. Summary statistics will be presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression), responses will be tabulated.

Safety Analysis

[00492] Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA version 17.1 or higher. Toxicity will be graded according to the NCI CTCAE version 4.03.

[00493] Safety analysis of patients in Part 1 will include a summary of dose-limiting toxicity events.

[00494] The period for treatment-emergent adverse events and safety findings will be 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 will be considered as treatment-emergent.

[00495] Tabular summaries will 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 will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

[00496] Laboratory data will be presented by cycle. Abnormal laboratory values will be 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 will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized.

[00497] Vital signs and ECG will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

[00498] Vital signs will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

Biomarker Subgroup Analysis

[00499] Analyses will be 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 will be performed when appropriate.

Pharmacokinetics Analysis

[00500] Plasma concentrations of nal-IRI and oxaliplatin will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated (nal-IRI) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., Cmax, AUC (area under the curve), will be used to examine any possible interactions between nal-IRI and oxaliplatin by comparing the least squares geometric

mean ratios (LS-GMR) of drug exposures. NONMEM®, Version 7.3, will be used to estimate individual PK parameters and simulate plasma exposures.

Sample Size Justification

[00501] The total number of patients enrolled in Part 1 of the study will depend on the number of dose cohorts required to identify the Part 2 dose. Escalation to the next dose cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to 6 subjects, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.

Background Toxicity Rate	**1%**	**5%**	**10%**	**20%**	**30%**	**40%**	**50%**
Probability of Dose Escalation	0.999	0.973	0.906	0.709	0.494	0.309	0.172

[00502] Part 2 of this study will include a comparison of the progression-free survival achievement rate at 24 weeks for each nal-IRI-containing arm versus the control arm.. In the phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab-paclitaxel with the median PFS of 5.5 months (compared with 3.7, i.e. 16 weeks, in the gemcitabine alone arm). The median PFS of 5.5 months corresponds to a PFS rate of 24 weeks of 50%.

[00503] The table below illustrates the power to detect differences in PFS

achievement rate at 24 weeks between an experimental arm and the control arm using a one-sided comparison at an unadjusted 0.10 level of significance. If the true rate for the control arm is 50%, the study would have 78% power to detect an improvement in an experimental arm that has a true rate of 70%.

Reference %	**Experimental %**	**Delta % pts**	**Power N=50/arm**
50	60	10	39%
50	65	15	59%
50	70	20	78%
50	71	21	80%
50	75	25	91%

[00504] **Extension Phase**

Following fulfillment of analysis requirements for the primary and/or secondary endpoints, the Sponsor may elect to close the study. At that time, all patients receiving treatment will be permitted to transition into the extension phase of the study, and will continue to receive treatment until disease progression, death, unacceptable toxicity, patient refusal, or start of any new anticancer treatment, whichever occurs first (see above for other discontinuation criteria).

[00505] Central collection of data will not be required for patients entering the extension phase of the study; only serious adverse events will be collected. Investigators may perform standard procedures and tests needed to treat and evaluate patients; however, the results of these assessments will not be routinely reported. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and procedures) may be requested by the Sponsor in order to evaluate the reported SAE. The patient's participation in the study extension will be completed once study treatment is discontinued. There will be no post-discontinuation period in the extension phase of the protocol.

[00506] **Study Administration**

Pre-Study Documentation

[00507] Prior to initiating the trial, the Investigator will provide to the Sponsor or designee the following documents:

i. A signed FDA Form 1572

ii. A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal Investigator

iii. A copy of the current medical license for the Investigator

iv. A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g., advertisements)

v. A copy of the IRB-approved informed consent document. A signed Investigator Protocol Agreement

[00508] A completed financial disclosure form for the Investigator

Additional documents that may be requested include:

i. A current (i.e. updated no more than 24 months prior) curriculum vitae for each sub-Investigator listed on the FDA Form 1572

ii. A copy of the current medical license for each sub-Investigator

iii. A completed financial disclosure form for all sub-Investigators

iv. A current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director

v. A list of current laboratory normal values for the reference laboratory

vi. The current IRB membership list for the reviewing IRB, or the multiple project assurance number from the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov)

Source Documents

[00509] The Investigator will maintain records separate from the eCRFs in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source

data sent as supporting documentation for serious adverse events will be de-identified to preserve confidentiality.

Trial Ethics

[00510] The study will be performed according to the principles of the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm), the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of the US FDA and/or local regulatory authorities regarding the conduct of human clinical trials.

Patient Informed Consent

[00511] No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the Investigator a sample informed consent document that includes all the requirements for informed consent according the ICH GCP, U.S. FDA guidelines (21 CFR 50) and/or local regulatory guidelines. However, it is up to the Investigator to provide a final informed consent that may include additional elements required by the Investigator's institution, and that has been IRB or EC approved. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the trial and who signs the informed consent will be given a copy of the signed, dated and witnessed document (the witness signature is only required for cases that fit the criteria for needing a witnessed signature). The provision of informed consent will be documented in the medical record.

Investigational Review Board/Ethics Committee Approval

[00512] The trial will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial by the local/central IRB or EC. The IRB/EC should be duly constituted according to local regulatory requirements. Approval must be in the form of a letter signed by the Chairperson or the Chairperson's designee, must be on official stationary and must include the protocol by name and/or by designated number. If an Investigator is a member of the IRB/EC, then the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the trial. The Investigator will also inform the IRB/EC of any SAEs that the Sponsor reports to regulatory authorities, will report on

the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB/EC a final summary of the results of the trial at the conclusion of the trial.

Monitoring

[00513] A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The Investigator will allow the Sponsor or designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. Monitoring visits will be conducted according to a study monitoring plan, and will include review of various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

[00514] During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor.

[00515] In addition to the above, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The Investigator must promptly inform Merrimack of any audit requests by health authorities, and will provide Merrimack with the results of any such audits and with copies of any regulatory documents related to such audits.

[00516] In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personally identifiable health information may be required for each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

[00517] **Example 2: Preclinical Anti-tumor Activity of Nanoliposomal Irinotecan (Nal-IRI, MM-398) + 5-FU + Oxaliplatin in Pancreatic Cancer**

[00518] FOLFIRINOX (5-FU/LV, irinotecan and oxaliplatin) is a

chemotherapy regimen active in first-line metastatic PDAC. The preclinical anti-tumor activity of a nal-IRI + 5-FU + oxaliplatin regimen relative to the FOLFIRINOX regimen was evaluated. Using pancreatic cancer cell lines, it was demonstrated that enhanced cell death occurs when nal-IRI treatment is simulated using prolonged exposure of SN-38 (the active metabolite of irinotecan) in combination with 5-FU and oxaliplatin. In cell line-derived and patient-derived xenograft models of pancreatic cancer, it was demonstrated that improved anti-tumor activity of nal-IRI relative to exposure-matched doses of unencapsulated irinotecan occurs. Further, nal-IRI consistently improved tumor growth inhibition and survival relative to unencapsulated irinotecan in preclinical models, both as a monotherapy and in combination with 5-FU and oxaliplatin. The addition of nal-IRI to 5-FU and/or oxaliplatin did not exacerbate the baseline toxicities of these agents, including weight loss and neutropenia, and tolerability. Baseline toxicities were reduced by delaying the administration of oxaliplatin to 1 day post-MM-398.

[00519] FIG. 12 shows line graphs that depicts cell viability following treatment with SN-38 or oxaliplatin as single agent or in combination. BxPC-3 (A) or CFPAC-1 (B) cells were plated at 1000 cells/well in a 348-well plate and treated with SN-38 or in combination with oxaliplatin for 4h or 72h, washed and then incubated for an additional 24h or 144h with fresh media, following which cell viability was assessed. 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.

[00520] FIG. 13 is a line graph depicting tumor growth in mice following various treatments. Tumor cells (A) BxPC-3 cells or (B) CFPAC-1 was implanted subcutaneously in mice. When tumors were well-established, and had reached a mean volume of ~300mm^3, IV treatment with MM-398 or oxaliplatin as monotherapy or in combination was initiated. Treatment doses are indicated in the figure beside each treatment, and were given 3 (CFPAC-1 model) or 4 (BxPC-3 model) times, at time points indicated by dashed lines on the graphs.

[00521] FIG. 14 is a line graph depicting 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 unencapsulated 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 4 times, at time points indicated by dashed lines on the graphs. The addition of 5-FU to MM-398 or unencapsulated 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.

[00522] FIG. 15 shows graphs depicting 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 ~250mm^3, IV treatment with MM-398 or unencapsulated 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. A) 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. B) 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. C) 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 unencapsulated irinotecan.

[00523] FIG. 16 is a table showing results of tumor growth and survival 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 ~250mm^3, IV treatment with MM-398 or unencapsulated 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. However, NAPOX was not

significantly different from NAPOLI.

[00524] FIG. 17 depicts 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 measure by loss of body weight, whereas as delaying oxaliplatin administration by 24h after MM-398 does not lead to significant changes in body weight.

[00525] FIG. 18 depicts bar graphs depicting hematological and liver toxicities following treatment with nal-IRI with or without oxaliplatin given either concurrently or sequentially with nal-IRI. Hematological toxicities (A-C) were improved by delayed administration of oxaliplatin. Liver enzymes (D-F) remained comparable to monotherapies when oxaliplatin administration was delayed.

[00526] FIG. 19 shows that prolonged exposure of SN-38 simulates nal-IRI treatment *in vitro*. (A) Nal-IRI treatment results in prolonged tumor exposure to the active metabolite, SN-38, compared to unencapsulated irinotecan (CPT-11). (B) Prolonged low-dose exposure of SN-38 mimics nal-IRI tumor delivery *in vitro*. (C) Prolonged low-dose exposure resulted in greater cell growth inhibition in multiple pancreatic cancer cell lines. (D) The benefit of prolonged exposure to low concentrations of SN-38 was also observed when combined with 5-FU (20.7mM for 48h) or oxaliplatin (12.3mM for 4h). Both combinations also increased sensitivity of resistance cell lines to prolonged low-dose SN-38.

[00527] **Example 3. A Randomized, Open-label, Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-Containing Regimens versus nab-Paclitaxel Plus Gemcitabine in Patients with Previously Untreated, Metastatus Pancreatic Adenocarcinoma (mPAC)**

[00528] **Background:**

[00529] Two combination chemotherapy regimens have emerged as standard of care for first-line treatment of mPAC:

- FOLFIRINOX (5-fluorouracil [5-FU] + leucovorin [LV] + irinotecan + oxaliplatin).
- Nab-paclitaxel + gemcitabine.

[00530] However, these regimens are associated with median overall survivals (OS) of less than one year in phase 3 studies (11.1 and 8.5 months, respectively).

(Conroy T, et al. *N Engl J Med.* 2011; 364(19): 1817-1825 and Von Hoff DD, et al. *N Engl J Med.* 2013; 369(18): 1691-1703).

[00531] Nal-IRI (ONIVYDE™ [irinotecan liposome injection]; MM-398) is a nanoliposomal formulation of irinotecan, a topoisomerase inhibitor, for intravenous use (Figure 6). (Ramanathan RK, et al. Poster presented at: Annual Meeting of the American Association for Cancer Research (AACR); April 5-9, 2014; San Diego, CA. Abstract CT224). Pharmacokinetic analyses showed extended circulation of irinotecan within the liposome inpatients with gastric cancer (Figure 7). (Roy AC, et al. Ann Oncol. 2013: 24(6): 1567-1573 and Ma WW, et al. Poster presented at: European Cancer Congress; September 25-29, 2015; Vienna, Austria. Poster 327). The liposome facilitates intratumoral drug deposition through the enhanced permeability and retention effect (Kalra AV, et al. *Cancer Res.* 2014; 74(23): 7003-7013). Nal-IRI promotes local activation of irinotecan's active metabolite, with SN-38 levels 5-fold higher in biopsied tumor tissue than in plasma at 72 hours after nal-IRI infusion (Figure 8). (Ramanathan RK, et al. Poster presented at: Annual Meeting of the American Association for Cancer Research (AACR); April 5-9, 2014; San Diego, CA. Abstract CT224.).

[00532] Nal-IRI was recently approved by the US Food and Drug Administration (FDA) for use in combination with 5-FU/LV for the treatment of patients with mPAC after disease progression following gemcitabine-based therapy, based in part on results from the primary analysis of the large (N = 417), international, randomized, phase 3 study (NAPOLI-1) of nal-IRI in this setting (Wang-Gillam A, et al. Lancet. 2015. Epub available ahead of print).

[00533] Median OS increased significantly with nal-IRI + 5-FU/LV relative to 5-FU/LV (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67 [95% confidence interval (Cl), 0.49-0.92]; $P = 0.012$; Figure 9)

[00534] Median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56 [95% Cl,0.41-0.75]; $P = 0.0001$) and objective response rate (ORR; 16% vs. 1%; P<0.0001) were also improved with nal-IRI + 5-FU/LV compared with 5-FU/LV.

[00535] Nal-IRI + 5-FU/LV demonstrated a predictable and manageable safety profile. The most frequently reported grade >3 treatment-emergent adverse events (AEs) were neutropenia, fatigue, diarrhea, and vomiting

[00536] **Study Objectives:**

[00537] The overall goal of the current study is to determine the preliminary safety and efficacy of nal-IRI +5-FU/LV with or without oxaliplatin, as compared with nab-paclitaxel + gemcitabine in previously untreated patients with mPAC (ClinicalTrials.gov Identifier: NCT02551991).

[00538] Part 1:

[00539] The primary objectives of Part 1 are to:

- Evaluate the safety and tolerability of nal-IRI + 5-FU/LV + oxaliplatin.
- Characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5-FU/LV + oxaliplatin and determine the Part 2 triplet combination dose.

[00540] The secondary objective of Part 1 is to characterize the pharmacokinetics of nal-IRI + 5-FU/LV + oxaliplatin.

[00541] Part 2:

[00542] The primary objective of Part 2 is to compare the PFS rate at 24 weeks in patients in each nal-IRI-containing regimen versus nab-paclitaxel + gemcitabine in first-line mPAC.

[00543] The secondary objectives of Part 2 are to:

- Compare the OS, PFS, and ORR in patients in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine.
- Assess tumor marker carbohydrate antigen 19-9 (CA19-9) response in patients in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine.
- Evaluate health-related quality of life (HRQoL) of patients in each treatment arm.
- Compare the safety and AE profile between treatment arms.

[00544] An additional exploratory objective is to evaluate patient blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI pharmacokinetics, toxicity, and/or response.

[00545] Key Eligibility Criteria:

[00546] Adults aged >18 years.

[00547] Pathologically confirmed, measurable or non-measurable mPAC, as defined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, that has not previously been 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 metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed.

[00548] Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

[00549] No known metastasis to the central nervous system.

[00550] No history of any second malignancy in the last 3 years.

[00551] Adequate hematologic parameters, and hepatic and renal function.

[00552] Normal electrocardiogram or electrocardiogram without clinically significant findings.

[00553] No use of strong CYP3A4 inhibitors or inducers.

[00554] No use of strong CYP2C8 inhibitors or inducers (Part 2 only).

[00555] No known contraindications or hypersensitivity to any study drugs (Part 2 only for nab-paclitaxel and gemcitabine).

[00556] No clinically significant gastrointestinal disorder, concurrent illnesses, active infection, or unexplained fever >38.5°C at screening/baseline, or any other condition deemed likely to interfere with the study.

[00557] **Study Design:**

[00558] This phase 2, open-label, comparative study is being conducted in 2 parts (Figure 10). Participating sites are located in 15 countries in North America, Europe, Asia-Pacific, and South America (Figure 11).

[00559] Part 1:

[00560] A dose-escalation safety run-in (traditional 3+3 design) is being performed to confirm an appropriate Part 2 dose regimen for the nal-IRI + 5-FU/LV + oxaliplatin triple combination arm (Table 15).

- If no DLTs are reported for a dose cohort within the first treatment cycle, the subsequent cohort will be initiated.
- If 1 patient in a dose cohort experiences a DLT within the first treatment cycle, the cohort will be expanded from 3 to 6 patients.
- If >2 patients within a dose cohort experience a DLT, that dose will be considered to

exceed the safety criteria and the dose will not be escalated further. The Part 2 dose will then be defined as the next lower dose level in which 6 patients were treated and >1 patient experienced a DLT.

Table 15. Dose-escalation Scheme

Oxaliplatin			**5-FU/LV**		**Nal-IRI**	
Level	**Dose (mg/m^2)**	**Dose day**	**Dose (mg/m^2)**	**Dose day**	**Dose (mg/m^2)[a]**	**Dose day**
1	60	1, 15	2,400/400	1, 15	80	1, 15
-1	60	1, 15	2,400/400	1, 15	60	1, 15
2	85	1, 15	2,400/400	1, 15	80	1, 15
-2A	75	1, 15	2,400/400	1, 15	80	1, 15
-2B	85	1, 15	2,400/400	1, 15	60	1, 15

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, nanoliposomal irinotecan.

Shaded dose levels are for de-escalation only. Enrollment in these dose levels will only be initiated upon agreement of the investigators, study sponsor, and medical monitor.

[a]The above nal-IR doses are expressed as the irinotecan HCl trihydrate, whereas doses in the US prescribing information are expressed as the irinotecan free base. Converting the dose is accomplished by substituting the molecular weight of irinotecan HCl trihydrate (677.19 g/mol) with that of irinotecan free base (586.68 g/mol), which results in a conversion factor of 0.866. The above doses of 80 and 60 mg/m^2 approximate to 70 and 52 mg/m^2, respectively, based on irinotecan free base.

[00561] Part 2:

[00562] Patients will be randomized (1:1:1) in the active-comparator phase to evaluate and compare efficacy, safety, and HRQoL between treatment arms.

- Randomization will be stratified based on region (East Asia vs. rest of the world) and ECOG PS0 versus 1.
- Part 2 will include the following 3 treatment arms (28-day cycles):
  - Arm 1: nal-IRI + 5-FU/LV + oxaliplatin at dosages determined in Part 1, on Days 1 and 15 of each cycle.
  - Arm 2: nal-IRI (80 mg/m^2 over 90 minutes [70 mg/m^2 based on irinotecan free base]) +

5-FU(2,400 mg/m^2 over 46 hours) + LV (400 mg/m^2) on Days 1 and 15 of each cycle.

o Arm 3: nab-paclitaxel (125 mg/m^2 over 35 minutes) + gemcitabine (1,000 mg/m^2 over30 minutes) on Days 1, 8, and 15.

[00563] Patients will be treated until disease progression, intolerable toxicity, withdrawal of consent, or at the discretion of the treating physician.

[00564] Primary efficacy endpoint: PFS rate at 24 weeks.

- Patients will be considered responders if they have at least one assessment of non-progressive disease, prior to progression or new anticancer therapy, at Week 24 or later.
- Each nal-IRI-containing arm will be assessed for an increased PFS rate at 24 weeks relative to the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at the 0.10 level of significance.
- If the true PFS rate at 24 weeks in the control arm is 50%, the study would have 78% power to detect an improvement in a nal-IRI-containing experimental arm that has a true rate of 70%.

[00565] **Study Populations:**

[00566] Several study populations will be used in the analyses of data (Table 16).

Table 16. Study Populations

Population	**Description**
Safety population	Part 1: patients receiving any part of ≥1 dose of study drug. This will be the only study population for assessing part 1
Intent-to-treat population	Part 2 only: all randomized patients; this population will be analyzed according to the randomized treatment arm. This is the primary population for efficacy evaluations
EQ-5D-5L population	Part 2 only: treated patients that have provided baseline and ≥1 post-baseline assessment for EQ-5D-5L
EORTC-QLQ-C30 population	Part 2 only: treated patients that have provided baseline and ≥1 post-baseline assessment for EORTC-QLQ-C30
Pharmacokinetic population	Nal-IRI treated patients with ≥1 post-study drug pharmacokinetic assessment

[00567] **Study Evaluations:**

[00568] Efficacy:

[00569] Tumor response will be evaluated at least every 8 weeks according to RECIST, version 1.1, based on CT or MRI imaging, until determination of progressive disease.

[00570] CA19-9 levels will be evaluated at least every 8 weeks during treatment and at the end-of-treatment visit. The maximum reduction (percent change from baseline) in CA19-9 will be computed, including analyses by time period.

[00571] Follow-up for survival status will continue at least once every 2 months after treatment discontinuation until death, lost to follow-up, withdrawal of consent, or study closure. OS will be descriptively summarized for each treatment arm using Kaplan-Meier methodology.

[00572] Safety and Tolerability:

[00573] Safety evaluations, including AE and hospitalization reporting, vital signs, complete blood count and serum chemistry, will be collected throughout the study.

[00574] AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, and will be summarized according to severity and relatedness to treatment.

[00575] Quality of Life:

[00576] HRQoL will be assessed via the EORTC-QLQ-C30 and EQ-5D-5L instruments at baseline, Day 1 of each subsequent cycle, and at the end-of-treatment visit.

[00577] Pharmacokinetics:

[00578] Plasma sampling for pharmacokinetic analyses of nal-IRI and oxaliplatin will occur on Days 1, 3, 8, and 15 of Cycle 1 (Parts 1 and 2, Arm 1 only).

[00579] Biomarkers:

[00580] Analyses will be performed to assess the associations between potential biomarkers (from plasma and archived tissue) and efficacy parameters.

[00581] Whole blood and plasma sampling for biomarker analyses will occur at baseline, Day 1 of each subsequent cycle, and at the end-of-treatment visit.

[00582] Examples of potential analyses include cytokine levels, growth factors, and enzyme levels.

[00583] Management of Toxicities:

[00584] Guidelines for specific dose modifications are provided in Table 17 and Table 18.

- Any patient who requires >2 dose reductions or a dose interruption of >2 weeks due to toxicity should be discontinued from study treatment.
- If oxaliplatin is not well tolerated in Arm 1, the patient may discontinue oxaliplatin and continue to receive nal-IRI + 5-FU/LV.

Table 17. Study Populations

Grade 3/4 toxicity[a]	**Nal-IRI**	**5-FU**	**Oxaliplatin (Arm 1 only)**
Neutropenia or febrile neutropenia	1st occurrence: reduce to 60 mg/m^2 2nd occurrence: reduce to 50 mg/m^2	1st occurrence: reduce dose by 25% 2nd occurrence: reduce dose by another 25%	***Grade ≥2 events:*** 1st occurrence: none 2nd occurrence: reduce to 60 mg/m^2
Other hematologic toxicity	1st occurrence: reduce to 60 mg/m^2 2nd occurrence: reduce to 50 mg/m^2	1st occurrence: reduce dose by 25% 2nd occurrence: reduce dose by another 25%	1st occurrence: reduce to 60 mg/m^2 2nd occurrence: maintenance of reduced dose of 60 mg/m^2
Hand-foot syndrome	1st occurrence: reduce to 60 mg/m^2 2nd occurrence: reduce to 50 mg/m^2	***Grade 2:*** 1st occurrence: reduce dose by 25% 2nd occurrence: reduce dose by another 25% ***Grade 3/4:*** discontinue therapy	None

Neuro-cerebellar toxicity	None	***Any grade:*** discontinue therapy	None
Cardiac toxicity	None	***Grade ≥2 events:*** discontinue therapy	None
Sensory neuropathy	None	None	*Persistent grade 2, or grade 3 that recovers prior to next cycle:* reduce to 60 mg/m^2 *Persistent grade 3, or grade 4:* discontinue therapy
Other non-hematologic toxicity[b]	1st occurrence: reduce to 60 mg/m^2 2nd occurrence: reduce to 50 mg/m^2	1st occurrence: reduce dose by 25% 2nd occurrence: reduce dose by another 25%	1st occurrence: none 2nd occurrence: reduce to 60 mg/m^2

Nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil.

Following dose reduction, the patient's dose should remain reduced for the duration of the study.

[a]Grade 3/4 toxicity unless otherwise noted.

[b]For grade 3/4 nausea and vomiting, patients should also receive optimized anti-emetic therapy.

Table 18. Dose Modification Guidelines for Arm 3		
Grade 3/4 toxicity[a]	**Nab-paclitaxel**	**Gemcitabine**

Hematologic or non-hematologic toxicity	1st occurrence: reduce to 100 mg/m^2 2nd occurrence: reduce to 75 mg/m^2	1st occurrence: reduce to 800 mg/m^2 2nd occurrence: reduce to 600 mg/m^2
Mucositis or diarrhea	Withhold until improves to grade ≤1; reduce dose per Row 1	
Cutaneous toxicity	**Grade ≥2 events:** reduce dose per Row 1; discontinue therapy if toxicity persists	
Periheral neuropathy	Withhold until improves to grade ≤1; reduce dose per Row 1	None
Febrile neutropenia	Withhold until fever resolves and ANC ≥1,500/mm^3; reduce dose per Row 1	
Neutropenia or thrombocytopenia	Detailed dose reduction and delay guidelines per administration day and severity of decreased ANC and/or platelet levels	

ANC, absolute neutrophil count.

Following dose reduction, the patient's dose should remain reduced for the duration of the study.

[a]Grade 3/4 toxicity unless otherwise noted.

[00585] **Summary**

[00586] Nal-IRI has demonstrated clinical activity and predictable and manageable toxicity in combination with 5-FU/LV in patients with mPAC following gemcitabine-based therapy, leading to its FDA approval in its setting. This phase 2 study will evaluate the preliminary safety and efficacy of nal-IRI + 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 nal-IRI combination treatment on patient HRQoL and identify potential biomarkers of response.

CLAIMS

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.

2. The method of claim 1, wherein the MM-398 liposomal irinotecan is administered in combination with leucovorin, and 5-fluorouracil to treat the pancreatic cancer in the human subject.

3. The method of claim 1, wherein the MM-398 liposomal irinotecan is administered in combination with oxaliplatin, leucovorin, and 5-fluorouracil to treat the pancreatic cancer in the human subject.

4. The method of any one of claims 1-3, wherein the amount of MM-398 liposomal irinotecan administered is from about 60 mg/m^2 to about 80 mg/m^2.

5. The method of claim 4, wherein the amount of MM-398 liposomal irinotecan administered is administered is 60 mg/m^2 or 80 mg/m^2.

6. The method of any one of claims 1 to 5, wherein the amount of oxaliplatin administered is from about 50 mg/m^2 to about 100 mg/m^2.

7. The method of claim 6, wherein the amount of oxaliplatin administered is from about 60 mg/m^2 to about 85 mg/m^2.

8. The method of claim 7, wherein the amount of oxaliplatin administered is 60 mg/m^2, 75 mg/m^2, or 85 mg/m^2.

9. The method of any one of claims 1 to 8, 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.

10. The method of claim 9, wherein the leucovorin is administered as a dose of 400 mg/m^2 of the (*l* + *d*)-form of leucovorin.

11. The method of claim 9, wherein the leucovorin is administered as a dose of 200 mg/m^2 of the (*l*)-form of leucovorin.

12. The method of any one of claim 1-11, wherein the amount of 5-fluorouracil administered is 2,400 mg/m^2.

13. The method of any one of claims 1 to 12, wherein the MM-398 liposomal irinotecan, leucovorin, and 5-fluorouracil are administered at least once.

14. The method of any one of claims 1 to 12, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered at least once.

15. The method of claim 13, wherein the MM-398 liposomal irinotecan, leucovorin, and 5-fluorouracil are administered on days 1 and 15 of a 28-day cycle.

16. The method of claim 15, wherein the oxaliplatin is administered on day 2 of the 28-day cycle.

17. The method of claim 16, wherein the oxaliplatin is administered on day 2 and day 16 of the 28-day cycle.

18. The method of claim 14, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered on days 1 and 15 of a 28-day cycle.

19. The method of claim 15 or claim 18, wherein multiple cycles are administered.

20. The method any one of claims 1-19, wherein the pancreatic cancer is adenocarcinoma of the pancreas.

21. The method of claim 20, wherein the pancreatic cancer is unresectable, locally advanced or metastatic adenocarcinoma of the pancreas.

22. The method of claim 21, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas.

23. The method of claim 22, wherein the pancreatic cancer is unresectable, locally advanced adenocarcinoma of the pancreas.

24. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received chemotherapy to treat the adenocarcinoma, the method comprising intravenously administering to the patient 80 mg/m^2 of MM-398 liposomal irinotecan, 60 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.

25. The method of claim 24, wherein the leucovorin is administered as 400 mg/m^2 of the (*l+d)* racemic form of leucovorin.

26. The method of claim 24 or 25, wherein the MM-398 liposomal irinotecan, leucovorin, 5-fluorouracil are administered to the patient beginning on day 1 of a 28-day cycle and the oxaliplatin is administered on day 2 of the 28-day cycle, wherein the method comprises multiple cycles.

27. The method of claim 24 or claim 25, wherein the MM-398 liposomal irinotecan, leucovorin, 5-fluorouracil, and oxaliplatin are administered to the patient beginning on day 1 of a 28-day cycle wherein the method comprises multiple cycles.

28. The method of claim 27, wherein the MM-398 liposomal irinotecan, leucovorin, 5-fluorouracil, and oxaliplatin are administered to the patient on day 1 and day 15 of a 28-day cycle.

29. The method of claim 27 or 28, wherein the oxaliplatin is administered to the patient prior to the leucovorin.

30. The method of claim 29, wherein the leucovorin is administered to the patient prior to the 5-fluorouracil.

31. The method of claim 30, wherein the MM-398 liposomal irinotecan is administered to the patient prior to the oxaliplatin, leucovorin, and 5-fluorouracil.

32. The method of claim 31, further comprising pre-medicating the patient with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan.

33. The method of claim 31 or claim 32, wherein the MM-398 liposomal irinotecan is administered intravenously to the patient over 90 minutes, the oxaliplatin is administered intravenously to the patient over 120 minutes, the leucovorin is administered intravenously to the patient over 30 minutes and the 5-FU is administered intravenously to the patient over 46 hours.

34. The method of claim 33, wherein the MM-398 liposomal irinotecan 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-fluorouracil over 46 hours.

35. The method of claim 34, wherein the MM-398 liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil are administered to the patient beginning on day 1 of a 28-day cycle, wherein the method comprises multiple cycles, and the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

36. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously been treated with any chemotherapeutic agent in the metastatic setting, the method comprising, intravenously administering to the patient, beginning on day 1 of a 28-day

cycle, 80 mg/m^2 of MM-398 liposomal irinotecan over 90 minutes, followed by 60, 75, or 85 mg/m^2 oxaliplatin, followed by 400 mg/m^2 of the (*l+d)* racemic form of leucovorin, followed by 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human subject.

37. The method of claim 36, wherein the method comprises multiple cycles.

38. The method of claim 37, wherein the oxaliplatin is administered over 120 minutes, the leucovorin is administered over 30 minutes and the 5-fluorouracil is administered over 46 hours.

39. A method of treating metastatic adenocarcinoma of the pancreas in a human subject wherein the subject has metastatic pancreatic cancer that has not been previously treated with a chemotherapeutic agent in the metastatic setting prior to the administration of MM-398, the method comprising, intravenously administering to the subject, beginning on day 1 of a 28-day cycle

(a) a corticosteroid and an anti-emetic; followed by

(b) 80 mg/m^2 of MM-398 liposomal irinotecan administered over 90 minutes; followed by

(c) 60 mg/m^2 oxaliplatin; followed by

(d) 400 mg/m^2 of the (*l+d)* racemic form of leucovorin; followed by

(e) 2,400 mg/m^2 5-fluorouracil.40. The method of claim 39, wherein the method comprises multiple cycles.

41. The method of claim 39, wherein the anti-emetic, MM-398 liposomal irinotecan, oxaliplatin, leucovorin and 5-flurouracil are administered on day 1 and day 15 of the 28-day cycle.

42. The method of any one of claims 39-41, wherein the oxaliplatin is administered over 120 minutes.

43. The method of claim 42, wherein the leucovorin is administered over 30 minutes followed by the administration of 5-fluorouracil over 46 hours.

44. The method of any one of claims 1-43, wherein no other anti-neoplastic agent is administered other than a liposomal irinotecan, 5-fluorouracil and oxaliplatin.

45. A method of treating pancreatic cancer in a human patient, the method comprising intravenously administering to the patient once every two weeks an antineoplastic therapy comprising:

a. a single administration of 80 mg/m^2 of the antineoplastic agent irinotecan encapsulated in a liposome,

b. a single administration of 60, 75, or 85 mg/m^2 of the antineoplastic agent oxaliplatin,

c. a single administration of 200 mg/m^2 of (l) form of leucovorin, and

d. a single administration of 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil to treat the pancreatic cancer in the patient; followed by

wherein no other antineoplastic agent is administered to the patient during the two week administration period.

46. The method of claim 45, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

47. The method of claim 45, wherein each administration of irinotecan is administered as an intravenous infusion of irinotecan liposome over 90 minutes, followed by the administration of leucovorin over 30 minutes, followed by the intravenous infusion of 5-fluorouracil over 46 hours.

48. The method of claim 45, wherein the pancreatic cancer has progressed in the human patient after treatment of the pancreatic cancer with a gemcitabine-based therapy prior to the administration of the irinotecan.

49. The method of any one of claims 45-48, wherein the antineoplastic therapy is administered for at least 6 weeks.

50. A method of treating pancreatic cancer in a human patient who has not received an anti-neoplastic agent for the treatment of the pancreatic cancer, the method comprising administering to the patient an anti-neoplastic therapy once every two weeks, the anti-neoplastic therapy consisting of:

a. a single administration of 80 mg/m^2 of the antineoplastic agent irinotecan encapsulated in a liposome, over a 90 minute infusion, followed by

b. a single administration of 85 mg/m^2 of the antineoplastic agent oxaliplatin,

c. a single intravenous administration of 200 mg/m^2 of (l) form of leucovorin over 30 minutes, and

d. a single intravenous administration of 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil over 46 hours,

to treat the pancreatic cancer in the patient.

51. The method of claim 50, wherein the pancreatic cancer has progressed in the human patient after treatment of the pancreatic cancer with a gemcitabine-based therapy prior to the administration of the irinotecan.

52. The method of claim 51, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

53. The method of any one of claims 50-52, wherein 5-fluorouracil is administered following the leucovorin.

54. The method of any one of claims 50-53, wherein the antineoplastic therapy is administered over a total of 48 hours.

55. The method of any one of claims 50-54, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

56. The method of any one of claims 50-55, wherein 5-fluorouracil is administered following the leucovorin.

57. The method of of any one of claims 50-56, wherein the antineoplastic therapy is administered for at least 6 weeks.

58. A method of treating pancreatic cancer in a human patient who has not received gemcitabine for the treatment of the pancreatic cancer, the method consisting of administering to the patient once every two weeks, an antineoplastic therapy comprising:

a. a single administration of 80 mg/m^2 of the antineoplastic agent irinotecan encapsulated in a liposome, over a 90 minute infusion, followed by

b. a single administration of 85 mg/m^2 of the antineoplastic agent oxaliplatin, followed by

c. a single intravenous administration of 200 mg/m^2 of (l) form of leucovorin over 30 minutes, followed by

d. a single intravenous administration of 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil over 46 hours,

to treat the pancreatic cancer in the patient.

59. The method of claim 58, wherein the antineoplastic therapy is administered for at least 6 weeks.

60. The method of claim 58 or 59, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

61. The method of of any one of claims 58-60, wherein the pancreatic cancer is metastatic adenocarcinoma of the pancreas that has progressed in the human patient after treatment of the pancreatic cancer with a gemcitabine-based therapy prior to the administration of the irinotecan.

62. A method of treating pancreatic cancer in a human patient wherein the patient has not been previously treated with gemcitabine for the pancreatic cancer, the method comprising administering to the patient an antineoplastic therapy once every two weeks, the antineoplastic therapy consisting of administering in a single treatment cycle:

a. a single administration of 80 mg/m^2 of the antineoplastic agent irinotecan encapsulated in a MM-398 irinotecan liposome, over a 90 minute infusion,

b. a single administration of 85 mg/m^2 of the antineoplastic agent oxaliplatin, followed by

c. a single administration of 200 mg/m^2 of (l) form of leucovorin over 30 minutes,

d. a single administration of 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil over 46 hours,

to treat the pancreatic cancer in the patient.

63. (New) The method of claim 62, wherein the antineoplastic therapy is administered for at least 6 weeks.

64. The method of of any one of claims 62-63, wherein the 200 mg/m^2 of the (l) form of leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

65. The method of of any one of claims 62-64, further comprising administering a second additional two-week treatment cycle identical to the first two-week treatment cycle.

66. The method of any one of claims 62-65, wherein the oxaliplatin is administered after the MM-398 irinotecan liposome.

67. The method of any one of claims 1-66, further comprising administering a corticosteroid 30 minutes prior to each administration of the irinotecan liposome.

68. The method of any one of claims 1-67, wherein the anti-neoplastic agent gemcitabine is not administered to the patient.

69. The method of any one of claims 1-68, wherein the anti-neoplastic agent cisplatin is not administered to the patient.

ABSTRACT

Methods of treating pancreatic cancer in a subject who has not previously received chemotherapy to treat the pancreatic cancer comprising administration of liposomal irinotecan, leucovorin and 5-flurouracil. Methods of treating pancreatic cancer in a subject who has not previously received chemotherapy to treat the pancreatic cancer comprising administration of liposomal irinotecan, oxaliplatin, leucovorin and 5-flurouracil. Methods include treating subjects having unresectable, locally advanced or metastatic adenocarcinoma of the pancreas.

FIG. 1

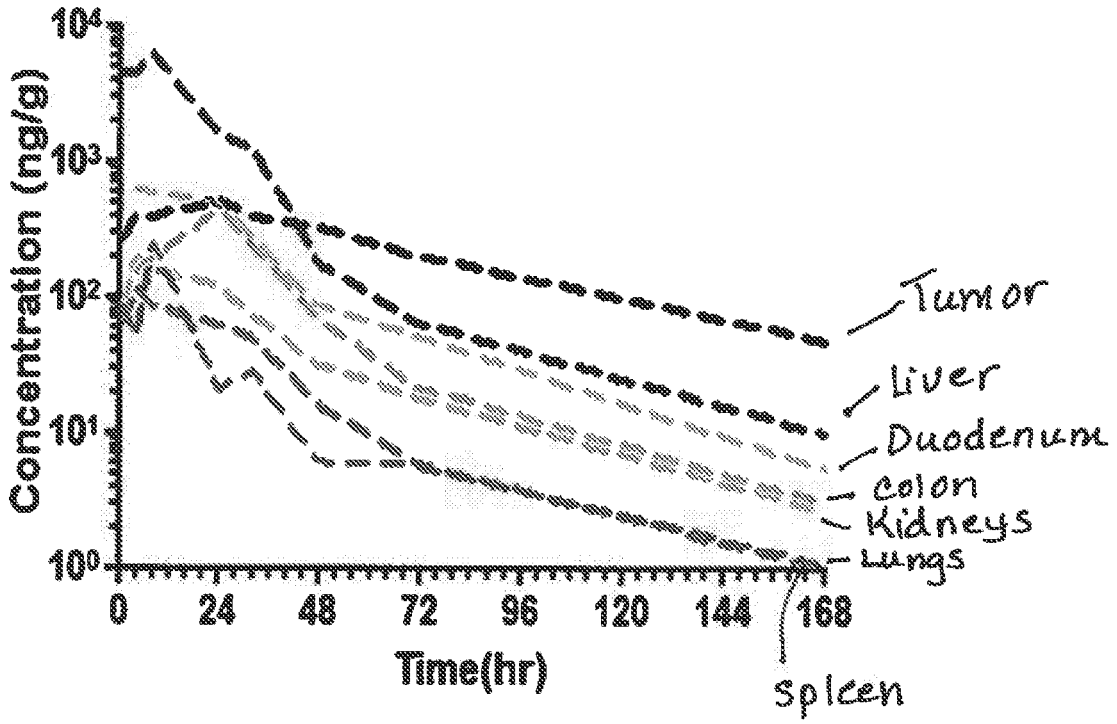

Concentration (ng/g)
10⁴
10³
10²
10¹
10⁰
0
24
48
72
96
120
144
168
Time(hr)
Tumor
liver
Duodenum
colon
Kidneys
Lungs
Spleen

FIG. 2

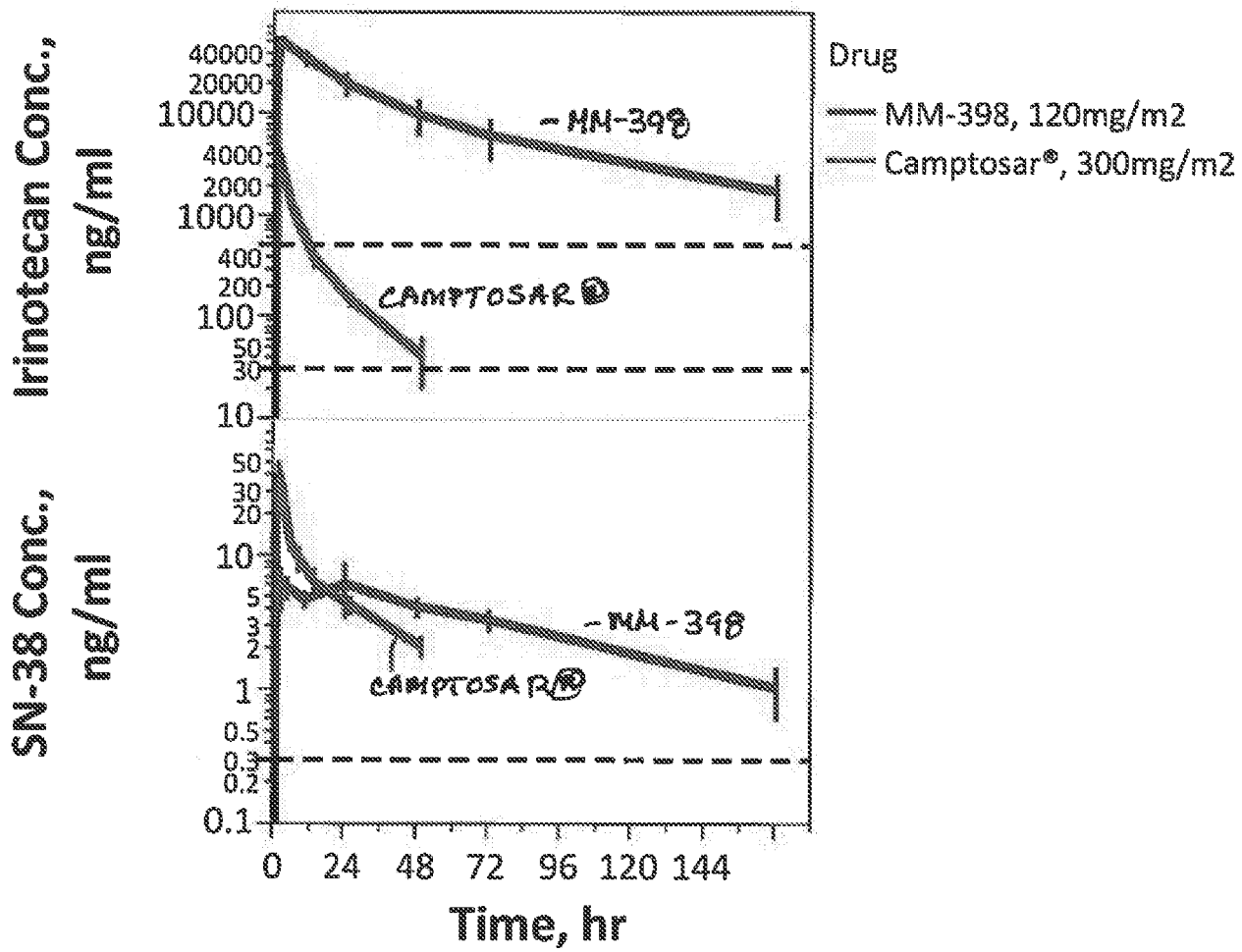

Irinotecan Conc., ng/ml
SN-38 Conc., ng/ml
40000
20000
10000
4000
2000
1000
400
200
100
50
30
10
50
30
20
10
5
3
2
1
0.5
0.2
0.1
MM-398
CAMPTOSAR®
MM-398
CAMPTOSAR®
0
24
48
72
96
120
144
Time, hr
Drug
MM-398, 120mg/m2
Camptosar®, 300mg/m2

FIG. 3

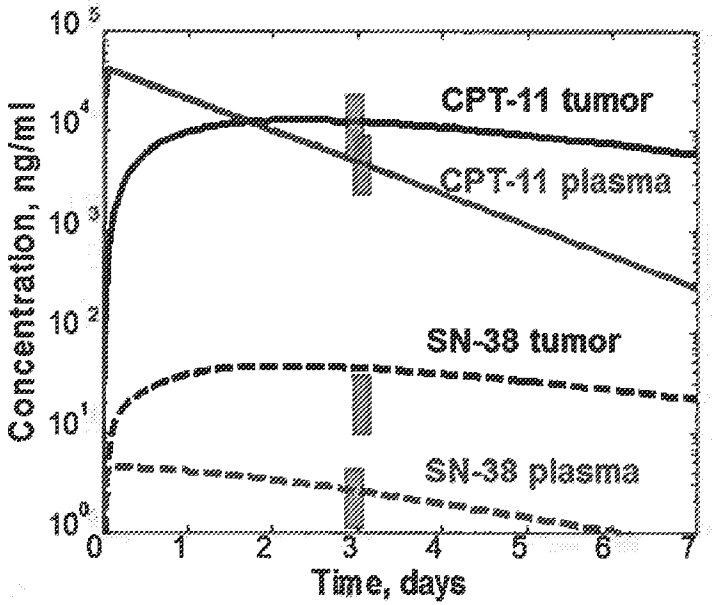


FIG. 3A

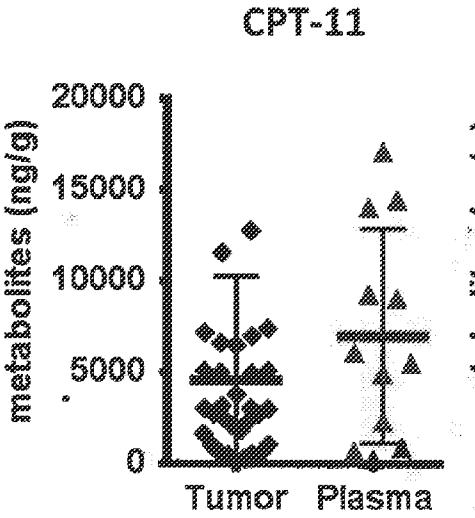


FIG. 3B

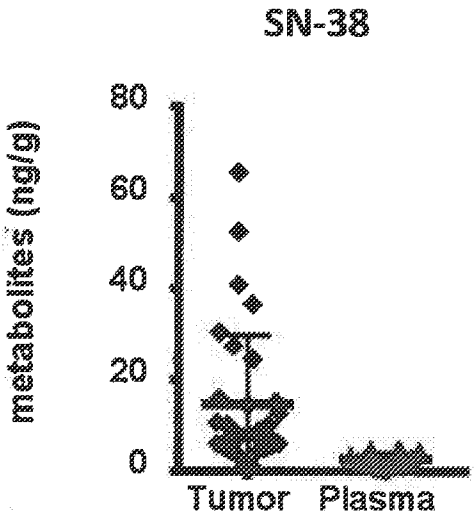


FIG 3C

FIG. 4A

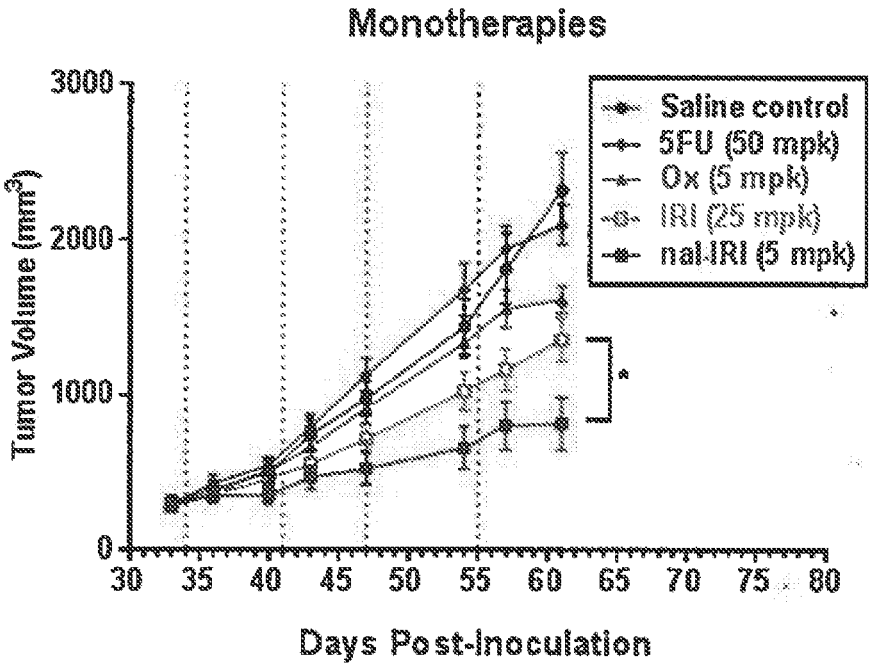

Monotherapies
Tumor Volume (mm3)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
5FU (50 mpk)
Ox (5 mpk)
IRI (25 mpk)
nal-IRI (5 mpk)
*

FIG. 4B

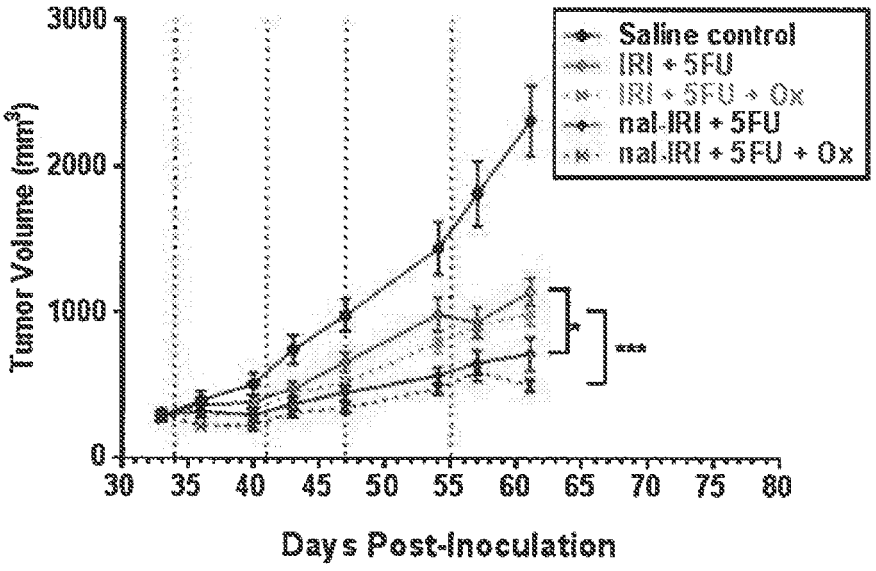

Tumor Volume (mm3)
3000
2000
1000
0
30
35
40
45
50
55
60
65
70
75
80
Days Post-Inoculation
Saline control
IRI + 5FU
IRI + 5FU + Ox
nal-IRI + 5FU
nal-IRI + 5FU + Ox
*
**

FIG. 5

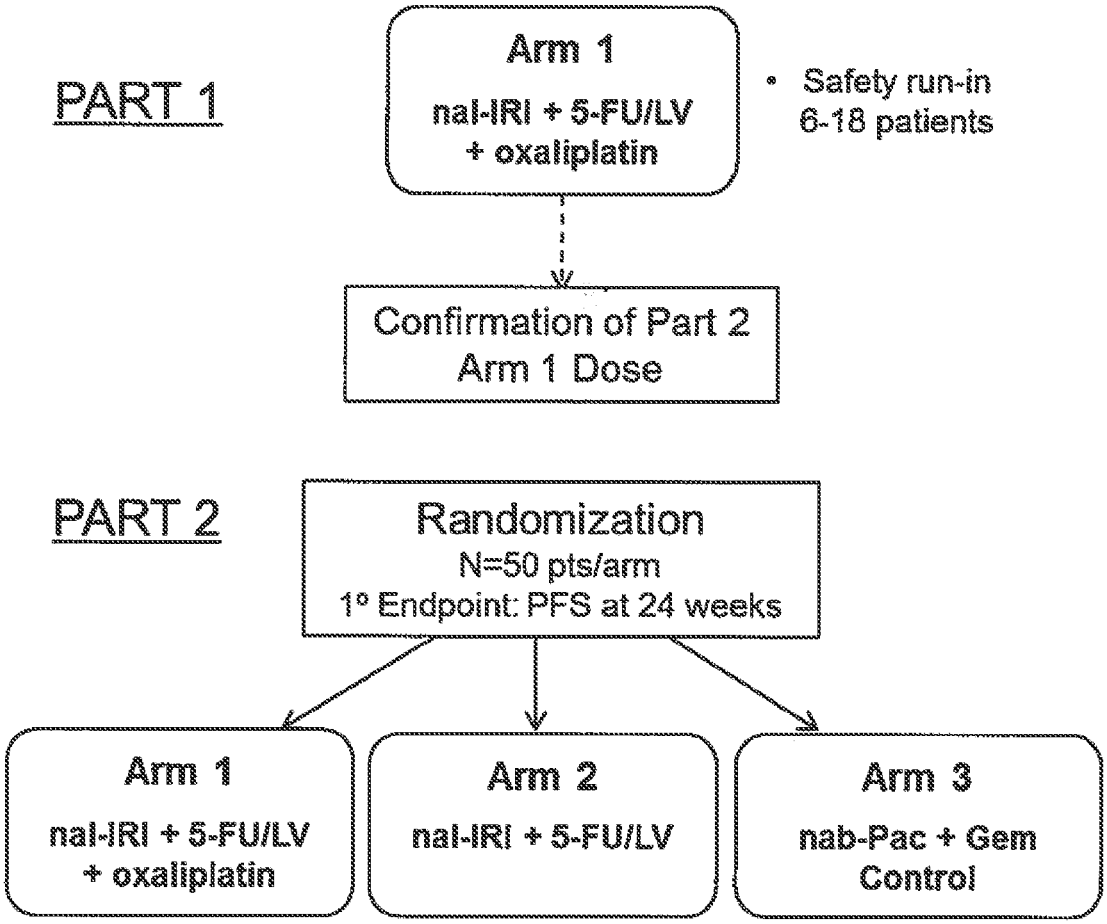

PART 1
Arm 1
nal-IRI + 5-FU/LV
+ oxaliplatin
• Safety run-in
6-18 patients
Confirmation of Part 2
Arm 1 Dose
PART 2
Randomization
N=50 pts/arm
1° Endpoint: PFS at 24 weeks
Arm 1
nal-IRI + 5-FU/LV
+ oxaliplatin
Arm 2
nal-IRI + 5-FU/LV
Arm 3
nab-Pac + Gem
Control
• Expected number of patients (Part 1 + Part 2): ~156-168

FIG. 6

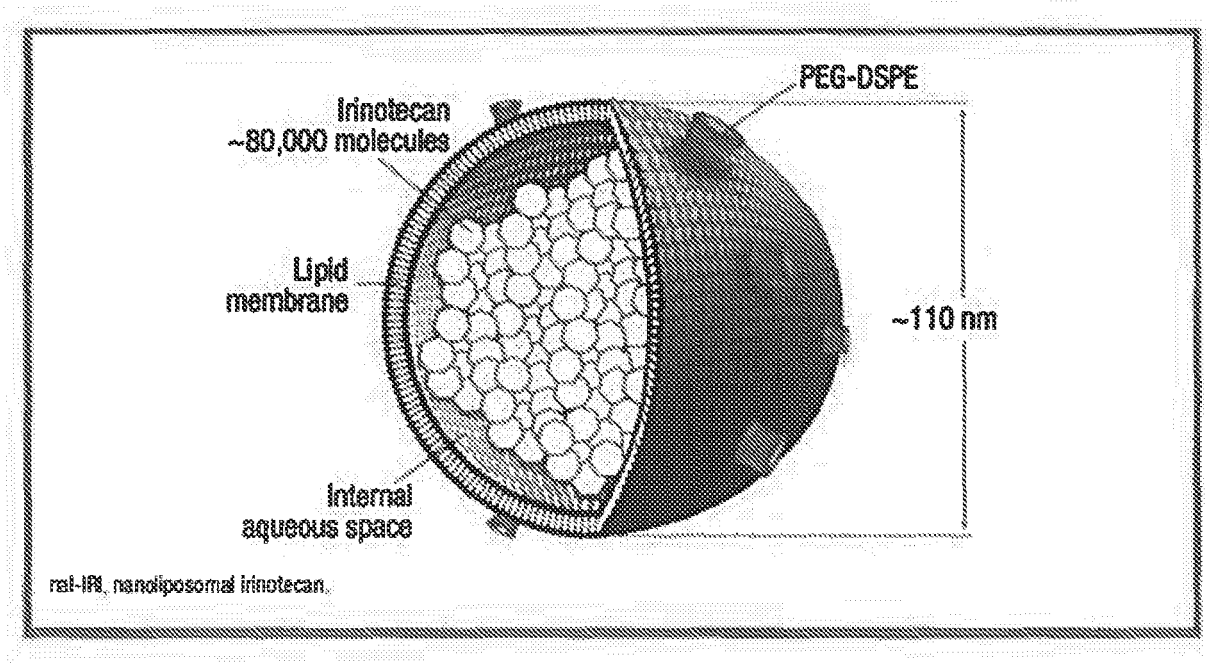
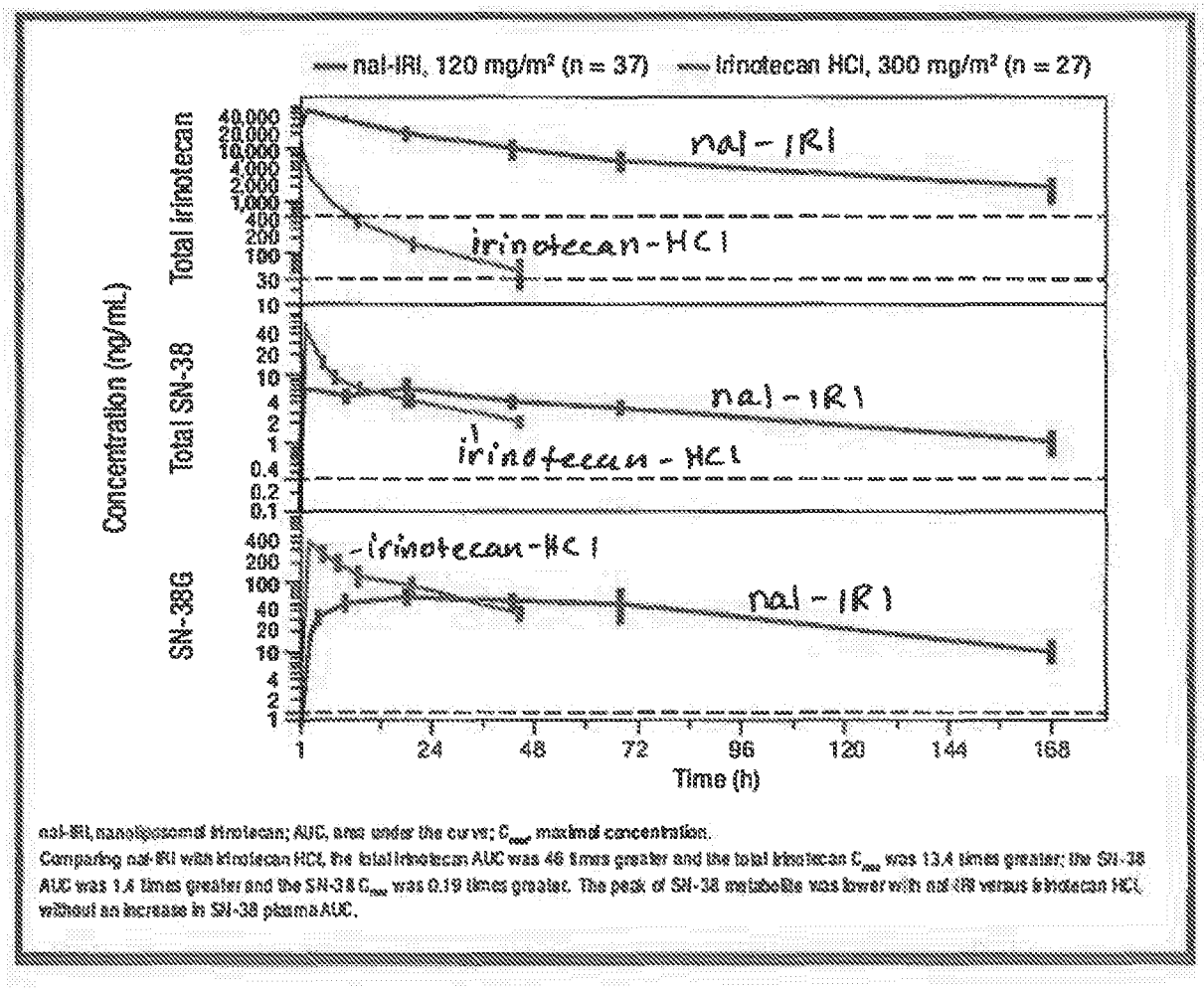

PEG-DSPE
Irinotecan
~80,000 molecules
Lipid
membrane
~110 nm
Internal
aqueous space
nal-IRI, nanoliposomal irinotecan.

FIG. 7



nal-IRI, nanoliposomal irinotecan; AUC, area under the curve; C_{max}, maximal concentration.

Comparing nal-IRI with irinotecan HCl, the total irinotecan AUC was 46 times greater and the total irinotecan C_{max} was 13.4 times greater; the SN-38 AUC was 1.4 times greater and the SN-38 C_{max} was 0.19 times greater. The peak of SN-38 metabolite was lower with nal-IRI versus irinotecan HCl, without an increase in SN-38 plasma AUC.

FIG. 8

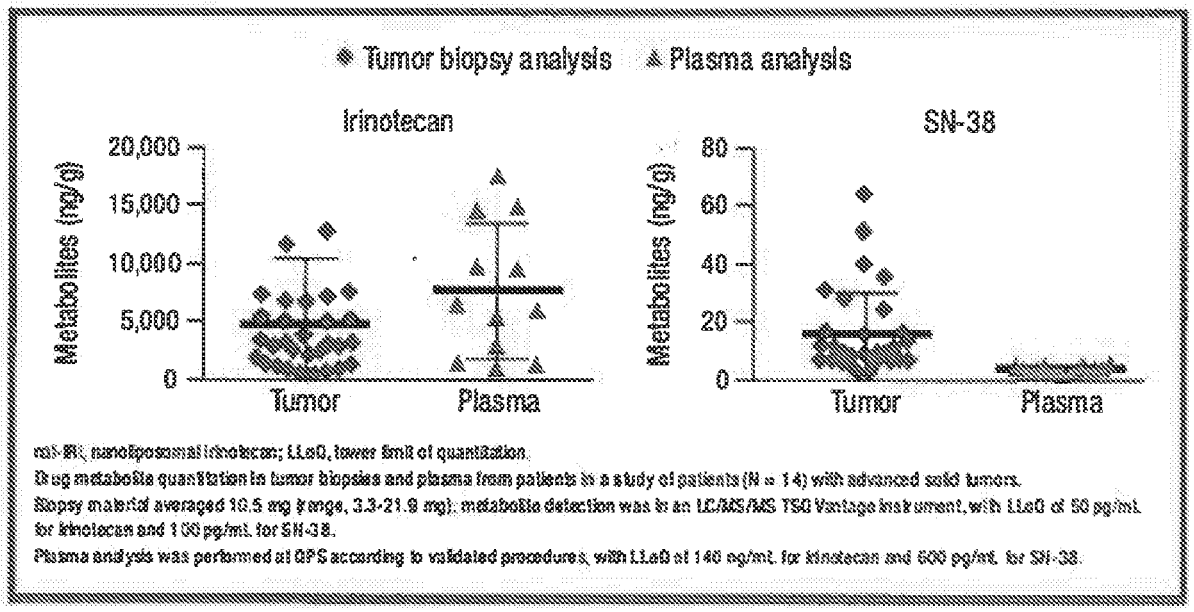
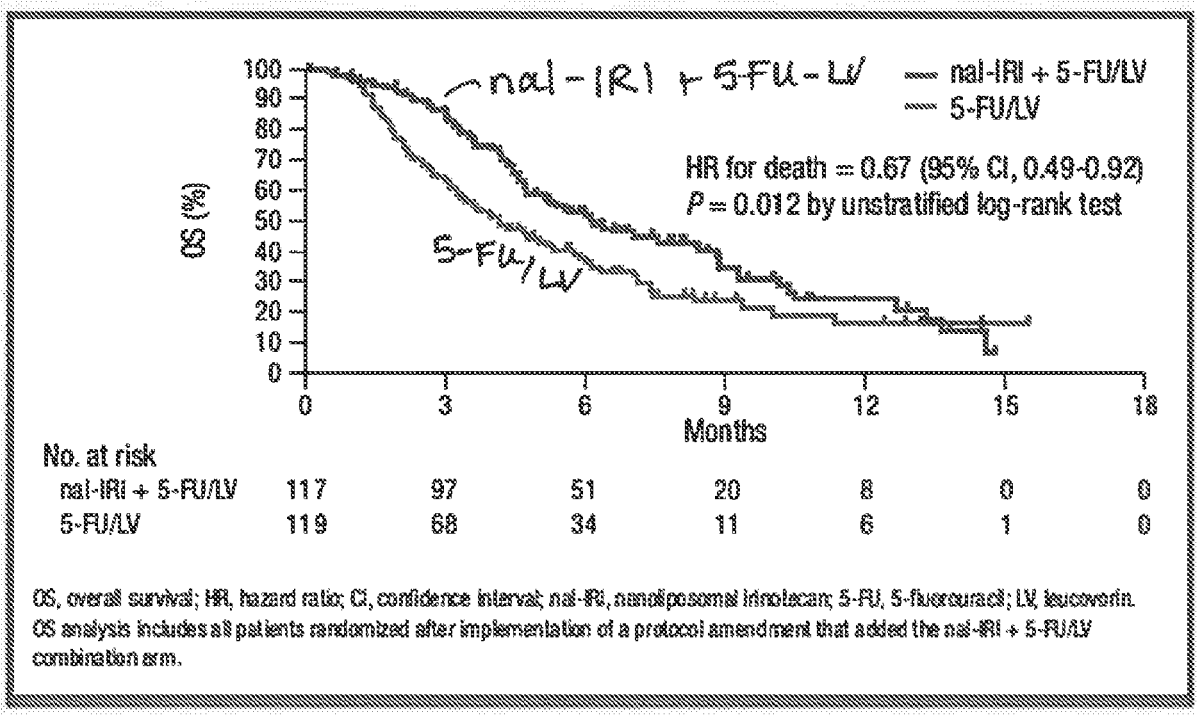

Tumor biopsy analysis
Plasma analysis
Irinotecan
SN-38
Metabolites (ng/g)
20,000
15,000
10,000
5,000
0
Tumor
Plasma
80
60
40
20
0
nal-IRI, nanoliposomal irinotecan; LLoQ, lower limit of quantitation.
Drug metabolite quantitation in tumor biopsies and plasma from patients in a study of patients (N = 14) with advanced solid tumors.
Biopsy material averaged 10.5 mg (range, 3.3-21.9 mg); metabolite detection was in an LC/MS/MS TSQ Vantage instrument, with LLoQ of 50 pg/mL for irinotecan and 100 pg/mL for SN-38.
Plasma analysis was performed at QPS according to validated procedures, with LLoQ at 140 ng/mL for irinotecan and 600 pg/mL for SN-38.

FIG. 9



OS, overall survival; HR, hazard ratio; CI, confidence interval; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin.
OS analysis includes all patients randomized after implementation of a protocol amendment that added the nal-IRI + 5-FU/LV combination arm.

FIG. 10

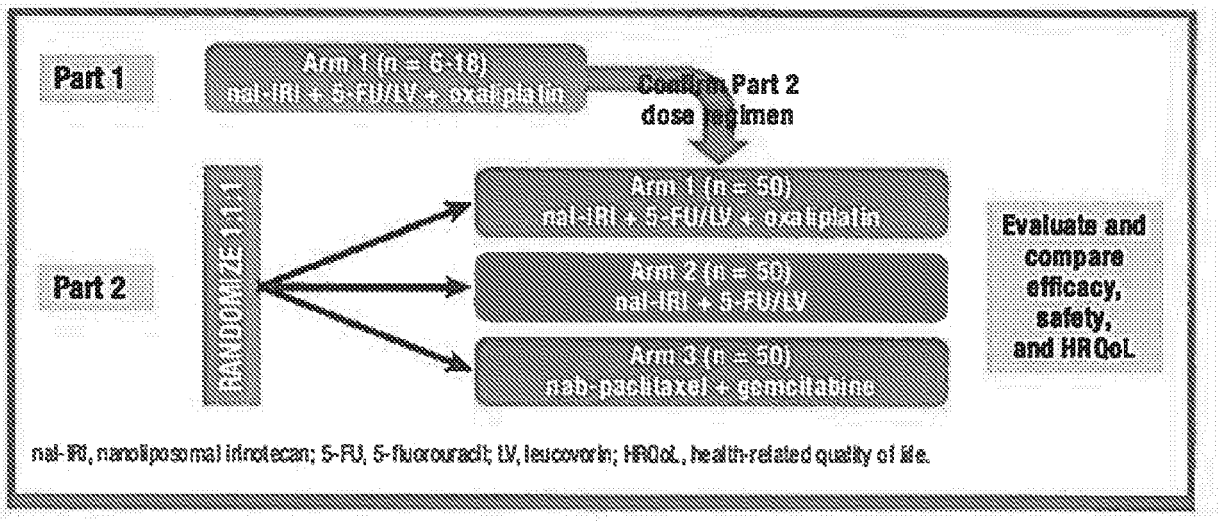

Part 1
Arm 1 (n = 6-18)
nal-IRI + 5-FU/LV + oxaliplatin
Confirm Part 2
dose regimen
Part 2
RANDOMIZE 1:1:1
Arm 1 (n = 50)
nal-IRI + 5-FU/LV + oxaliplatin
Arm 2 (n = 50)
nal-IRI + 5-FU/LV
Arm 3 (n = 50)
nab-paclitaxel + gemcitabine
Evaluate and compare efficacy, safety, and HRQoL
nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HRQoL, health-related quality of life.

FIG. 11

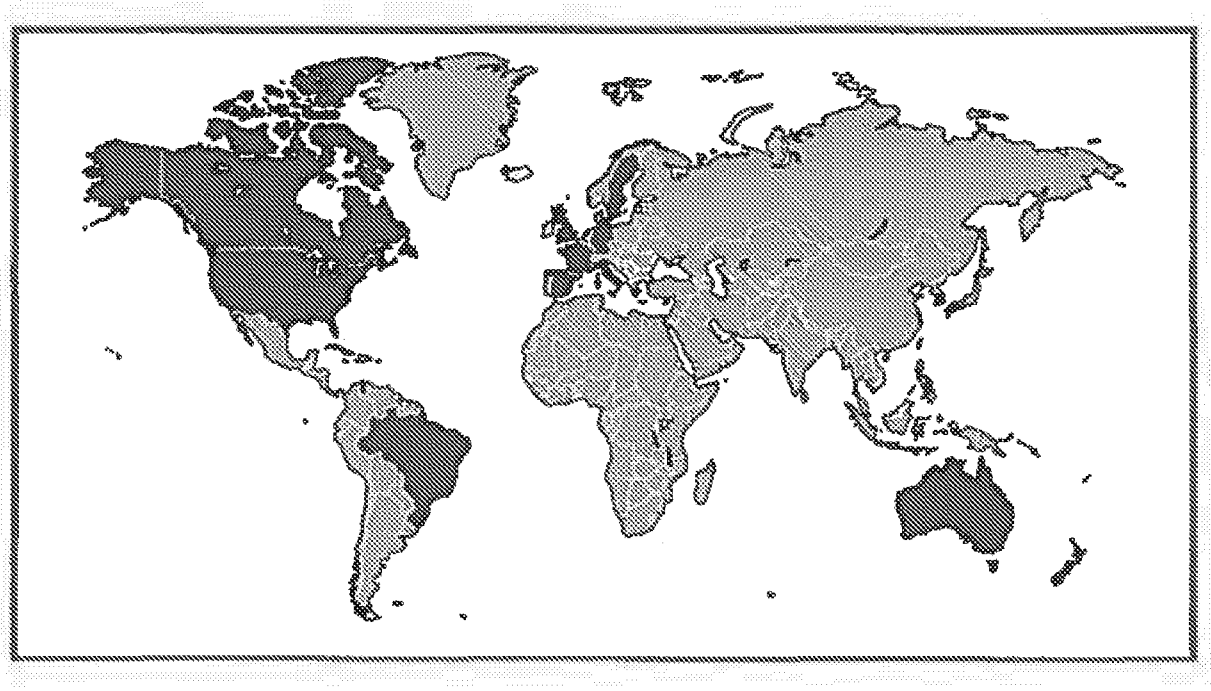
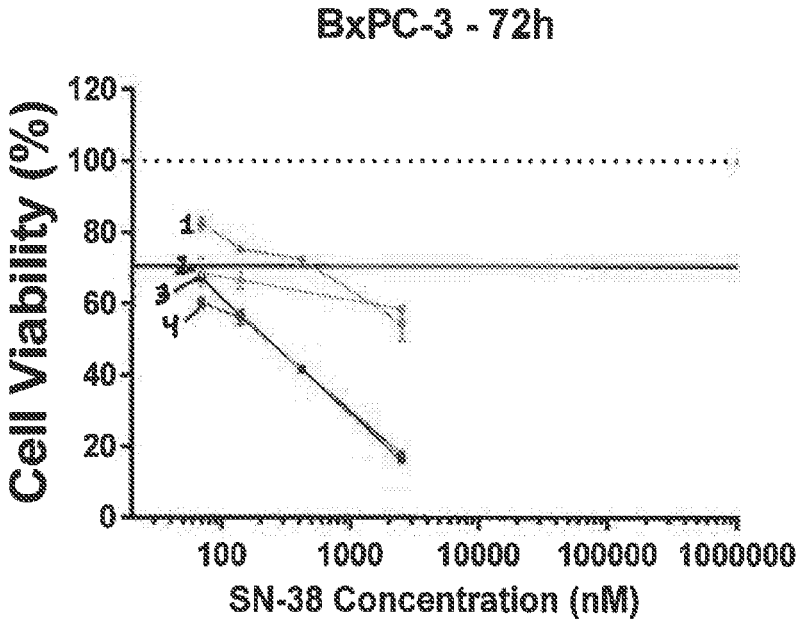
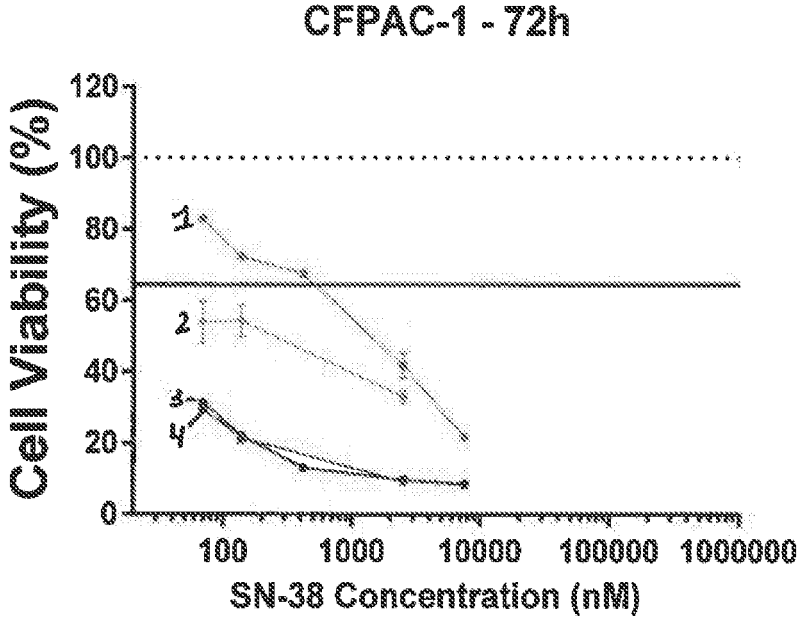


FIG. 12

A

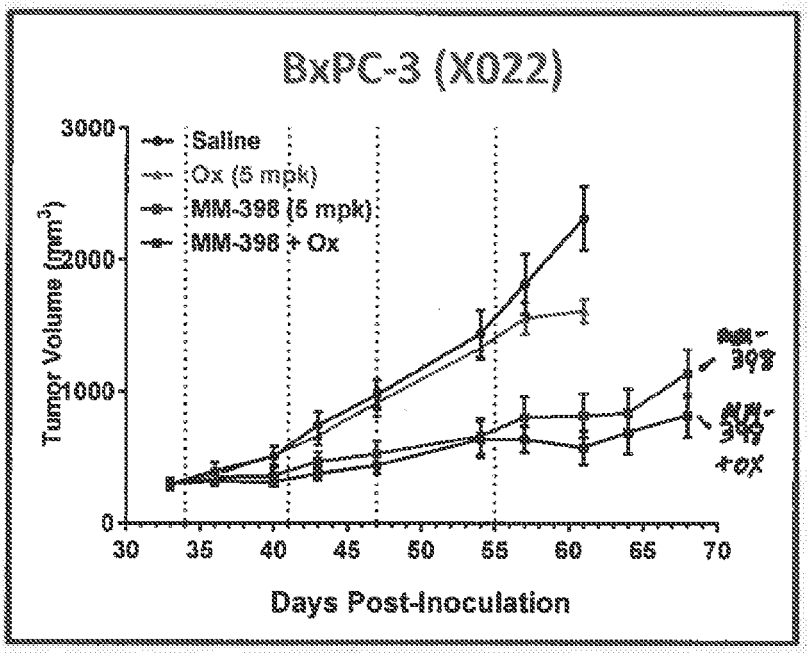


B



1 — SN38@4/24h 2 — SN38@4/24h + Ox
3 — SN38@72/144h 4 — SN38@72/144h + Ox

A


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

B

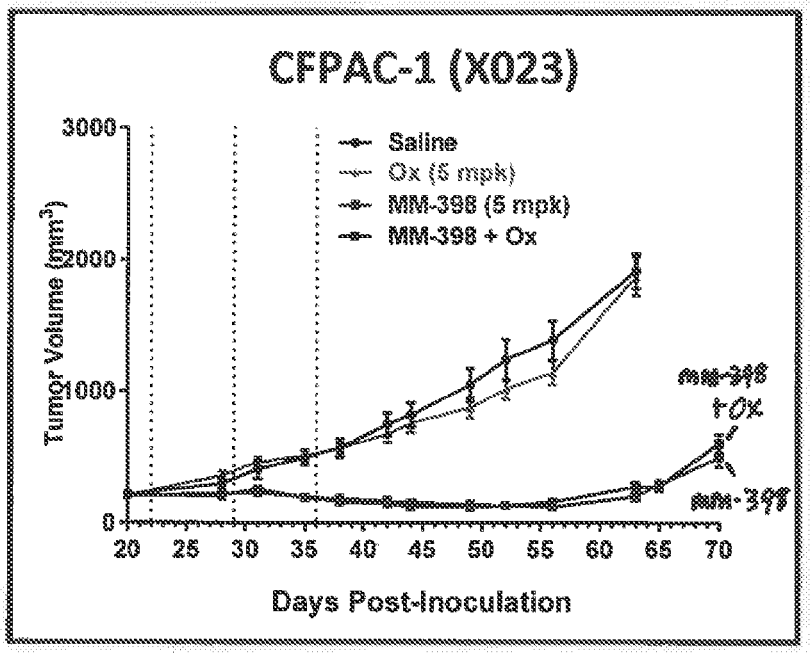
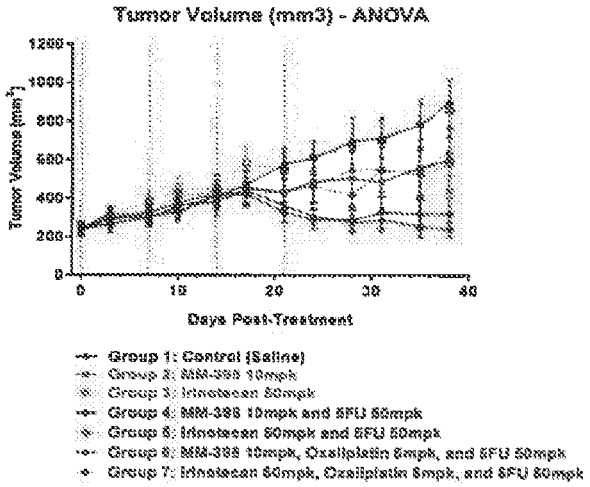
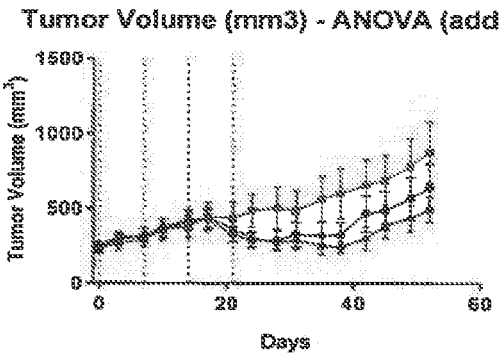

CFPAC-1 (X023)
Saline
Ox (5 mpk)
MM-398 (5 mpk)
MM-398 + Ox
Tumor Volume (mm3)
3000
2000
1000
0
20
25
30
35
40
45
50
55
60
65
70
Days Post-Inoculation

FIG. 14

14A



14B



14C

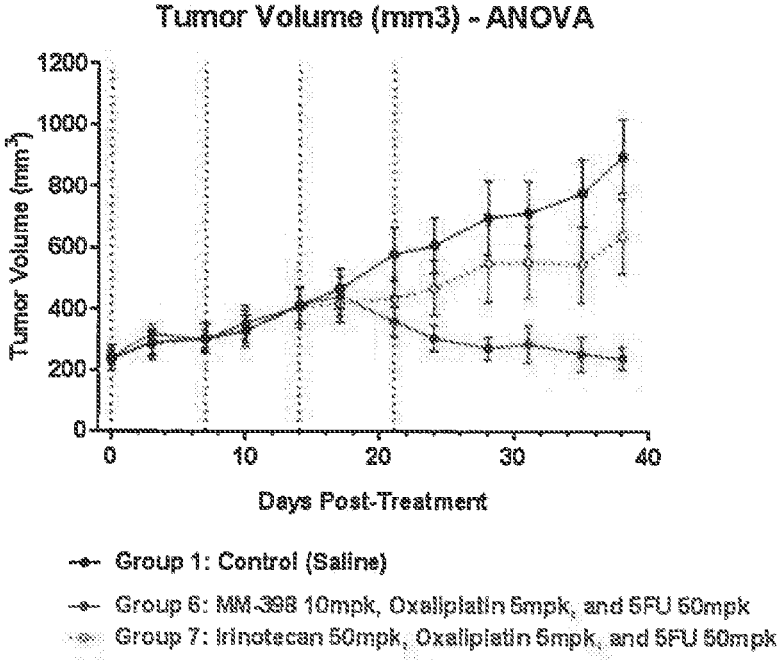


FIG. 15

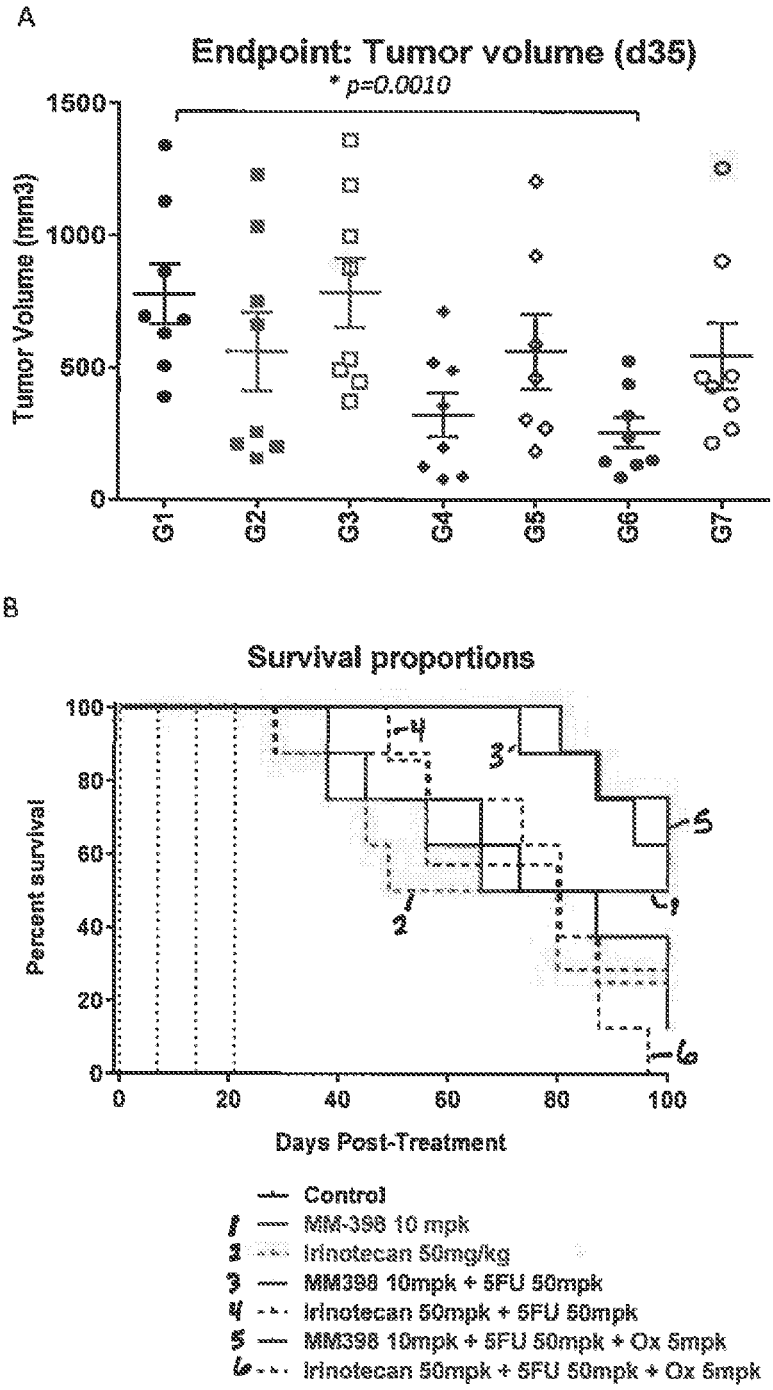
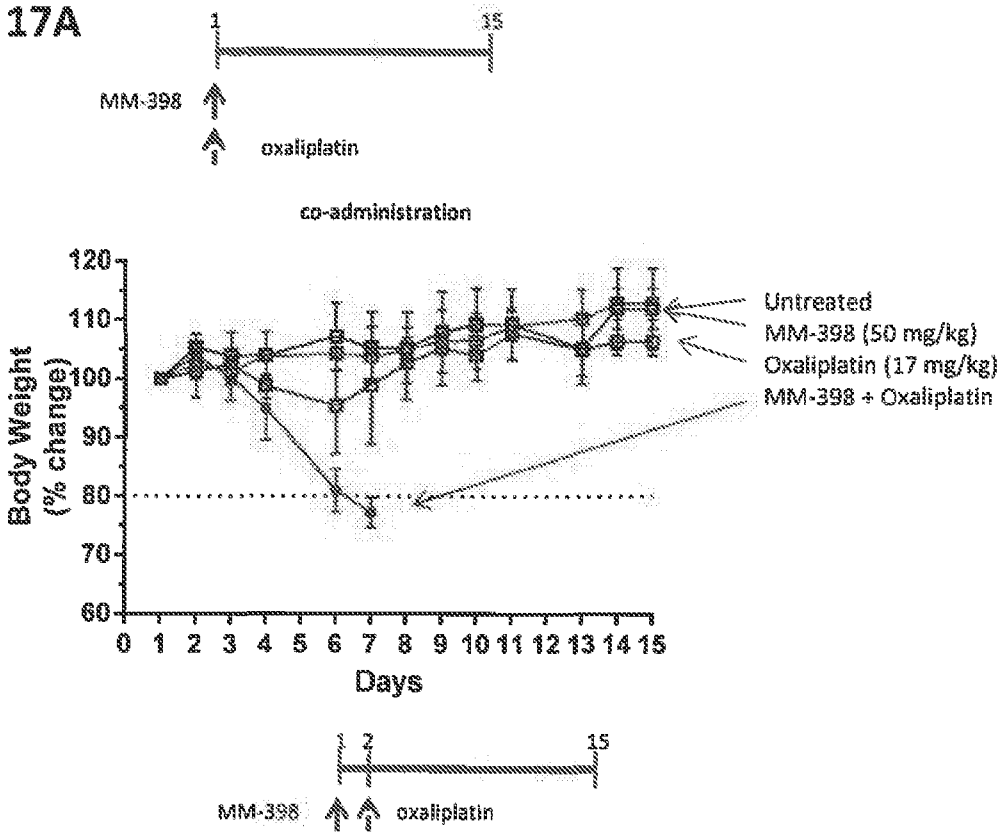

A
Endpoint: Tumor volume (d35)
* p=0.0010
Tumor Volume (mm3)
1500
1000
500
0
G1
G2
G3
G4
G5
G6
G7
B
Survival proportions
Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
Days Post-Treatment
Control
MM-398 10 mpk
Irinotecan 50mg/kg
MM398 10mpk + 5FU 50mpk
Irinotecan 50mpk + 5FU 50mpk
MM398 10mpk + 5FU 50mpk + Ox 5mpk
Irinotecan 50mpk + 5FU 50mpk + Ox 5mpk

FIG. 16

	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. 17


17A
1
15
MM-398
oxaliplatin
co-administration
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
Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin
1
2
15
MM-398
oxaliplatin

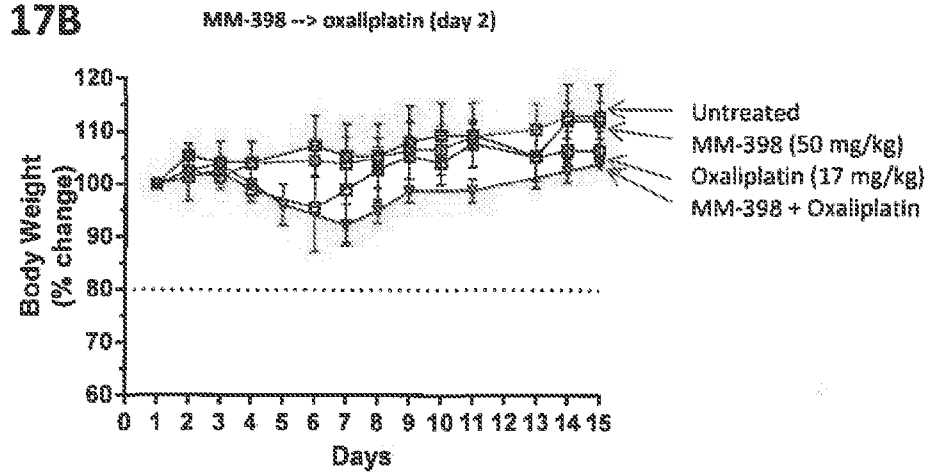

17B
MM-398 --> oxaliplatin (day 2)
Body Weight (% change)
120
110
100
90
80
70
60
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days
Untreated
MM-398 (50 mg/kg)
Oxaliplatin (17 mg/kg)
MM-398 + Oxaliplatin

FIG 18

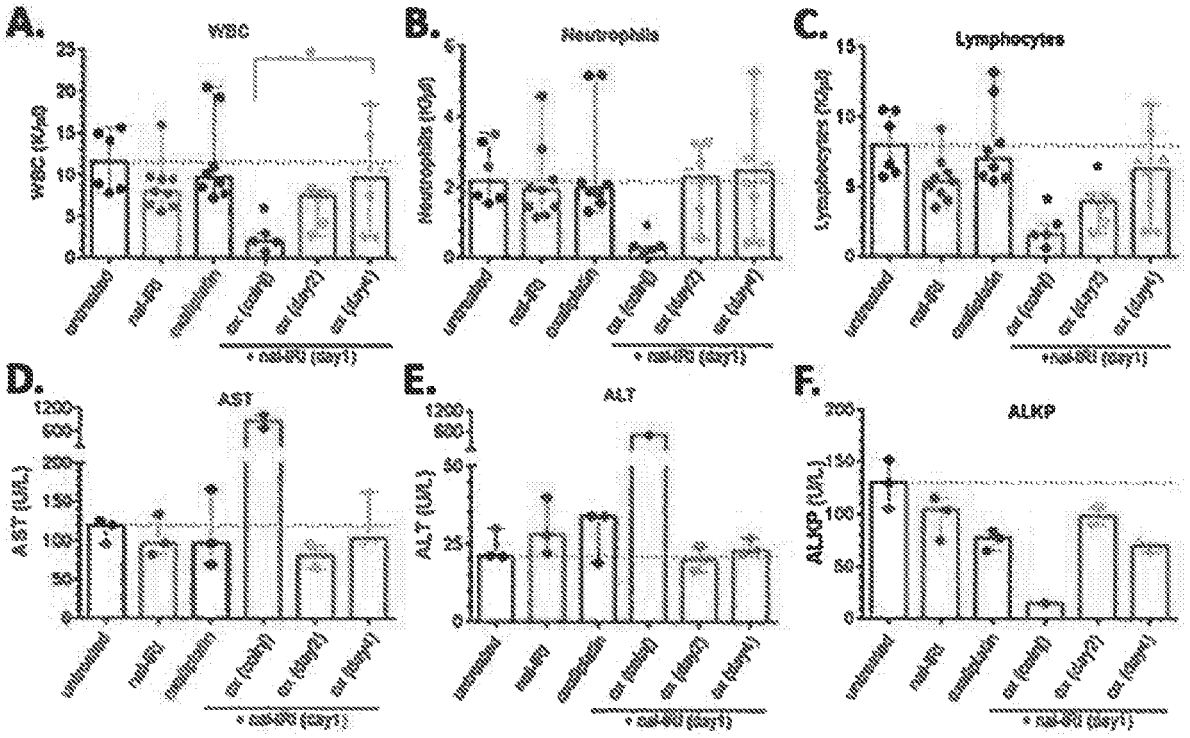
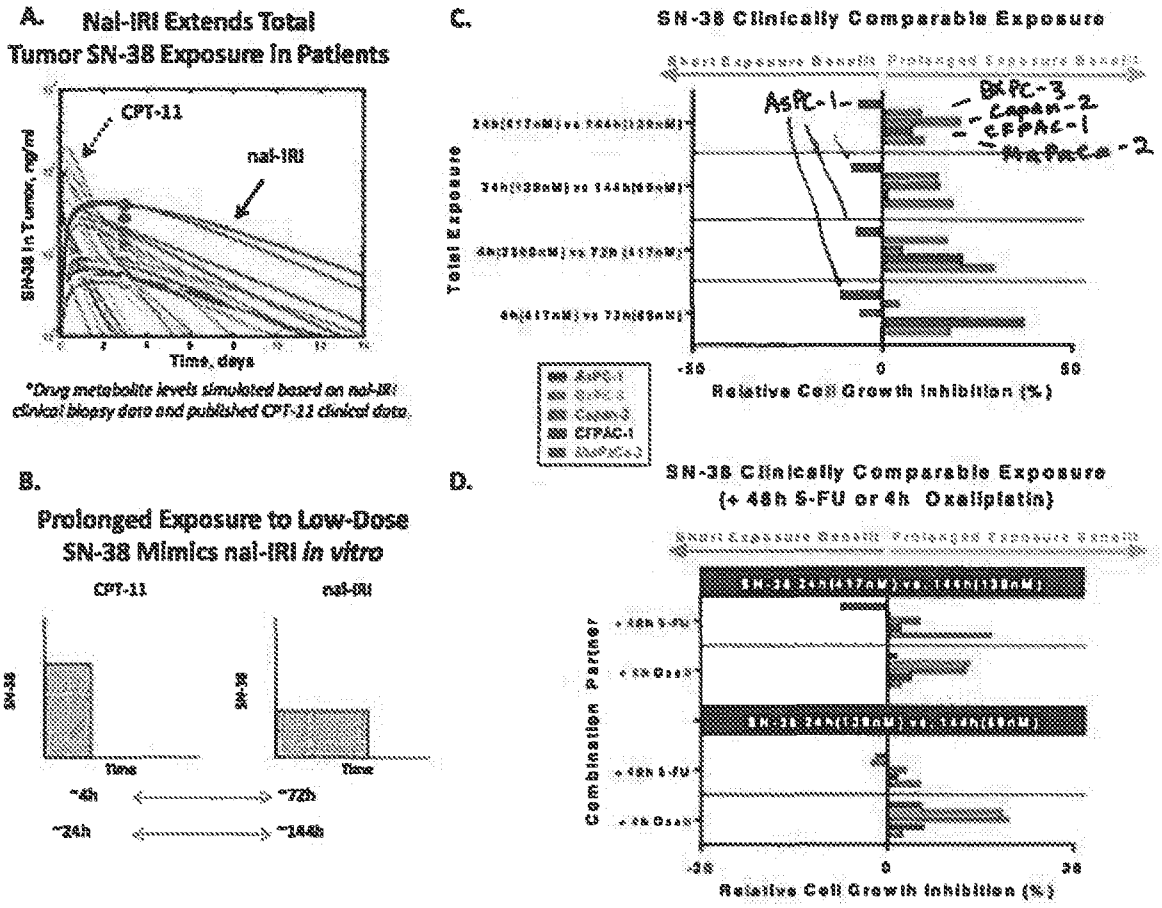


FIG. 19


A.
Nal-IRI Extends Total Tumor SN-38 Exposure in Patients
CPT-11
nal-IRI
Time, days
*Drug metabolite levels simulated based on nal-IRI clinical biopsy data and published CPT-11 clinical data.
B.
Prolonged Exposure to Low-Dose SN-38 Mimics nal-IRI in vitro
CPT-11
nal-IRI
SN-38
Time
~4h
~72h
~24h
~144h
C.
SN-38 Clinically Comparable Exposure
Short Exposure Benefit
Prolonged Exposure Benefit
Total Exposure
AsPC-1
BxPC-3
Capan-2
CFPAC-1
MiaPaCa-2
-38
0
38
Relative Cell Growth Inhibition (%)
D.
SN-38 Clinically Comparable Exposure
(+ 48h 5-FU or 4h Oxaliplatin)
Short Exposure Benefit
Prolonged Exposure Benefit
Combination Partner
+ 48h 5-FU
+ 4h Oxali
-38
0
38
Relative Cell Growth Inhibition (%)

Electronic Acknowledgement Receipt

EFS ID:	25509173
Application Number:	62323245
International Application Number:	
Confirmation Number:	6719
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	133156
Filer:	Noel E. Day/Andrea Nelson
Filer Authorized By:	Noel E. Day
Attorney Docket Number:	239669-393537
Receipt Date:	15-APR-2016
Filing Date:	
Time Stamp:	16:41:34
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$660
RAM confirmation Number	4491
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1085.pdf	4786692 ed9fdde21b3ead3be60533dbbcaef3761ac69c58	yes	171

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	2
Provisional Cover Sheet (SB16)	3	4
Application Data Sheet	5	10
Power of Attorney	11	12
Miscellaneous Incoming Letter	13	13
Specification	14	141
Claims	142	150
Abstract	151	151
Drawings-other than black and white line drawings	152	171

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	31809 1cbef1ecd39258bf4ea7d750c5d09d97bd4c4826	no	2

Warnings:

Information:

Total Files Size (in bytes):	4818501

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 62323245 Document Date: 04/15/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013