Document Coversheet

Study Title: Phase 2 Single-Arm Study of Nanoliposomal Irinotecan with Fluorouracil and Leucovorin in Refractory Advanced High Grade Neuroendocrine Cancer of GI, Unknown or Pancreatic Origin

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PROTOCOL TITLE:

Phase 2 Single-Arm Study of Nanoliposomal Irinotecan with Fluorouracil and Leucovorin in Refractory Advanced High-Grade Neuroendocrine Cancer of GI, Unknown, or Pancreatic Origin

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Confidentiality Statement

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1 OBJECTIVES

1.1 Primary Objective

- To determine the objective response rate of nanoliposomal irinotecan (Nal-IRI) + fluorouracil (5-FU) and leucovorin in patients with refractory advanced high-grade neuroendocrine cancer of GI, unknown, or pancreatic origin.

1.2 Secondary Objective

- To determine overall survival, progression-free survival, time to treatment failure, safety, clinical response and, quality of life (QOL) changes resulting from the combination treatment of nanoliposomal irinotecan (Nal-IRI) + fluorouracil (5-FU) and leucovorin.

1.3 Exploratory Objective

- Genetic profiling for mutations will be conducted on pre-study tumor samples and correlated with response. This prospective assessment may help identify response biomarkers that could serve as a guide in determining what treatment options may be best for a patient based on pretreatment tumor from biopsy or liquid profiling mutations.

2 BACKGROUND

Each year, an estimated 300,000 people are diagnosed with GI cancers, with over 150,000 people dying annually [1]. Almost 145,000 cases of colorectal cancer (CRC) are projected to be diagnosed in the US in 2019; with more than 51,000 deaths from the disease [1]. CRC and pancreatic cancers are the second and fourth leading causes of cancer death in both sexes the US [1]. Therefore, GI cancers are a major area of need for new drug development.

Encapsulation of irinotecan in a liposomal nanoparticle allows for a longer circulation time for irinotecan leading to an increase in irinotecan and its major metabolite, SN-38 levels in the tumor. In tumor xenografts nanoliposomal irinotecan (MM-398) achieves higher intra-tumor concentrations of both irinotecan (142-fold) and SN38 (9-fold) when compared to free Irinotecan [2]. Nanoliposomal irinotecan (MM-398) has been evaluated in clinical trials. In colorectal cancer, 5-FU plus nanoliposomal irinotecan had activity in patients with progression on FOLFOX [3]. Promising activity was also reported in patients with gastric and gastro-esophageal junction tumors (GEJ) [4]. In pancreatic cancer, nanoliposomal irinotecan plus 5-FU demonstrated significant clinical activity in second line setting [5]. Nanoliposomal irinotecan is well tolerated. Commonly observed side effects (≥ 20%) are diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia.

2.1 Nanoliposomal Irinotecan (Nal-IRI): Pharmaceutical and Therapeutic Background

Nal-IRI is irinotecan (also known as CPT-11) encapsulated in a liposome drug delivery system (liposomal 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 [6-8]. Irinotecan is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38 [9]. 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 [10 11].

Drug carrier technologies represent a rational strategy to improve the PK and bio-distribution of irinotecan while protecting it from premature metabolism. Nal-IRI employs a novel intra-liposomal drug stabilization technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high in vivo stability. The stable nano-liposome 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 PK, high intravascular drug retention in the liposomes, and 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 release the active drug and convert it locally to the substantially more cytotoxic SN-38. The preferentially local bio-activation should result in reduced exposure to potential sites of toxicity and increased exposure to neighboring cancer cells within the tumor.

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of Nal-IRI can be found in the Investigator's Brochure.

2.1.1 Nal-IRI Preclinical Experience

Nal-IRI has been shown in preclinical 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 [2 12]. 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 [13].

2.1.2 Nal-IRI Preclinical Pharmacokinetics

The PK properties of Nal-IRI were evaluated in an HT-29 colon cancer subcutaneous xenograft model [2]. Both irinotecan and SN-38 were cleared very rapidly (within 8 hours) from the plasma following non-liposomal 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 Cmax 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 (Figure 1). Activation of irinotecan to SN-38 by the liver is the primary path for SN-38 tumoral accumulation when non-liposomal 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 non-liposomal irinotecan administration formed the basis for clinical development.

Figure 1 Tissue Distribution of Nal-IRI in an HT-296 Xenograft Study

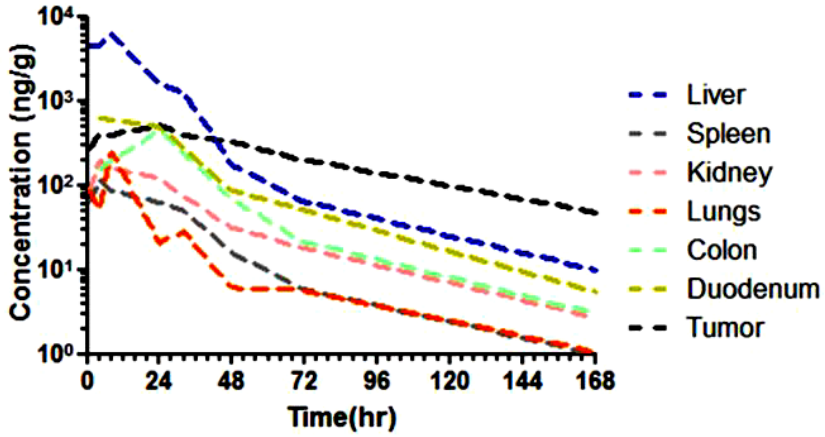
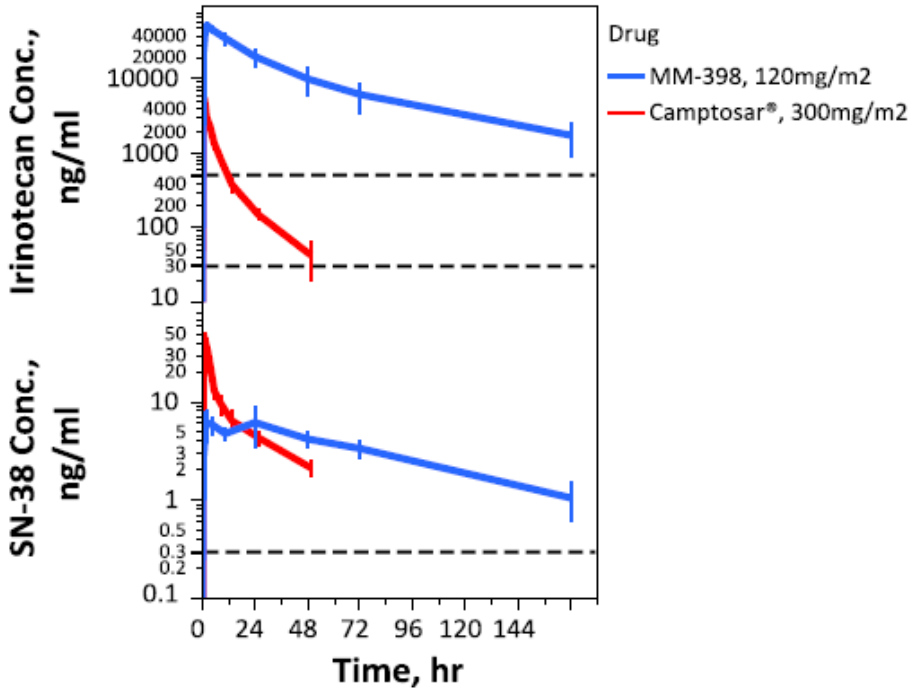


Figure 1: Levels of SN-38 in various tissues following a single Nal-IRI (20 mg/kg) dose are shown. Prolonged accumulation of SN-38 (~168 h) seen in tumor compared to other organs (~48 h).

2.1.3 Nal-IRI Pharmacokinetics in Humans

The PK 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 [4] direct comparison of the PK 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 (Cmax: 13.4-fold, AUC0-∞: 46.2-fold, t1/2: 2.0-fold), and higher SN-38 t1/2 (3-fold) and marginally higher AUC0-∞ (1.4-fold), however, SN-38 Cmax was reduced by 5.3-fold (Figure 2).

Figure 2 Mean Plasma Concentrations of Total Irinotecan and SN-38 Following the Administration of Either MM-398 (120 mg/m^2) or Camptosar® (300 mg/m^2) in Study PEP0206



Gastric cancer patients received either Nal-IRI (MM-398) at a dose of 120 mg/m^2 (blue line) or, non-liposomal 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 consist of two LLOQ values because of two different irinotecan assays were used to measure low and high range of concentrations. The concentrations less than LLOQ values were set to the corresponding LLOQ [Data on file, Merrimack Pharmaceuticals; Ma 2015].

In other PK studies of single agent Nal-IRI, similar findings were observed when compared to standard doses of conventional irinotecan. Based on population PK 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 1).

Table 1 Summary Statistics of Nal-IRI PK Parameters across Multiple PK Studies

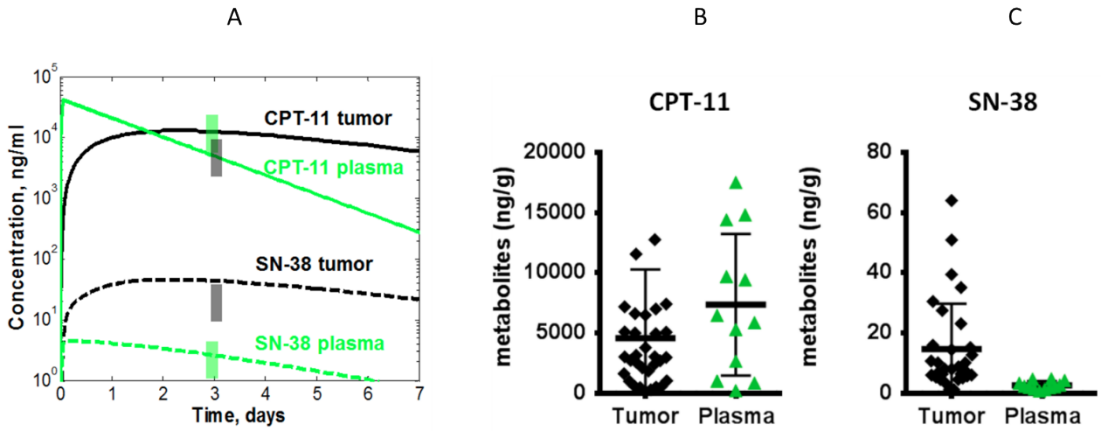
PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max}, µg/mL or ng/mL	60	4	28.8	86	4	3.8	226
	80	25	38.0	36	25	4.7	89
	90	6	53.6	37	6	7.5	89
	100	11	41.9	41	11	6.2	79
	120	45	59.4	32	45	7.2	57
	180	4	102.4	87	4	11.8	89
$T_{1/2}$	60	4	22.0	87	3†	145.1	233
	80	23†	26.85	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	1123	6	506	102
	100	11	919	256	10†	453	99
	120	45	1258	192	40†	574	64
	180	4	2076	90	4	1069	183
Vd, L/m^2	60	4	3.0	87	NA		
	80	23†	2.2	55			
	90	6	1.5	40			
	100	11	2.2	24			
	120	45	1.9	52			
	180	4	2.1	30			

†$T_{1/2}$ and $AUC_{0-\infty}$ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available. C_{max} 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 [Data on File, Merrimack Pharmaceuticals, Inc.].

The above PK results obtained from patients treated with either Nal-IRI or non-liposomal irinotecan confirmed the preclinical observation that Nal-IRI extended plasma PK of both CPT-11 and SN-38 compared to treatment with non-liposomal irinotecan. Further, a Phase I clinical study of Nal-IRI monotherapy [14] 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 3 B-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.

Figure 3 Clinical Evidence for Local Activation and Accumulation of SN-38 in Tumor Tissue



A) 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.
B) CPT-11 levels
C) SN-38 levels, as measured from patient tumor (black) and plasma (green) samples collected 72h post-Nal-IRI infusion [14].

2.1.4 Nal-IRI Safety in Humans

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 un-encapsulated 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 [Camptosar®, Pfizer]. 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. 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). 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 2 (refer to ONIVYDE® package insert, revised: 06/2017) summarizes the most common ≥Grade 3 adverse events with ≥2% incidence compared with the control arm from the NAPOLI-1 trial comparing Nal-IRI + 5-FU/LV (at a dose of 80 mg/m^2 given on an every-2-week schedule), or Nal-IRI monotherapy (at a dose of 120 mg/m^2 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.

Table 2 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, %[a]			
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, %[a, b]			
Neutrophil count decreased	20	16	2
Hemoglobin decreased	6	7	5
Platelet count decreased	2	1	0

[a] Per CTCAE Version 4
[b] Includes only patients who had at least one post-baseline assessment

2.2 Fluorouracil and Leucovorin (5-FU/ LV)

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthase, 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.

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 synthase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthase.

2.3 Rationale for Combination Therapy

Patients with neuroendocrine carcinomas (NECs) grade 3 have a poor prognosis. Etoposide–platinum combination is considered the standard chemotherapy, but duration of benefit is short and survival ~ one year or less, and currently no standard second line therapy exists. Irinotecan alone or in combination has shown some efficacy in patients treated for small cell lung cancer which had pathological similarities with neuroendocrine tumors and temozolomide and capecitabine has shown efficacy but with limited response rates in non-pancreatic NETs. The Nordic study evaluated survival in patients who received either platinum or temozolomide based regimens first line and reported survival of ~11-13 months in both groups. Currently the ECOG – ACRIN Cancer research group is studying the optimal first line regimen in NCT 02595424.

In a retrospective study to determine safety and efficacy of the FOLFIRI regimen in patients with NECs grade 3 after failure of etoposide–platinum combination, efficacy was seen in patients with high grade NECs. Among 39 patients who failed etoposide–platinum combination, 19 (49%; 12 women, median age 53 (29–78) years) received the FOLFIRI regimen with a median number of 6 (1–16) courses. Six patients (31%) had at least one episode of grades 3–4 toxicity (neutropenia, n=3; diarrhea, n=3) without toxic death. Six patients (31%) had objective response, 6 (31%) stable disease, and 7 (38%) tumor progression. Median progression-free survival under FOLFIRI was 4 months. Overall survival was 18 vs 6.8 months in ineligible patients. The authors concluded that FOLFIRI regimen is a safe and potentially efficient chemotherapy given as second-line in patients with NECs grade 3 who remain in good condition and with reasonable LFTs after failure of etoposide–platinum combination, however to our knowledge this has not yet been studied prospectively. Others have shown FOLFOX has activity in NETs of all grades, as well as Temodar® and capecitabine is a commonly used regimen confirming the role of both irinotecan and 5-FU in this disease. [17, 18, 19]

The NAPOLI trial in second line advanced pancreatic adenocarcinoma showed the safety and tolerability and success of nanoliposomal irinotecan in this setting and was recently approved for use. The regimen is well-tolerated and most frequent toxicities seen are neutropenia, diarrhea, vomiting, and fatigue. The most recent SEER database publication updating survival of all Nets shows that grade 3 and 4 Nets have a median survival of 10 months, with no new therapies under development for these patients clearly represent an area of unmet need.

5-FU based therapy is the current practice although it is not standard and we hypothesize that Nal-IRI+ 5-FU would offer significant response, with maintenance of QOL, and be a viable second line option for these patients.

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Age ≥ 18 years.
2. Participant must have a locally advanced and unresectable or metastatic gastroenteropancreatic neuroendocrine carcinoma of the gastrointestinal (GI) tract, pancreas, or of other known or unknown primary site where 5FU based therapy would be considered reasonable by the treating MD, lung primary is excluded. Patients may have

either progressed on therapy or within 6 months of completing therapy or be intolerant of therapy to be considered eligible.

3. Participant must have tissue available for central pathology review and, must have pathologically/histologically confirmed high grade neuro endocrine defined as Ki-67 proliferative index of 20-100% ***or***, must have evidence of at least 10 mitotic figures per 10 high powered fields.
4. Comprehensive Genomic Profiling must be ordered per institutional guidelines prior to enrollment using archival tissue, fresh tissue, or blood sample as part of standard of care. If no archival tissue is available, then patient must have fresh biopsy prior to treatment administration if clinically indicated. If fresh biopsy is not required as part of standard of care, then a blood sample will be collected and used instead.
5. Have an ECOG Performance Status of 0 - 2. **Appendix H**
6. Have the following clinical laboratory values:
    - Leukocytes $\geq 3{,}000/mm^3$
    - Absolute neutrophil count $\geq 1{,}500/mm^3$
    - Hemoglobin ≥ 9 g/dL
    - Platelets $\geq 100{,}000/mm^3$
    - Total bilirubin $\leq$ institutional upper limit of normal (ULN) or ≤ 1.5 X institutional ULN (if the patient has liver metastases)
    - Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT])/alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) ≤ 2.5 X institutional ULN or (≤ 5 X institutional ULN if the patient has liver metastases)
    - Serum or plasma creatinine ≤ 1.5 X institutional ULN **or**
      Measured or calculated creatinine clearance by Cockcroft Gault Equation ≥ 50 mL/min for subjects with creatinine levels > 1.5 X ULN (refer to Appendix F).
7. Have measurable disease per RECIST 1.1 criteria present.
8. Participant must have a life expectancy of ≥ 12 weeks as determined clinically by the treating physician.
9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., barrier or hormonal plus barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
    - A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)
    - Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study
10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix A** for the ***ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA*** checklist.

3.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
2. Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency.
3. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
4. Known hypersensitivity to any of the components of Nal-IRI, other liposomal products, fluoropyrimidines, or leucovorin.
5. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study.
6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Pregnant or nursing female participants.
8. Unwilling or unable to follow protocol requirements.
9. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.

Refer to **Appendix B** for the ***ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA*** checklist.

3.3 Special Populations

The following special populations will be excluded:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

3.4 Inclusion of Women and Minorities

Men, women, and members of all races and ethnic groups are eligible for this study.

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 37 evaluable participants at multiple sites, including Roswell Park, are required. To account for non-evaluable patients, a total of 41 patients may be accrued.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified/recruited/screened from patients at the Gastrointestinal Center at Roswell Park and from GI clinics at participating sites, from multi-disciplinary conference discussion and from community referral.

6 MULTI-SITE RESEARCH

It is the responsibility of the principal Investigator to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to **Appendix C**: Instructions for Multiple Site Studies.

7 STUDY TIMELINES

A maximum of 37 evaluable participants at multiple sites, including Roswell Park, will be enrolled. Accrual is expected to take approximately 6 years.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- Objective Response Rate as determined by RECIST 1.1

8.2 Secondary Endpoints

To determine overall survival, progression-free survival, time to treatment failure, safety, clinical response and, quality of life (QOL)

- Overall Survival: Determined from time of first dosing of study treatment combination to time of death or initiation of a new therapy, whichever occurs first
- PFS: Determined from time of first dosing of study treatment combination to documented disease progression by RECIST 1.1.
- Time-to Treatment Failure (TTF): Defined as the time from study enrollment to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

- The proportion of patients achieving an objective response based on prior response to platinum etoposide
- Clinical benefit response (i.e., either achievement of pronounced and sustained [≥4 weeks contiguous] improvement in pain intensity, analgesic consumption, or performance status, or a combination of these, without any worsening in any of the other factors, or stability in pain intensity, analgesic consumption, and performance status with pronounced and sustained [≥4 weeks contiguous] weight gain)
- QOL: EORTC-QLQ-C30
- Safety

8.3 Exploratory Endpoint

- Comprehensive molecular profiling for mutations, immune-oncology biomarkers (Tumor Mutational Burden and Microsatellite Instability) and for select protein expression biomarkers (ERCC1, MGMT, PD-L1, TOP2A, TS) will be conducted on all pre-study tumor samples (tissue or liquid biopsy) and will be correlated with patient treatment outcome.

9 DESIGN

This is an open-label, single-arm, multi-center Phase 2 study of Nal-IRI + 5-FU/LV in patients with refractory advanced high-grade neuroendocrine cancer of GI, unknown or pancreatic origin.

10 TREATMENT

10.1 Dosing and Administration

Nal-IRI + 5-FU/LV: Day 1 and Day 15 of each 28-day cycle

- Nal-IRI 70 mg/m^2 (equivalent to 80 mg/m^2 irinotecan HCl trihydrate salt) IV infusion over 90 minutes (-10 min/+ 15 min) followed by,
- Leucovorin (l + d racemic form) 400 mg/m^2, IV over 30 min (± 5 minutes) then,
- 5-FU 2400 mg/m^2 IV over 46 hours (±60 minutes), on Days 1 and 15 of each 28-day cycle.

According to the Prescribing Information, the recommended starting dose of Nal-IRI in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. The dose may be increased to 70 mg/m^2 after the first cycle in the absence of drug-related toxic effects.

Investigators are advised to counsel subjects assigned to receive 5-FU about risk of photosensitivity and to take sun protection measures accordingly.

10.1.1 Premedication

A corticosteroid and an antiemetic should be administered 30 minutes prior to Nal-IRI infusion.

10.1.2 Administration of Nal-IRI

Prior to administration, the appropriate dose of Nal-IRI must be diluted in 5% Dextrose Injection (D5W) or 0.9% Sodium Chloride Injection to a final volume of 500 mL. Care should be taken not to use any diluents other than D5W or 0.9% sodium chloride.

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.

- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Discard unused portion.
- Nal-IRI will be administered on Days 1 and 15 of each 28-day cycle. Given the variability of infusion pumps, a window of -10 minutes and +15 minutes is permitted (i.e., infusion time is 90 minutes: -10 min/+15 min).

Treatment will continue until disease progression or intolerable toxic effects arise.

Reported adverse events (AEs) and potential risks are described in Section 13. Appropriate dose modifications are described in Section 10.2**.**

Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

10.2 Dose Modifications and Treatment Delays

Nal-IRI and 5-FU/LV have class specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs which can be clearly attributed to Nal-IRI or 5-FU/LV, or AEs without clear attribution to either study treatment, management of toxicity should include temporary hold or permanent discontinuation of both agents.

Table 3 Recommended Dose Modifications for Nal-IRI

Toxicity NCI CTCAE v5.0	Occurrence	Nal-IRI adjustment in participants receiving 70 mg/m^2	Participants homozygous for UGT1A1*28 without previous increase to 70 mg/m^2
Grade 3 or 4 adverse reactions	Withhold Nal-IRI.		
Diarrhea	Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1, resume Nal-IRI at:		
	First	50 mg/m^2	43 mg/m^2
	Second	43 mg/m^2	35 mg/m^2
	Third	Discontinue Nal-IRI	Discontinue Nal-IRI
Interstitial Lung Disease	First	Discontinue Nal-IRI	Discontinue Nal-IRI
Anaphylactic Reaction	First	Discontinue Nal-IRI	Discontinue Nal-IRI

10.2.1 Diarrhea

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. 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 below (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.

Therapy for Diarrhea

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. Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Diarrhea should be managed according to institutional guidelines. In general, for grade 3 or 4 diarrhea, Nal-IRI should be withheld. Loperamide should be initiated for late-onset diarrhea of any severity. Intravenous or subcutaneous atropine 0.25 to 1 mg should be administered (unless clinically contraindicated) for early-onset diarrhea of any severity.

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.

10.2.2 Neutropenia

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.

- Withhold Nal-IRI for absolute neutrophil count below 1500/mm^3 or neutropenic fever: monitor blood cell counts periodically during treatment.

10.2.3 Hypersensitivity

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.

- Nal-IRI can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue Nal-IRI in patients who experience a severe hypersensitivity reaction.

10.2.4 Interstitial Lung Disease (ILD)

Nal-IRI can cause severe and fatal ILD.

- Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation.
- Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

10.2.5 Colitis/ Ileus

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

10.2.6 Thromboembolism

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

10.2.7 Patients at Particular Risk

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.

10.2.8 Acute Infusion Associated Reactions

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 can tolerate further infusions without complications. See Section 10.3.3 for guidelines on the management of infusion reactions.

10.2.9 Other Potential Toxicities

Nal-IRI, the liposomal formulation of irinotecan is different from irinotecan in un-encapsulated 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.

10.2.10 Pregnancy

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.

10.3 General Concomitant Medication and Supportive Care

10.3.1 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

10.3.2 Care of Intravenous Site

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.

10.3.3 Management of Infusion Reactions

Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 5.0) definitions of an allergic reaction or anaphylaxis as defined below:

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

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

- Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hrs.
- Grade 3: 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)
- Grade 4: Life-threatening consequences; urgent intervention indicated

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):

- Grade 1: Not applicable
- Grade 2: Not applicable
- Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
- Grade 4: Life-threatening consequences; urgent intervention indicated

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

Grade 1

- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for Nal-IRI), at the discretion of the Investigator

Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV and acetaminophen 650 mg orally.
- Future infusions may be administered at a reduced rate (e.g., over 120 minutes for Nal-IRI), at the discretion of the Investigator

Grade 3

- Stop infusion and disconnect infusion tubing from patient

- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment will be permitted

Grade 4

- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV and other medications as medically necessary
- Consider hospital admission for observation
- No further treatment will be permitted

For patients who experience a second grade 1 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be pre-medicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally or as per institutional guidelines.

10.4 Prohibited Therapy

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 or 5-FU or leucovorin should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. No live attenuated vaccines should be given to participants. Refer to package inserts of 5-FU and leucovorin for any other drug interactions.

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

a) Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or antibodies

b) Potentially curative radiotherapy: palliative radiotherapy is permitted

c) Any other investigational therapy

10.5 Other Considerations

10.5.1 Contraception

Nal-IRI and 5-FU/LV may have adverse effects on a fetus in utero. Furthermore, it is not known if Nal-IRI and 5-FU/LV have transient adverse effects on the composition of sperm.

Female and male participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for six (6) months after the last dose of study drug by complying with one of the following:

1 Practice abstinence from heterosexual activity; **OR**

2 Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are:

- Single method (one of the following is acceptable):
  - Intrauterine device (IUD)
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - Cervical cap with spermicide (nulliparous women only)
  - Contraceptive sponge (nulliparous women only)
  - Male condom or female condom (cannot be used together)
  - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study participants of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to six (6) months after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

10.5.2 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with Nal-IRI and Nal-IRI, the subject will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Ipsen without delay and within 24 hours to the Sponsor and within 2 working days to Ipsen if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Ipsen and followed as described in Section 17.2.2.

10.6 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime, and participant withdraws from study.

11 PROCEDURES INVOLVED

11.1 Participant Registration:

Eligibility of each participant will be established prior to registration.

Informed consent MUST be completed prior to receiving any study related procedures.

11.2 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Appendix D**.

11.2.1 Baseline/ Screening Visit

The screening phase will begin once the patient signs the informed consent form. All procedures for screening and baseline are outlined in Appendix D: Schedule of Procedures and Observations. For further descriptions of the clinical and laboratory assessments required, please refer to Sections 11.3 and 11.4 respectively.

11.2.2 On-Study Visits

Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled into the study. The first dose (Cycle 1 Day 1) must be given within 7 days of enrollment. All study procedures and assessments are outlined in Sections 11.3, 11.4, and Appendix D.

During the treatment period, a window of ±2 days will apply to all visits, unless otherwise stated.

11.2.3 End of Treatment Visit

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 outlined in Appendix D.

11.2.4 Long-term Follow-up

After the End of Treatment visit, patients should continue to be followed for survival status once every 8 weeks (± 7 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 in Section 11.3.6below.

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

11.3 Clinical Procedures

11.3.1 Medical History and Pre-existing Conditions

A medical history will include all pertinent prior medical conditions, surgeries or other medical procedures, along with demographic information, as applicable.

11.3.2 Physical Examination and Vital Signs

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

11.3.3 Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be obtained at Screening and within 72 hours of enrollment by the Investigator or his/her designee via questioning of the patient about their functional capabilities (Appendix A).

11.3.4 Electrocardiogram (ECG)

A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall clinical interpretation. If the ECG is abnormal, clinical significance or non-significance should be indicated.

11.3.5 Adverse Event Assessment

The Investigator 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.

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. For detailed information on adverse event reporting, see Section 17. In addition, information on patient hospitalizations and/or hospital visits should also be collected, whether or not associated with an adverse event.

11.3.6 Disease Evaluation

Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [12], 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 for each lesion must be used throughout the study. Investigators should select target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

Tumor assessments should be completed until it has been determined that the patient has progressive disease (in accordance with RECIST v1.1).

For patients who do not have documented disease progression per RECIST v. 1.1 at the time of treatment termination, imaging studies should continue to be performed into the follow-up period every 8 weeks until radiological disease progression is documented.

11.3.7 EORTC-QLQ-C30

Health-related quality of life (HRQL) will be assessed by the EORTC-QLQ-C30. The EORTC-QLQ-C30 is a reliable and widely used 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 (Appendix E).

Patients will be required to complete the EORTC-QLQ-C30 at the time points outlined in the Schedule of Procedures and Observations (Appendix D). On days that the patient is to receive study drug, assessments should be completed prior to study drug administration.

11.4 Laboratory Procedures

Whole blood samples will be collected and assessed locally at baseline, Day 1 of every treatment cycle and at the End of Treatment follow-up visit.

Note: Blood and urine samples will be processed and analyzed in accordance with each participating sites' institutional guidelines and standard operating procedures.

11.4.1 Hematology

Complete blood count (CBC) with automated differentials: Must include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

11.4.2 Chemistry

Comprehensive metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap. In addition:

- Magnesium
- Phosphate

11.4.3 UGT1A1*28

A whole blood sample will be collected and assessed locally at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of Nal-IRI.

11.4.4 Urine or Serum Pregnancy Test

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 End of Treatment 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 24 consecutive months).

11.4.5 Comprehensive Genomic Profiling

Archival tissue (if available) or fresh tissue (if archival not available, and if clinically indicated to re-biopsy) or blood sample should be submitted for Comprehensive Genomic Profiling (using any

NGS laboratory per institutional guidelines) or data collection of prior results, as per standard of care, in order to meet inclusion criteria. Archival or fresh tissue, blood, or data collection of prior results must be obtained for genomic profiling at baseline and prior to treatment initiation.

If a site is utilizing a commercial vendor for NGS, they will fill the appropriate forms to conduct standard of care comprehensive genomic profiling and send the tumor biopsy samples or blood sample for comprehensive genomic profiling.

NETWORK SITES: Data collection of results of comprehensive genetic profiling conducted prior to enrollment, as part of standard of care, will meet baseline inclusion criteria for comprehensive genetic profiling.

For patients that have not had prior comprehensive genetic profiling performed prior to enrollment, tissue, archival or fresh, or a blood sample for profiling can be performed at a NGS Laboratory, per institutional guidelines of the participating sites as part of standard of care at baseline.

Blood sample collection for FoundationOne®, processing and shipping information at the two other timepoints, see the FoundationOne® Appendix I.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.4.6 Central Pathology Review

Patient eligibility must be confirmed by central pathology review of existing histology specimens. The preference is for primary diagnostic tumor, rather than post-treatment tumor tissue.

The following slides of neuroendocrine tumor of GI tract (or unknown primary) and the corresponding surgical pathology report are required for this review:

- Representative H&E
- Ki-67 stained slide
- Pathology Report

FOR EXTERNAL (NETWORK) SITES: The slides and report should be labeled with the Clinical Study number (I-64518), Subject's Study ID number and initials, and the Surgical Accession number. Network sites should use their own preferred shipping method to send the materials for Central Pathology review to the address below. Email CRSLabPathTeam@RoswellPark.org at time of submission with shipment information (e.g. courier tracking #) and slide return instructions.

Roswell Park Cancer Institute
c/o CSPO - Study I-64518
GBSB Room S-636
Elm and Carlton Streets
Buffalo, NY 14263
CRSLabPathTeam@RoswellPark.org
Ph: 716-845-1678

Fax: 716-845-3216

12 WITHDRAWAL OF SUBJECTS

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity: treatment related or unrelated
- Investigator judgment
- The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal
- Sponsor decision.

13 RISKS TO SUBJECTS

The most 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, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia (see package insert).

14 POTENTIAL BENEFITS TO SUBJECTS

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.

In addition, results from the NAPOLI-1 Phase 3 trial show statistically significant improvement of OS of the Nal-IRI + 5-FU/LV doublet in patients with metastatic pancreatic cancer previously treated with gemcitabine [15 16].

15 DATA AND SPECIMEN BANKING

Not Applicable: All tissue samples will be sent directly to the NGS lab that the institute chooses for analysis.

16 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [12]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria (refer to Appendix G for summary of RECIST 1.1 criteria).

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8weeks (± 1 week) following initial documentation of objective response.

16.1 Response Parameters

Clinical assessments including QOL forms using EORTC QLQ 30 will occur at baseline and monthly while on study.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF. However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

17.2.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 5.0.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.

- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.2.2 Reporting and Follow-Up of Pregnancy

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 six (6) months after the completion of the study medication must also be reported to the Sponsor.

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.

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.

17.3 Reporting Adverse Events:

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.

- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.4.1 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.7**for details on reporting Unanticipated Problems.

17.5 Investigator Reporting: Notifying the Study Sponsor

Investigators MUST report within 1 business day upon becoming aware, to Ipsen ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

FAX: 866-681-1063 **or**

Email to: drugsafety.USA@ipsen.com

17.6 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.7 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    a. The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.

b. The characteristics of the participant population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.4.

17.7.1 Reporting Unanticipated Problems:

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

The genomic profiling results will be sent to the requesting Investigator at each site. The study coordinator will be responsible for entering results into the study database.

18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19 STATISTICAL PLAN

This is an open-label, single-arm, multi-center Phase 2 study of Nal-IRI + 5-FU/LV in patients with refractory advanced high-grade neuroendocrine cancer of GI, unknown or pancreatic origin.

19.1 Sample Size Determination

A maximum of 37 participants evaluable for the primary outcome will be enrolled in this study. We expect to enroll approximately 6-7 patients per year; therefore accrual is expected to take 6 years. The budget will allow for including of 10-15% more patients in case some are unevaluable for primary endpoint.

The sample size calculations are based on the primary analysis, using the Simon two-stage design based on the minimax criterion to evaluate the following hypotheses: H_0: $\pi \leq \pi_0$ versus H_A: $\pi > \pi_0$. Historically, the objective response rate of this patient population is $\pi_0=0.15$. We expect the true response rate (π) of the proposed treatment to be $\pi=0.30$; as such, the study design ($n_1=18$ $n_2=19$) achieves 80% power at a significance level of $\alpha = 0.1$.

To account for patients that may be non-evaluable for response and are replaced, a total of 41 patients may be accrued.

19.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.3 Primary Analysis

The primary objective of this study is to evaluate the objective response rate (ORR) of nanoliposomal irinotecan with fluorouracil (5-FU) and leucovorin in advanced high-grade neuroendocrine cancer of GI, unknown or pancreatic origin. The primary outcome is objective response (based on best overall response (CR+PR), as defined by the RECIST 1.1 criteria, within 6 months of treatment initiation. Objective response will be treated as binary data and will be summarized using frequencies and relative frequencies; with the ORR estimated using an 80% confidence interval obtained using Jeffrey's prior method.

Historically, the ORR in this patient population is approximately 0.15. As such, a treatment with an ORR less than or equal to 0.15, it will not be considered promising, while a treatment with an ORR above 0.15 will be considered promising. Therefore, the primary analysis will utilize the Simon two-stage design (based on the minimax criterion) to test the following hypotheses:

H_0: π=0.15 versus H_A: π>0.15,

where π is the true response rate of the proposed treatment combination.

In stage 1, n_1=18 will be enrolled and response evaluated. If T_1=3 or fewer responses are observed, then the study will terminate and the treatment will not be considered promising; otherwise, an additional n_2=19 patients will be enrolled in stage 2. If T=8 or fewer of the total $n=n_1+n_2=37$ patients have a response the treatment will not be considered promising; otherwise the treatment will be considered promising for further study.

Subject replacement: Patients that drop-out of the study prior to evaluation of response due to clinical progression, toxicity, or other disease/treatment-related reasons will be treated as non-responses. Patients who do not complete a response assessment prior to study drop-out due to non-disease and non-treatment related reasons will be considered 'non-evaluable for the primary outcome' and will be replaced.

19.4 Secondary Analyses

The secondary objectives are to determine overall survival, progression-free survival, time to treatment failure, safety, clinical response and, quality of life (QOL).

Overall survival, progression-free survival, and time to treatment failure are treated as bivariate time-to-event data and will be summarized using standard Kaplan-Meier methods, where estimates of the median time will be obtained with 90% confidence intervals. The definition of the start- and end-dates for these variables is provided in Section 8.2.

Clinical benefit response (defined in Section 8.2) will be treated as binary data and summarized using frequencies and relative frequencies. The clinical benefit response rate will be estimated using a 90% confidence interval obtained by Jeffrey's prior method.

The quality of life (QOL) measures based on the EORTC-QLQ-C30 will be treated as quantitative data and summarized by time-point using the mean and standard deviation. The QOL scores at each follow-up time may be compared with base-line levels using the paired t-test or sign test.

19.5 Safety Analysis

Toxicities and adverse events will be summarized by attribution and grade using frequencies and relative frequencies. High grade (3+) toxicity and adverse event rates may be estimated using 90% confidence intervals obtained by Jeffrey's prior method. DSMB monitoring will also occur periodically to ensure safety of study subjects.

19.6 Interim Analysis

The primary efficacy analysis utilizes a Simon two-stage design based on the minimax criterion. In stage 1, n_1=18 will be enrolled and response evaluated. If T_1=3 or fewer responses are observed, then the study will terminate and the treatment will not be considered promising; otherwise, an additional n_2=19 patients will be enrolled in stage 2.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

All Roswell Park studies will be reviewed at the scheduled Early Phase Clinical Trial Committee meetings and the minutes are forwarded to the IRB for review.

The Roswell Park Data and Safety Monitoring Committee (DSMC) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) suspension of, or (d)termination of the study.

21 VULNERABLE POPULATIONS

Not Applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not Applicable.

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

All treatment will be conducted on an outpatient basis at the Gastrointestinal Center within Roswell Park and at the participating sites. Potential study participants will be identified and recruited from current GI Center patients and from community referral.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Not Applicable.

27 PRIOR APPROVALS

Not Applicable.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-8195.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor

(716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32 DRUGS OR DEVICES

32.1 Nanoliposomal Irinotecan

Nal-IRI (ONIVYDE®), in combination with fluorouracil and leucovorin, is approved by the FDA for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Nal-IRI- will be provided by the study sponsor at no cost to the participant.

32.1.1 Active Substance and Source

Nanoliposomal irinotecan is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl] ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL.

32.1.2 Drug Shipment

Nanoliposomal irinotecan will be provided by Ipsen and shipped to each participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.1.3 Preparation

Refer to package insert.

32.1.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility and, in accordance with the applicable regulatory requirements.

- Store Nal-IRI at 2ºC to 8ºC (36°F to 46°F).
- Do NOT freeze.
- Protect from light.

Drug storage temperature will be maintained and recorded, as applicable.

32.2 Fluorouracil and Leucovorin

Fluorouracil and Leucovorin costs will be covered by the participant or the participant's medical insurance provider as standard of care treatment.

33 REFERENCES

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34 APPENDICES/ SUPPLEMENTS

Appendix A Inclusion Criteria Checklist

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: Phase 2 Single-Arm Study of Nanoliposomal Irinotecan with Fluorouracil and Leucovorin in Refractory Advanced High-Grade Neuroendocrine Cancer of GI, Unknown, or Pancreatic Origin

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years.	
☐	☐	☐	2. Participant must have a locally advanced and unresectable or metastatic gastroenteropancreatic neuroendocrine carcinoma of the gastrointestinal (GI) tract, pancreas, or of other known or unknown primary site where 5FU based therapy would be considered reasonable by the treating MD, lung primary is excluded. Patients may have either progressed on therapy or within 6 months of completing therapy or be intolerant of therapy to be considered eligible.	
☐	☐	☐	3. Participant must have tissue available for central pathology review and, must have pathologically/histologically confirmed high grade neuro endocrine defined as Ki-67 proliferative index of 20-100% or, must have evidence of at least 10 mitotic figures per 10 high powered fields.	
☐	☐	☐	4. Comprehensive Genomic Profiling must be ordered per institutional guidelines prior to enrollment using archival tissue, fresh tissue, or blood sample as part of standard of care. If no archival tissue is available, then patient must have fresh biopsy prior to treatment administration if clinically indicated. If fresh biopsy is not required as part of standard of care, then a blood sample will be collected and used instead.	
☐	☐	☐	5. Have an ECOG Performance Status of 0 - 2. Refer to Appendix H.	
☐	☐	☐	6. Have the following clinical laboratory values: • Leukocytes ≥ 3,000/mm^3 • Absolute neutrophil count ≥ 1,500/mm^3 • Hemoglobin ≥ 9 g/dL • Platelets ≥ 100,000/mm3 • Total bilirubin ≤ institutional upper limit of normal (ULN) or ≤ 1.5 X institutional ULN (if the patient has liver metastases) • Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT])/alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) ≤ 2.5 X institutional ULN or (≤ 5 X institutional ULN if the patient has liver metastases) • Serum or plasma creatinine ≤ 1.5 X institutional ULN **OR,**	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
			Calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 X ULN using Cockcroft-Gault equation (refer to Appendix F).	
☐	☐	☐	7. Have measurable disease per RECIST 1.1 criteria present.	
☐	☐	☐	8. Participant must have a life expectancy of ≥ 12 weeks as determined clinically by the treating physician.	
☐	☐	☐	9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., barrier or hormonal plus barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. • A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months) • Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study	
☐	☐	☐	10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix B Exclusion Criteria Checklist

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: Phase 2 Single-Arm Study of Nanoliposomal Irinotecan with Fluorouracil and Leucovorin in Refractory Advanced High-Grade Neuroendocrine Cancer of GI, Unknown, or Pancreatic Origin

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.	
☐	☐	☐	2. Participants with known dihydropyrimidine dehydrogenase (DPD) deficiency.	
☐	☐	☐	3. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).	
☐	☐	☐	4. Known hypersensitivity to any of the components of Nal-IRI, other liposomal products, fluoropyrimidines, or leucovorin.	
☐	☐	☐	5. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study.	
☐	☐	☐	6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	7. Pregnant or nursing female participants.	
☐	☐	☐	8. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	9. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix C Instructions for Multi-Site Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Comprehensive Cancer Center
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org
Elm and Carlton Streets
Buffalo, New York 14263
Telephone:
Monday - Friday; 8:00 AM to 4:30 PM EST
716-845-8084
After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

Roswell Park does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and email it to the Roswell Park Network Coordinator at CRSNetworkCoordinators@RoswellPark.org.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific; they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** “transfer”, “borrow” or “replace” supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network Monitor within 1 business day of being made aware of the SAE to SafetyEventReporting@roswellpark.org. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- MedWatch 3500A

A complete follow-up report must be sent to the Roswell Park Network QA Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.7**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and emailing it to the Roswell Park Network QA Coordinator.

Appendix D Schedule of Procedures and Observations

Evaluation	Baseline/ Screening	Treatment Phase			Follow-Up Phase	
	-28 days	Every Treatment Cycle[3]		Every 8 weeks after 1st dose of study drug treatment	End of Treatment Follow-up Visit[4]	Long Term Follow-Up[5]
		Day 1	Day 15			
Medical History	X[1]					
Pre-Existing Conditions	X[1]					
Physical Examination[6], including vital signs[7]	X[2]	X	X		X	
Comprehensive Genomic Profiling[11]	X					
Foundation liquid testing[22]				X (one time see Appendix I)		X[22]
Central Pathology Review[23]	X					
ECOG Performance Status	X[2, 12]	X			X	
EORTC-QLQ-C30	X[2]	X				
12-lead electrocardiogram (ECG)[8]	X[1, 13]				X	
Hematology[9]	X[2, 14]	X	X		X	
Chemistry[10]	X[2, 14]	X	X		X	
UGT1A1*28 testing	X[2, 15]					
Pregnancy Test (Urine or Serum)	X[2]	X			X	
Disease Assessment (CT/ MRI: chest, abdomen, pelvis)[17]	X[1a]			X[21]	X	
Study Drugs: Nal-IRI + 5-FU/LV[18]		X	X			
Concomitant Medications	X[16]	X	X	X	X	
Adverse Events	X[19]	X	X	X	X	
Survival Status[20]						X

1	Procedures to be completed within 28 days prior to 1st dose of study drug. 1a. CT/MRI scan (of chest, abdomen, and pelvis) should be completed within 28 days or at the Sponsor's (Principal Investigator) discretion prior to 1st dose of study drug.
2	Procedures to be completed within 7 days prior to 1st dose of study drug
3	All cycles are 28-day cycles, unless modified due to toxicity.
4	The End of Treatment (EOT) Follow-Up visit should occur 30 days (± 14 days) after last dose of study drug.
5	Long-tern follow-up: Follow-up contact should be made every 8 weeks (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.
6	Standard of care physical exam may be used if performed within 2 weeks prior to signed consent.
7	Vital signs will include height (at baseline/screening only), weight, resting blood pressure, pulse, respiratory rate and temperature.
8	To be repeated as clinically indicated during the study.
9	Hematology (CBC) with automated differentials: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated
10	Chemistry (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap. ***In addition***: magnesium, phosphate.
11	Comprehensive Genomic Profiling results are required for eligibility. Sites should use their preferred clinical lab for standard of care NGS testing on tissue or blood. Note: Prior genomic profiling results from any clinical laboratory, at any time prior to enrollment, can be used to meet this baseline criteria.
12	ECOG to be performed at Screening and within 72 hours of enrollment.
13	Two independent readings at least 1 minute apart.
14	After screening, samples should be obtained within 2 days from scheduled date of collection.
15	Result not required prior to enrollment in the study or prior to receiving the initial dose of Nal-IRI.
16	Medications ongoing, or discontinued, within 1 week prior to first dose of study drug.
17	Disease evaluation according to RECIST v. 1.1 (see Section 16).
18	Administered on Day 1 and Day 15 of each 28-day Cycle. Refer to Section 10.1for dosing and administration. Study drug administration should occur ±2 days from scheduled date of administration.
19	Adverse events that occur during baseline/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 baseline/screening.
20	Data collected should include overall survival status as well as subsequent treatment information.
21	Disease evaluations should be done every 8 weeks (± 7 days) after 1st dose.
22	Two 8.5 mL tubes of blood will be collected from each patient at two different time points: during the first follow-up scan (around 8 weeks) and at disease progression. Please see Appendix I at all sites.
23	High grade neuroendocrine tumor must be confirmed by Central Pathology Review at Roswell Park. Refer to Section 11.4.6 for specimen submission instructions.

Appendix E EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix F Calculation for Serum or plasma Creatinine Clearance

Cockcroft-Gault Equation:

Serum or Plasma Creatinine Clearance =

$$\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

Serum or Plasma Creatinine Clearance =

$$\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

Appendix G RECIST 1.1 Summary

Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. RECIST 1.1 will be used to assess objective tumor response.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Complete Response (CR): Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as references 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 at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither a sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

Non-Target Lesions

All other small lesions (longest diameter < 10 mm or lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses / abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-Complete Response/Non-Progressive Disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.

Progressive Disease: Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time.

Evaluation of Response

Time point response assessments will be performed every 8 weeks. To determine time point response, refer to **Table 4** and **Table 5** below.

Table 4 Time Point Response Criteria: target (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 5 Time Point Response Criteria: non-target disease only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1 Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until disease progression/recurrence, taking into account any requirement for confirmation. In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

- Residual Disease: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.
- Symptomatic Deterioration: Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment include, but is not limited to, symptoms such as:

- Weight loss of > 10% of body weight.
- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of > 1 level on ECOG scale.

Confirmation Measurement

A confirmatory assessment is required no less than 6 weeks after a PR or CR is deemed.

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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 is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Appendix H ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix I FoundationOne® Liquid testing (for all sites)

Background and Significance:
Over the past few years, circulating tumor DNA (ctDNA) has emerged as an important diagnostic and predictive tool in different solid tumors. A recent study performed in non-small cell lung cancer showed that a comprehensive ctDNA analysis identified biomarkers more rapidly and completely than tissue-based genotyping. Another study in melanoma patients showed that ctDNA levels correlate with treatment response and predict disease relapse before radiologic progression. A pilot study performed in 10 pancreatic NET patients (including 1 high grade) detected tumor specific mutations and copy number variations in the ctDNA, however, there is very limited data on the molecular concordance between tissue and ctDNA in high-grade GEP-NETs. The long-term goal of our project is to identify if ctDNA can be used as an alternative to tissue-based genotyping in high-grade GEP-NETs. Besides we also aim to identify if ctDNA level can predict response to treatment in this population. Finally, using ctDNA, we want to assess if there is a genomic evolution of high-grade NETS during treatment.

Methods: Patient samples from the proposed non-randomized, open-label, single-arm, Phase 2 study evaluating the efficacy of nanoliposomal irinotecan with fluorouracil and folinic acid in refractory advanced high-grade neuroendocrine cancer of GI, unknown or pancreatic origin (NCT03736720) will be used. Two 8.5 mL tubes provided by Foundation Medicine in their standard liquid biopsy kit and a custom requisition/manifest form with an FMI study ID on it will be provided to ensure each sample is processed as part of the clinical trial.
For External Sites: For the research on treatment and follow-up samples, please obtain the FoundationOne® kit directly from FoundationOne® for use for this study. Please use the special customized study requisition form when submitting the research FoundationOne® samples.
Two 8.5 mL tubes of blood will be collected from each patient at two different time points: during the first follow up scan (around 8 weeks) and at disease progression. (If a patient shows progression at 8 weeks or prior, only one sample will be collected). Collected blood will be sent for FoundationOne® Liquid assay which uses a hybrid-capture, next-generation sequencing test method combined with computational algorithms that enable accurate variant calls by discriminating sequencing artifacts from bona fide mutations. The liquid assay identifies base substitutions, indels, CNAs, and rearrangements in 70 commonly altered oncogenes. ctDNA will be measured by quantification of Mutant Allele Fraction (MAF). To compare MAF pre and post therapy, a paired t-test will be used. A multivariate Cox proportional hazards regression analysis will be performed to correlate changes in MAF with progression-free survival and overall survival. All tests are two-sided and will be performed at a nominal significance level of 0.05.

Please see FoundationOne® liquid specimen instructions on the following page.

Shipping address:
Specimens will be sent to the address below:

Attn: Prospective Clinical Trial Specimen
Foundation Medicine
150 Second Street
Cambridge, MA 02141

Specimen Instructions

Peripheral Whole Blood

FOUNDATIONONE®LIQUID

Use only tubes provided inside the FoundationOne®Liquid Specimen Collection and Shipping Kit. Other tubes will not be accepted.

Instructions For Use

Accurate analysis of cell-free DNA requires proper collection technique and handling of the sample. Failure to adhere to these instructions can compromise results by diluting cell-free DNA with DNA from white blood cell lysis.

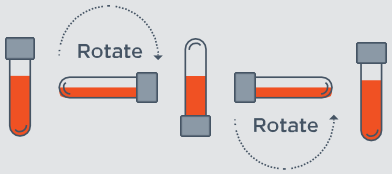
☐ 1 Check special tubes provided in FoundationOne Liquid kits to confirm liquid is clear and without cloudiness or crystals.

☐ 2 Label tubes with date of collection and two patient identifiers.

☐ 3 Collect two tubes of whole blood (8.5mL per tube).

- Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient.
- Collect specimen by venipuncture according to CLSI H3-A6.[1]
- Fill tubes completely (8.5mL per tube).

☐ 4 Remove the tube from adapter and immediately **mix by gentle inversion 8 to 10 times.** Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180°, and back per the figure below.



☐ 5 Place specimen, completed requisition form (TRF) (remember to include patient's diagnosis), insurance information, available reports, and accompanying documents into the FoundationOne Liquid Specimen Collection and Shipping Kit (copies of pathology reports and/or other clinical documentation).

- Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).

☐ 6 Preferably on the same day of collection, ship via FedEx priority overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples.

Temperature is important. Keep at room temperature (43-99° F, 6-37° C).

DO NOT FREEZE.

Shipping Instructions

1. Place the samples, FoundationOne Liquid requisition form, insurance information, and any other attachments into the FoundationOne Liquid Specimen Collection and Shipping Kit.
2. Place the specimen kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. tubes) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second St
Cambridge, MA 02141
Phone: 888

ReferenceClinical and Laboratory Standards Institute. H3-A6, Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard-sixth edition.

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