Phase II Trial of FOLFIRINOX in Metastatic High Grade Gastroenteropancreatic Neuroendocrine Carcinomas

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Phase II trial of FOLFIRINOX in metastatic high grade gastroenteropancreatic neuroendocrine carcinomas

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SYNOPSIS

Title of Study: A phase II study FOLFIRINOX in metastatic high-grade gastroenteropancreatic neuroendocrine carcinomas

Investigators: Dr. Jonathan Strosberg. Statistician: Michael Schell, PhD

Study Center(s): Moffitt Cancer Center

Concept and Rationale:

The number of patients with gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) is increasing worldwide. Currently they account for as much as 10% to 20% of digestive neuroendocrine neoplasms and behave aggressively. These tumors are mainly localized in the esophagus, pancreas, ampulla of Vater and large bowel. Unfortunately, more than 50% of patients have metastatic disease at the time of diagnosis. Review of the NECs patients with stage IV disease in the SEER database showed an overall survival of only 5 months (95% CI, 4.7-5.4 months) and a 2-year survival rate of 11%. Despite the fact that the GI tract is the most common site for extrapulmonary NEC, treatment strategies for GI-NECs are often extrapolated from the treatment paradigm for small cell lung cancer (SCLC) and advocate the use of platinum-based chemotherapy combined with etoposide. This combination has resulted in high response rates (range, 42%-67%) and median survivals of 15 to 19 months, but has not been validated in large clinical trials. Much less consensus exists about the best strategy for refractory disease. 5-FU, capecitabine, temozolomide, oxaliplatin, irinotecan and taxanes have shown activity in NECs. Therefore, FOLFIRINOX, a regimen containing 5FU, irinotecan and a platinum (oxaliplatin) could have activity in GEP-NECs and should be considered for this disease. In fact, Zhu *et al* showed that FOLFIRINOX led to substantial tumor responses in 2 patients with high-grade metastatic pancreatic neuroendocrine carcinoma. In this case series, one patient with metastatic pancreatic NEC achieved near-CR with first-line modified FOLRIRINOX. Another patient that received modified FOLFIRINOX as fourth-line treatment achieved partial response and had disease control for more than 7 months. Based on these data and rationale, we believe that the use of FOLFIRINOX should be prospectively study in patients with high grade GEP-NECs.

Primary Objective(s): evaluate efficacy of FOLFIRINOX in patients with gastroenteropancreatic high-grade neuroendocrine carcinomas.

Secondary Objective(s): evaluate the safety profile on FOLFIRINOX on this population

Primary Endpoint(s): objective radiographic response rate (ORR), as defined by RECIST v1.1.

Secondary Endpoint(s):

1. progression free survival
2. overall survival
3. duration of response
4. time to treatment failure
5. adverse effects

Study Design: Single arm phase II study**.** Patients will receive modified FOLFIRINOX which consists of 85 mg/m^2 of oxaliplatin, 400 mg/m^2 of leucovorin over the first 2 hours, 165 mg/m^2 of irinotecan in a 90-minute infusion on day 1, followed by a continuous, 46-hour infusion of 5-FU at a dosage of 2,400 mg/m^2. A cycle will be repeated every 14 days. G-CSF prophylaxis will be allowed after each cycle. Patients will undergo re-staging studies every 8 weeks. Patients will receive up to 12 cycles during the study. Additional cycles will be determined per investigators' discretion.

Number of Patients: 28 evaluable patients split evenly between 1st line cytotoxic treatment and ≥2nd line treatment

Main Criteria for Inclusion/Exclusion:

Inclusion criteria:

- Cytologically or histologically confirmed high grade neuroendocrine carcinoma of gastrointestinal tract (including pancreas). Patients with unknown origin for the neuroendocrine carcinoma in which a gastrointestinal origin is suspected (per pathologist or investigator's discretion) will be eligible for the study
- Tumors must have a Ki-67 index greater than 20% and/or >20 mitotic figures/10 high-power fields.
- Patient must have metastatic disease.
- Patients must measurable disease, as defined by RECIST 1.1 criteria.
- Any line of treatment (first line versus beyond first line)
- Age ≥18 years
- Eastern Cooperative Oncology Group performance status of 0,1 or 2 (see appendix A)
- Patients must have adequate hepatic, renal and hematological functions. See protocol for details.
- Ability to understand and willingness to sign a written informed consent

document Main Exclusion criteria:

- Prior treatment with 5-FU, leucovorin, irinotecan and/or oxaliplatin
- Patients with a secondary primary cancer (excluding skin non-melanomatous) within 1 year of the diagnosis of neuroendocrine carcinoma
- Patients with childbearing potential who are not willing to use adequate contraception precautions during the study and for 3 months after stopping study chemotherapy

Intervention and Mode of Delivery: FOLFIRINOX will be administered **i**ntravenously every 2 weeks

Duration of Intervention and Evaluation: up to 12 cycles, after that patients will be allowed to enter a maintenance phase per investigator's discretion.

Sample Size Justification:

For our primary endpoint, based on historical data and taking into account a mix population of first line versus beyond first line treatment patient population, we estimate a response rate with either cisplatin or carboplatin with etoposide is 30% (H0:p=0.30) and we hypothesize that FOLFIRINOX will have a response rate of 50% (H1:p=0.50). Using an alpha error of 0.10 and a beta error (1 minus power) of 0.20, based on the Simon two-stage design, we estimate that we will need to accrue 28 evaluable patients. Patients who consent but are unable to begin treatment will be replaced. For the stage 1 part of this trial, 12 patients will be enrolled. If 3 or fewer patients achieve ORR, the trial will be stopped. If 4 or more patients achieve ORR, another 16 patients will be enrolled. By the end of the trial, if 11 or less patients achieve ORRs, this trial will be considered a failure and no further investigation is warranted. We estimate that accrual will take 2-3 years. Primary endpoint will be evaluated after stage 1 and after stage 2.

APPENDICES

1. BACKGROUND

1.1 Overview of neuroendocrine tumors and classification

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating in various locations but as most commonly seen in the gastroenteropancreatic tract. [1] The disease management poses a significant challenge because of the heterogeneous clinical presentations and varying degree of aggressiveness. Although the majority of patients has slow grown tumors, some patients have more aggressive disease. [2]

Tumor differentiation and grade are important prognostic and predictive factors. While often used interchangeably, differentiation and grade are not identical terms: differentiation refers to the resemblance between the morphology of the tumor and tissue of origin, whereas tumor grade is measured through markers of cell proliferation such as mitotic rate and Ki-67 index. Well-differentiated tumors consist of small monomorphic cells arranged in islets or trabeculae with a 'salt and pepper' chromatin pattern. In contrast, poorly differentiated tumors are often characterized as sheets of pleomorphic cells with extensive necrosis. Tumor grades are defined numerically with low-grade tumors having a mitotic rate of 0-1 per 10 high powered fields (HPF) or ki-67 index of 0-2%, intermediate-grade tumors having mitotic rate of 2-20 or ki-67 of 3-20%, and high-grade tumors having mitotic rate or Ki-67 index >20.[3] Guidelines require that tumor grade be measured in the most mitotically active areas of the biopsy specimen. In the 2010 WHO classification, well-differentiated tumors are subdivided as either low or intermediate-grade tumors (NETs) whereas poorly differentiated tumors are considered equivalent to high-grade are named as neuroendocrine carcinomas (NEC). However, there are several pitfalls in this classification. One is that it negates the possibility of a well-differentiated high-grade tumor, an entity which clearly exists (poorly differentiated low-grade tumors are less common).[4] Another flaw of a numerical grading classification is that there can be significant heterogeneity in mitotic activity between different tumors within the same patient and even within a particular tumor.[5] Despite these concerns, current grading systems have proven to be of prognostic value.

NEC encompasses 2 histologic entities: small cell carcinoma and large cell NEC. [6] Awareness of the latter is essential, because large cell NECs can be difficult to distinguish from poorly differentiated adenocarcinomas, and the need for routine immunostaining for synaptophysin and CgA in such tumors has been suggested. Interestingly, up to 40% of NECs contain elements of non-neuroendocrine histology, which varies depending on the primary location. [7] By definition, the neuroendocrine component in a mixed tumor has to exceed 30% to be classified as an NEC; otherwise, it is classified as an adenocarcinoma with neuroendocrine differentiation. [6] Tumors are classified as mixed adenoneuroendocrine carcinoma (MANEC) if the gland-forming elements exceed 30%.[6] The prognostic or predictive significance of a non-NEC component remains uncertain, [8] [9] and, currently, treatments for NEC and MANEC are similar.

The number of patients with gastroenteropancreatic NECs is increasing [10] [11] and currently they account for as much as 10% to 20% of digestive neuroendocrine neoplasms [12]. These tumors are mainly localized in the esophagus, pancreas, ampulla of Vater, and large bowel. [13]. In 2014 Sorbye and colleagues demonstrated that between 1973 and 2012, a total of 2546 patients were diagnosed with high-grade gastroenteropancreatic NECs in the US based on SEER data. [14] This study also showed that 57% of patients are diagnosed with metastatic disease. In patients that were diagnosed with localized disease, the median survival was 38 months (95% confidence interval [CI], 31-45 months). Unfortunately, patients that were diagnosed with metastatic disease had a median overall survival of only 5 months (95% CI, 4.7-5.4 months). Additionally, the 2-year survival rate was 11%, and the 3-year survival rate was 8% for patients with stage IV disease at the time of diagnosis. [14]

1.2 Treatment of neuroendocrine carcinomas

Despite the fact that gastroenteropancreatic tract is the most common site for extrapulmonary NEC, accounting for 35% to 55% of all NECs outside the lung, [15] [16] treatment strategies for extrapulmonary NEC are often extrapolated from the treatment paradigm for small cell lung cancer (SCLC). [17] [18] Therefore, guidelines for the treatment of advanced GEP-NEC advocate the use of platinum-based chemotherapy combined with etoposide, [15] [19]. Treatment with cisplatin/etoposide has resulted in high response rates (range, 42%-67%) and a median survival of 15 to 19 months. [20] [21] A 3-drug regimen (carboplatin, etoposide, and paclitaxel) produced a higher response rate, but median survival did not seem to improve, and grades 3 or 4 toxicity were frequent. [22] In a retrospective study, 252 patients with advanced GEP-NEC received cisplatin/etoposide or carboplatin/etoposide.[10] In that study,

the response rate was 31%, the median progression-free survival (PFS) was 4 months, and the median survival was 11 months. No differences in outcome were observed when comparing cisplatin versus carboplatin. The variables performance status, Ki-67 index, platelet count, lactate dehydrogenase, and primary tumor location were prognostic for response and survival. Multivariate analyses identified performance status as the strongest prognostic factor. A Ki-67 threshold of 55% was predictive for response to first-line platinum-based chemotherapy. Tumors with a Ki-67 index <55% were much less responsive to platinum-based chemotherapy (response rate, 15% vs 42%), but the patients with those tumors had a significantly longer survival (median OS, 14 months vs 10 months) compared with the patients who had higher Ki-67 levels.

However, there are many clinical differences between SCLC and extrapulmonary NEC and therefore some have questioned the rationale for using SCLC treatments in GEP-NEC. For instance, SCLC is more strongly associated with smoking, brain metastases are more common, and responses to platinum-based chemotherapy are generally better. [17] [18] [23] Naturally, alternative treatments have been investigated and several recent retrospective, multicenter studies have been published using novel treatment strategies for GEP-NEC.[24] [10] [25]

For example, Sorbye reviewed the outcomes of 258 patients with poorly differentiated GEP-NEC. In his cohort, irinotecan/etoposide was used as first-line treatment in 62% of patients.[14] A multivariate analysis identified a primary hepatobiliary and pancreatic tumors and a performance status of 2 as unfavorable prognostic factors for survival. Although the response rate and survival were numerically better for irinotecan/etoposide treatment compared with cisplatin/etoposide treatment, the treatment schedule was not an independent factor for survival

Furthermore, there is no consensus about the best second-line therapy for this subgroup of patients. Fluorouracil (5-FU), capecitabine, temozolomide, irinotecan, oxaliplatin and taxanes have been shown to have activity in GEP-NECs and/or small cell tumors. Malka *et al* [26] published a retrospective analysis of 20 patients with high grade neuroendocrine carcinomas that received FOLFOX as salvage treatment after failing cisplatin based chemotherapy. This analysis reported that 29% of patients had a partial response to treatment. Another 35% had stable disease. Interestingly, there was no correlation between response to cisplatin as first line and response to FOLFOX. Recently, Zhu *et al* [27] showed that FOLFIRINOX led to substantial tumor responses in 2 patients with high-grade metastatic pancreatic neuroendocrine carcinomas. In this case report, one patient with metastatic pancreatic NEC achieved near CR with modified FOLRIRINOX as first line. The second patient received modified FOLFIRINOX as fourth line treatment achieved partial response and disease control for more than 7 months. Based on these reports, we hypothesize that regimen containing 5FU, irinotecan and a platinum (FOLFIRINOX) could have a have a higher activity in GEP-NEC. Therefore, we propose to prospectively study FOLFIRINOX in this setting.

2. STUDY OBJECTIVES

Assess the efficacy of FOLFIRINOX in patient with gastroenteropancreatic high grade neuroendocrine carcinomas.

2.1 Primary endpoint:

Objective radiographic response (ORR), as defined by RECIST v1.1

2.2 Secondary endpoints:

- Progression free survival
- Overall survival
- Duration of response
- Time to treatment failure
- Adverse effects (AEs)

3. STUDY DESIGN

This is a prospective phase II open-label trial, stratifying gastroenteropancreatic high grade neuroendocrine carcinomas patients equally into two cohorts (first-line versus beyond first-line).

4. PATIENT SELECTION

4.1 Eligibility Criteria

4.1.1 Patients must have histologically or cytologically confirmed neuroendocrine carcinoma of the GI tract. Patients with unknown origin for the neuroendocrine carcinoma in which a gastroenteropancreatic origin is suspected (per pathologist or investigator discretion) will be eligible for the study.

4.1.2 Tumors must have a Ki-67 index greater than 20% and/or >20 mitotic figures/10 high-power fields.

4.1.3 Patients must have metastatic disease.

4.1.4 Patients must measurable disease, as defined by RECIST 1.1 criteria

4.1.5 Any line of treatment (first line versus beyond first line)

4.1.6 Age $\geq$18 years.

4.1.6 Life expectancy of greater than 12 weeks.

4.1.7 ECOG performance status of 0, 1 or 2 (see Appendix A).

4.1.8 Patients must have adequate organ and marrow function as defined below:

X	absolute neutrophil count	$\geq$1,500/mm^3
X	platelets	$\geq$100,000/mm^3
X	total bilirubin	$\leq$1.5 X institutional upper limit of normal
X	AST(SGOT)/ALT(SGPT)	$\leq$3.0 X institutional upper limit of normal
X	creatinine	within normal institutional limits
	OR	
X	creatinine clearance	$\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

4.1.9 Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Patients who have had chemotherapy or radiotherapy within 3 weeks prior to entering the study.

4.2.2 Patients may not be receiving any other investigational agents.

4.2.3 Patients with untreated brain or meningeal metastases

4.2.4 Prior treatment with 5-fluorouracil, irinotecan or oxaliplatin

4.2.5 Patients with pre-treatment peripheral neuropathy greater than grade 1 per the CTCAE, version 4.0 will be excluded.

4.2.6 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.

4.2.7 Patients with a secondary primary cancer (excluding baso/squamous cell carcinoma of skin) within 1 year will be excluded.

4.2.8 Active viral hepatitis or autoimmune hepatitis. The work-up to confirm active hepatitis or autoimmune hepatitis will only be done if clinical suspicion based on investigator discretion"

4.2.9 Patients with childbearing potential who are not willing to use adequate contraception precautions during the study and for 3 months after stopping study chemotherapy. *

*The effects of *FOLFIRINOX* on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of childbearing potential (and men) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Female patients of childbearing age will be required to have a negative pregnancy test within a week prior to consenting for study.

All women are considered of childbearing potential, unless they meet at least one of the following criteria:

a) Females who are menopausal, defined as follows: i) Females who are younger than 55 years old will be considered menopausal if they satisfy all the following three requirements during screening: 1) they are in amenorrhea, defined as absence of menstruation for the previous 12 months; 2) they have a negative urine pregnancy test; and 3) they have a serum FSH level within the laboratory reference range for postmenopausal females; ii) Females who are older than 55 years old: they will be considered menopausal if they are in amenorrhea, defined as absence of menstruation for the previous 12 months before screening.

b) Females who have a documented hysterectomy and/or bilateral oophorectomy and/or tubal ligations.

All men are considered of childbearing potential, unless they meet at least one of the following criteria:

a) Males who have a documented vasectomy more than 6 months prior to the administration of the first study treatment.

b) Female partner/partners who are menopausal (as previously defined) and/or who have a documented hysterectomy and/or bilateral oophorectomy and/or tubal ligations.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5. ENROLLEMENT PROCEDURES

- Obtain signed written informed consent
- Confirm eligibility as defined in the Section 4. "Patient Selection".
- Subjects must begin the protocol treatment plan within 14 days of protocol initiation

6. TREATMENT PLAN

6.1 FOLFIRINOX Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 8. Appropriate dose modifications for each of the components of FOLFIRINOX are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The FOLFIRINOX regimen consists of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intra-venous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 165 mg per square meter, given

as a 90-minute intravenous infusion through a Y-connector. This treatment is immediately followed by a continuous intravenous infusion of 2400 mg per square meter of 5-FU over a 46-hour period every 2 weeks. No 5FU intravenous bolus will be given in the attempt to minimize toxicity without compromise efficacy. [28] [29]. Leucovorin will be kept as part of the regimen despite the lack of 5FU bolus.

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of irinotecan and fluorouracil with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator will be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. See Appendix C for list of potential interactions.

The use of G-CSF will not be mandatory as primary prophylaxis, but will be allowed at investigators' discretion. If febrile neutropenia occurs, than the use of G-CSF will be mandatory after each following cycle of treatment.

6.3 Duration of Therapy

It is recommended that patients remain on all 3 cytotoxic drugs for up to 12 cycles, unless dose modifications are required. Transition to a maintenance regimen in which irinotecan or oxaliplatin (or both drugs) are omitted is permitted at the discretion of the treating physician. Treatment may continue until one of the following criteria applies:

- X Disease progression,
- X Intercurrent illness that prevents further administration of treatment,
- X Unacceptable adverse event(s),
- X Patient decides to withdraw from the study,
- X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- X Initiation of other anticancer therapy.

6.4 Duration of Follow-Up

Patients who discontinue chemotherapy prior to progression will continue to undergo scans every 8 weeks in order to evaluate for progression-free survival. Patients who discontinue treatment will continue to be monitored for overall survival via visits or phone calls at roughly 3 month intervals unless they specifically decline such follow-up.

6.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 6.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form that will be submitted to our institution IRB.

7. DOSING DELAYS/DOSE MODIFICATIONS

Dosage adjustment guidelines for toxicities

All dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0).

Once a dose is decreased, re-escalation is not permitted. Patients will be taken off study if they develop the same grade 4 toxicity despite a first dose reduction. The dose of leucovorin is not modified for toxicity.

7.1 Hematologic toxicity

Do not retreat until the granulocyte count is ≥ 1.5 x 10^9/L and the platelet count is ≥ 75 x 10^9/L.

Blood counts at Day 1	**Delay of cycle**	**Dose reduction**		
		Irinotecan	**Oxaliplatin**	**Fluorouracil**
Granulocytes < 1.5 x 10^9/L	Hold treatment until granulocytes ≥ 1.5 x 10^9/L (one or two weeks if necessary). In case of non-recovery after 2 weeks delay, stop treatment*	1st occurrence: reduction of dose to 150 mg/m^2 2nd occurrence: maintain the dose at 150 mg/m^2 3rd occurrence: treatment discontinuation	1st occurrence: no reduction of dose 2nd occurrence: reduce the dose to 60 mg/m^2 3rd occurrence: treatment discontinuation	N/A
Platelets < 75 x 10^9/L	Hold the treatment until recovery (platelets ≥75 x 10^9/L). In case of non-recovery after 2 weeks delay, stop treatment	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose to 150 mg/m^2 3rd occurrence: treatment discontinuation	1st occurrence: reduce the dose to 60 mg/m^2 2nd occurrence: maintenance of the reduced dose 3rd occurrence: treatment discontinuation	1st occurrence: the continuous infusion to 75% of the original doses

7.1b. According to the low nadir blood counts or in case of infection

ADVERSE EVENTS	**REDUCTION OF DOSE FOR SUBSEQUENT CYCLES**
Febrile neutropenia **Grade 4 neutropenia during more than 7 days** **Infection with concomitant grade 3-4 neutropenia**	1st occurrence: reduce the dose of irinotecan to 150 mg/m^2 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m^2 3rd occurrence: treatment discontinuation
Grade 3-4 thrombocytopenia	1st occurrence: reduce the oxaliplatin dose to 60 mg/m^2 and the continuous 5-FU dose to 75 % of the original dose 2nd occurrence: reduce also the dose of irinotecan to 150 mg/m^2 and the dose of continuous 5FU of additional 25 % 3rd occurrence: treatment discontinuation

Use Filgrastim or pegfilgrastim for recurrent grade 3/4 neutropenia despite a first-dose reduction or after febrile neutropenia.

7.2. Gastrointestinal toxicities

Patients must be instructed in the use of loperamide as treatment for diarrhea, and must have a supply of this drug upon starting FOLFIRINOX. Patients should not be retreated with irinotecan until recovery from diarrhea (without loperamide for at least 24 h) has occurred.

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Diarrhea grade 3-4 **or** **Diarrhea + fever and/or neutropenia grade 3-4**	1st occurrence: reduce the irinotecan dose to 150 mg/m^2 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m^2 and reduce the dose of continuous 5FU to 75 % of the original dose 3rd occurrence: investigator's discretion
Diarrhea ≥ 48 h despite high doses loperamide	No systematic reduction of the irinotecan, oxaliplatin or 5FU doses after complete recovery, unless grade 3-4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3-4

7.3. Mucositis or "hand-foot" syndrome

In case of grade 3-4 toxicity, a reduction in dosage of 25% of continuous 5FU will be carried out for the subsequent cycles.

7.4. Cardiac toxicity

In case of unstable angina or myocardial infarction, the protocol will be discontinued.

7.5. Increase of bilirubin

In case of elevation of bilirubin, it is suggested to exclude an obstruction of the biliary tract or stent or progressive disease and postpone chemotherapy. If bilirubin is >1.5xULN, irinotecan is not recommended. If chemotherapy is medically indicated, it is necessary to provide a dose adjustment of irinotecan at investigator's discretion.

7.6. Other toxicities

Any other toxicity grade 2 or greater, except anemia and alopecia, can justify a reduction of dose if medically indicated, for example reduction of irinotecan to 150 mg/m^2 and/or oxaliplatin to 60mg/m^2 and/or 5FU of 25% depending of the type of adverse event.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 8.1) and the characteristics of an observed AE (Section 8.2) will be collected. The principal investigator will review all serious adverse events. Additionally, serious adverse effects will be reported to our IRB.

Safety and tolerability will be assessed according to the NIH/NCI CTC version 4.0. Please refer to: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

8.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

This list corresponds to the list of grade 3 and 4 adverse events that occurred in more than 5% of the patients with adenocarcinoma of the pancreas that received FOLFIRINOX in the metastatic locally advanced setting.

Hematological adverse effects:
Neutropenia - 45%
Thrombocitopenia – 9%
Anemia – 8%
Febrile neutropenia – 5%

Non-hematological side effects:
Fatigue - 24%
Vomiting -15%
Diarrhea - 13%
Peripheral neuropathy - 9%
Elevated alanine aminotransferase - 7.3%
Thromboembolism - 6.6%
Alopecia - 11.4% (grade 2)

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
  .

- **"Expectedness"**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are listed under section 8.1 (CAEPR).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

8.3 Laboratory Test Abnormalities

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Clinically significant laboratory results are those requiring a change in the patient's treatment, further diagnostic testing or specific clinical intervention (i.e., treatment delays or dose modifications, etc). Therefore, the following laboratory abnormalities should be captured on the nonseries AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

8.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Study Drug through 30 days after discontinuation of the Study Drug.
All serious AEs will be reviewed by the Protocol Monitoring committee (see section 14.3.3).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value/status is available;
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).

9. PHARMACEUTICAL INFORMATION

9.1 Drug Formulation, Storage, Availability, Preparation, Toxicity

All the drugs on the FOLFIRINOX regimen (5- flourouracil, leucovorin, irinotecan and oxaliplatin) are available commercially therefore we do not anticipate any problems in delivering the drugs to patients. The drugs will be administered per institutional guidelines.

9.1.1 Oxaliplatin

Availability
Oxaliplatin is commercially available as an aqueous solution in vials containing 50 mg and 100 mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use.

Storage and Stability
Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

Preparation
The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Administration
Oxaliplatin will be administered by intravenous infusion over 120 minutes in patients receiving FOLFOX. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia.

Oxaliplatin is unstable in the presence of choride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

Toxicity
The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myleosuppression. Three neurotoxicity syndromes have been seen:

Acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesias, dysesthesias, and hypothesia of the hands, feet and perioral regions. Jaw spasm, abnormal tongue sensation, dyarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested to order to minimize pharyngolaryngeal

dysesthesia. Antianxiety agents (e.g. lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesia, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Various agents have been used in an attempt to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, pregabalin). Their routine use requires further confirmation of efficacy. They may be used in this study at the discretion of the treating physician.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dyspnea) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5- FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

For more information on toxicities associated with oxaliplatin, please see the package insert.

9.1.2 5-Fluorouracil (5-FU; fluorouracil; Adrucil®)

Availability
5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials

Preparation
Inspect for precipitate: if found, agitate or gently heat in water bath.

46-48 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5 FU should not be mixed in the same solution with most parenteral anti-emetics.

Storage and Stability
Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and diluent. Please refer to appropriate reference sources for additional information.

Administration
In this study, 5-FU is administered as 2400 mg/m^2 by IV infusion over 46 to 48 hours.

Toxicity
Nausea, diarrhea, vomiting (mild); stomatitis (5-8 days after treatment initiation); myelosuppression; granulocytopenia (9-14 days); thrombocytopenia (7-14 days); alopecia; loss of nails; hyperpigmentation: photosensitivity; maculopapular rash; palmar-plantar erythrodysethesias: (42-82% receiving continuous infusion); CNS effects: cerebral ataxia (rare); cardiotoxicity: MI, angina: asymptomatic S-T changes 68%; ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

Drug Interactions
Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Patients receiving both drugs should be followed with weekly INRs.
Please refer to the package insert for complete product information.

9.1.3 Leucovorin Calcium (Folinic Acid; calcium folinate; citrovorum factor; N 5-formyltetrahydrofolate; 5-formyl-FH4; folinic acid).

Availability
Leucovorin calcium is commercially available in: 50 mg, 100 mg, 350 mg vials for reconstitution.

Storage and Stability
Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with BWI are stable for at least 7 days at room temperature.

Preparation
Leucovorin may be reconstituted with Bacteriostatic Water for Injection (BWI) or with Sterile Water For Injection. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for infusion over two hours.

Administration
Leucovorin will be administered as a 400mg/m^2 IV infusion over 2 hours after oxaliplatin administration. Leucovorin may also be administered concurrently with oxaliplatin as a separate IV infusion.

Toxicity
The only adverse reactions associated with leucovorin are allergic reactions. These are extremely uncommon.

Please refer to the package insert for complete product information.

9.1.4 Irinotecan (CPT-11, Camptosar).

Availability
Irinotecan is commercially available in a concentration of 20mg/mL in 2mL, 5mL, and 25 mL vials.

Storage and Stability
Intact vials should be stored at controlled room temperature 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius) and protected from light. Solutions diluted in D5W are reported to be stable for 48 hours under refrigeration and protected from light. Irinotecan solutions should not be frozen as the drug may precipitate.

Preparation
Irinotecan is diluted in 5% dextrose (D5W) 500 mL to a final concentration of 0.12 – 1.1 mg/mL.

Administration
In this study, irinotecan is administered by IV infusion over 90 minutes

Toxicity

Virtually all phase I and II studies of irinotecan have reported neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after the irinotecan administration as the dose limiting toxicities (depending on the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; this syndrome is thought to be cholinergically mediated, and may be treated and subsequently prevented with atropine. Sporadic cases of pulmonary toxicity, manifested as shortness of breath, non-productive cough and transient infiltrates on chest x-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed.

Please refer to the package insert for further information regarding irinotecan. Of note, concerns related to adverse effects:

• Bone marrow suppression: [U.S. Boxed Warning]: May cause severe myelosuppression. Deaths due to sepsis following severe myelosuppression have been reported. Therapy should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count is $<1000/mm^3$. The dose of irinotecan should be reduced if there is a clinically significant decrease in the total WBC ($<200/mm^3$), neutrophil count ($<1500/mm^3$), hemoglobin (<8 g/dL), or platelet count ($<100,000/mm^3$). Routine administration of a colony-stimulating factor is generally not necessary, but may be considered for patients experiencing significant neutropenia.
• Colitis: Colitis, complicated by ulceration, bleeding, ileus, and infection has been reported.
• Diarrhea: [U.S. Boxed Warning]: Severe diarrhea may be dose-limiting and potentially fatal; two severe (life-threatening) forms of diarrhea may occur. Early diarrhea occurs during or within 24 hours of receiving irinotecan and is characterized by cholinergic symptoms (eg, increased salivation, diaphoresis, abdominal cramping); it is usually responsive to atropine. Late diarrhea occurs more than 24 hours after treatment which may lead to dehydration, electrolyte imbalance, or sepsis; it should be promptly treated with loperamide. Patients with diarrhea should be carefully monitored and treated promptly.
• Hypersensitivity reactions: Severe hypersensitivity reactions have occurred.
• Renal toxicity: Renal impairment and acute renal failure have been reported, possibly due to dehydration secondary to diarrhea.

Disease-related concerns:
• Bowel obstruction: Patients with bowel obstruction should not be treated with irinotecan until resolution of obstruction.
• Hepatic impairment: Use with caution in patients with hepatic impairment.
• Hyperbilirubinemia: Patients with even modest elevations in total serum bilirubin levels (1-2 mg/dL) have a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were <1 mg/dL. 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. Use caution when treating patients with known hepatic dysfunction or hyperbilirubinemia; dosage adjustments should be considered.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done $\leq$2 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Radiographic evaluation must include cross-sectional imaging of the chest, abdomen and pelvis. Options include CT chest/abdomen/pelvis with intravenous contrast, or MRI abdomen/pelvis with intravenous contrast along with CT chest with or without intravenous contrast. Scans will be performed every 8 weeks. In cases of treatment delays, efforts will be made to maintain scans at every 8 week +/- 2 week intervals regardless of the cycle number. For all the visits and related procedures, a 7 days window from the anticipated treatment date will be permitted if necessary to accommodate any necessary date modifications. The schedule below illustrates calendar for 1st 12 weeks.

	Pre-Study (within 2weeks cycle 1)	**C 1**	**C 2**	**C 3**	**C 4**	**C 5**	**C 6**	**C 7**	**C 8**	**C 9**	**C 10**	**C 11**	**C 12**	**Maintenance treatment [c] Or Off treatment/ study**
Informed consent	X													
Demographics	X													
Medical history	X	X	X		X	X		X		X		X	X	X
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X		X		X				X		X
Vital signs	X	X	X	X	X	X	X	X	X			X		X
Height	X													
Weight	X	X	X	X		X		X		X		X		X
Performance status	X	X	X	X		X		X		X		X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
B-HCG[b]	X													
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor measurements [d]	X					X				X			X	X

A: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: Serum pregnancy test (women of childbearing potential).

c: after 12 cycles patient will be allowed to continue on a maintenance treatment per investigators discretion.
d: CT chest/abdomen/pelvis, or MRI abdomen/pelvis with CT chest. Tumor/radiological measurements are repeated every 8 weeks +/-2 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease. Patients on maintenance, off-treatment and/or study will be scanned every 8 weeks as part of routine follow-up.

Long Term/Survival Follow-up Procedures

Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

11. MEASUREMENT OF EFFECT

The primary efficacy endpoint is objective response rate as determined by radiology review.

11.1 RECIST Criteria for response

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines[30] will be employed in this study. For the purposes of this study, measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

To be considered pathologically enlarged and measurable, a lymph node must be =15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow- up, only the short axis will be measured and followed.
Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-measurable lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Blastic bone lesions are non-measurable. Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression (by RECIST 1.1) in the lesion.

Target lesions: all measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at

baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target lesions: All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

11.1.1 Evaluation of target lesions

Complete response (CR): complete disappearance of all target lesions, confirmed by repeat assessments at no less than 4 weeks after the criteria for response are first met. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum longest diameter. This must be confirmed by repeat assessment at no less than 4 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 reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease.

11.1.2 Special notes on the assessment of target lesions

• Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.

• Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.

• Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

11.1.3 Evaluation of non-target lesions

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

Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

• When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

• When patient has only non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

11.1.4 New lesions

The appearance of new malignant lesions denotes disease progression.

• The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).

• If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

• A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Cytology and Histology: if the measurable disease is restricted to a solitary lesion, its neoplastic nature should ideally be confirmed by cytology or histology. These techniques can be used to differentiate between PR and CR in rare cases.

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, stable disease, and progressive disease.

11.1.5 Evaluation of response

Evaluation of Best Overall Response: the best overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 11-1-5-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 11-1-5-1. Evaluation of best overall response in patients with measurable disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Inevaluable	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	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

When patients have non-measurable (therefore non-target) disease only, Table 11-1-5-2 is to be used.

Table 11-1-5-2. Evaluation of best overall response in patients with non-measurable disease

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or no	PD
Any	Yes	PD

Inevaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

11.2 Guidelines for Evaluation of Measurable Disease

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. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable. Ultrasound (US) should not be used to measure tumor lesions.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response. Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease). Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

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11.3 Confirmation Measurement/Duration of Response

Confirmation: To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression Free Survival (PFS): PFS is defined as the time from the date of first study treatment to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

Time to Treatment Failure: Time from administration of the initial dose of treatment until study discontinuation for any reason (e.g. disease progression, toxicity, death, withdrawal of consent).

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

This will be a prospective, single-institution, open- label, phase II clinical trial.

12.2 Sample Size/Accrual Rate

For our primary endpoint, based on historical data and taking into account a mixed population of first-line versus beyond-first-line treatment patient population, we estimate response rate of 30% with standard platinum-based chemotherapy (H0:p=0.30). We hypothesize that FOLFIRINOX will have a response rate of 50% (H1:p=0.50). Using an alpha error of 0.10 and a beta error (1 minus power) of 0.20, based on the Simon two stage design, we estimate that we will need 28 evaluable patients to complete this trial. For the stage 1 part of this trial, 12 patients will be enrolled. If 3 or fewer patients achieve ORR, the trial will be stopped. If 4 or more patients achieve ORR, another 16 patients will be enrolled. By the end of the trial, if 11 or fewer patients achieve ORR, this trial will be considered a failure and no further investigation is warranted. We estimate that accrual will take 2 to 3 years. Primary objective will be evaluated after stage 1 and after stage 2, once the sample size is achieved. Patients who consent for the trial but do not receive any dose of treatment will be considered dropouts and will be replaced.

12.3 Stratification Factors

First-line metastatic treatment versus 2nd-line and beyond. We will enroll 14 patients who have not received prior cytotoxic chemotherapy in the metastatic setting, and 14 patients who have received prior cytotoxic chemotherapy.

12.4 Analysis of Endpoints

a) Response rates defined by RECIST criteria, version 1.1. Best response rates to treatment will be summarized in 4 ordinal categories: complete response, partial response, stable disease or progression of disease.

b) Data on progression-free survival (initiation date of therapy to disease progression or death) and overall survival (initiation date of therapy to death) will be collected. Patients alive and free of progression by the time of analysis will be censored and patients who progress or died will be classified as “failures” for statistical analysis purpose. Kaplan-Meier methodology will be used to summarize time-to-event variables.

c) Safety analysis will be analyzed by collecting date on treatment-related morbidity and mortality. We will collect data on frequency, type and severity of all adverse events that occur on or after Cycle 1, Day 1 according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0). Results will be presented as a table.

12.5 Replacement of Dropouts

Patients who enroll but do not receive the initial cycle of FOLFIRINOX will be considered dropouts and will be replaced.

13. DATA COLECTION

Once eligibility has been established and the participant successfully registered, the participant is assigned a protocol case number. This number is unique to the participant on this trial and must be used for case report form (CRF) completion in Oncore.

Data Managers must enter the information required by the protocol onto CRFs.

14. REGULATORY CONSIDERATIONS

14.1 Protocol review and amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing the study location.

Any change or addition (excluding administrative) to the study protocol or informed consent form protocol must be submitted as amendments and must be reviewed and approved by Pharmacyclics and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

14.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval. The original signed copy of the consent document must be retained in the medical record or research file.

14.3 Committees

14.3.1 Scientific Review Committee (SRC)

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at the Cancer Center. Each SRC is responsible for evaluation the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process.

14.3.2 Data Safety Monitoring Committee (DSMC)

The DSMC will meet on a monthly basis and will continually assess for subject safety and recommend changes to protocol and study as required to preserve subject safety and prevent any untoward toxicity.

14.3.3 Protocol monitoring Committee (PMC)

This study will be reviewed by the PMC for data and safety monitoring. The PMC monitors its assigned ongoing research protocol for: serious adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

14.4 Internal monitoring

The trial will be monitored per Moffitt Cancer Center policy MRI-P.PSO.03, *Monitoring of Investigator Initiated Clinical Research.* Data will be captured in Oncore, Moffitt's Clinical Trials Database, Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice, and applicable regulatory requirements.

14.5 Ethics and Good Clinical Practice (GCP)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.6 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

14.7 Study documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.
Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.8 Retention of records

Retained records will include all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 5 years after the investigation is completed.

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APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Cytochrome P450 Enzymes Involved in Drug Metabolism: Substrates, Inducers, and Inhibitors

Isozyme	Substrates	Inhibitors	Inducers
CYP1A2	Clozapine Cyclobenzaprine Fluvoxamine Imipramine Mexiletine Propranolol Theophylline	Cimetidine Ciprofloxacin Clarithromycin Enoxacin Erythromycin Fluvoxamine Ofloxacin Ticlopidine	Polycyclic Aromatic Hydrocarbons (Cigarette Smoke) TCDD (dioxin)
CYP2C9	Diclofenac Flurbiprofen Ibuprofen Losartan (not candesartan or telmisartan) Naproxen Phenytoin Piroxicam Sulfamethoxazole Tolbutamide Warfarin	Amiodarone Fluconazole Fluoxetine Isoniazid Paroxetine Ticlopidine Zafirlukast	Phenobarbital Rifampin
CYP2C19	Amitriptyline Clomipramine Cyclophosphamide Diazepam Imipramine Lansoprazole Nelfinavir Omeprazole Phenytoin	Cimetidine Fluoxetine Fluvoxamine Ketoconazole Lansoprazole Omeprazole Paroxetine Ticlopidine	Carbamazepine Norethindrone
CYP2D6	Amitriptyline Clomipramine Codeine Desipramine Dextromethorphan Imipramine Metoprolol Nortriptyline Oxycodone Paroxetine Propranolol Risperidone Thioridazine Timolol	Amiodarone Fluoxetine Haloperidol Indinavir Paroxetine Quinidine Ritonavir Sertraline	Rifampin
CYP2E1	Acetaminophen Chlorzoxazone Ethanol Enflurane Halothane Isoflurane	Disulfiram	Chronic Ethanol Isoniazid
CYP3A	Alprazolam Astemizole Buspirone Calcium Channel Blockers Carbamazepine Cisapride Cyclosporine Protease Inhibitors Lovastatin Midazolam Simvastatin Tacrolimus Triazolam	Amiodarone Cimetidine Clarithromycin Erythromycin Grapefruit Juice Itraconazole Ketoconazole	Carbamazepine Glucocorticoids Phenytoin Rifampin Ritonavir