DF/HCC Protocol #: 17-311

TITLE: A pilot study of FOLFIRINOX in combination with neoadjuvant radiation for gastric and GE junction cancers

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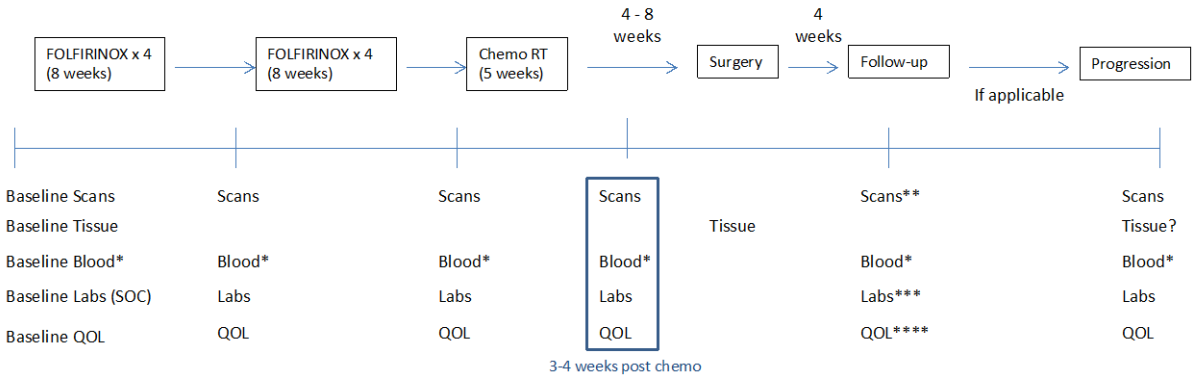
Agent(s): *5*-Fluorouracil, Leucovorin calcium, Oxaliplatin, Irinotecan, Carboplatin, Paclitaxel, Proton or Photon Beam Irradiation

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: *May 11, 2018*

SCHEMA

Patients with locally-advanced (T 3/4 or N+) gastric or GE junction cancer



*blood = for cTDNA and ELISA

**follow-up scans = every 6 mos, yrs 1-2; every 12 mos, yrs 3-5

***follow-up labs = every 3 mos, yrs 1-3; at least every 6 mos, yrs 4-5

****follow-up QOL = at routine follow-up appointments (at 1, 3, 6, 12, 18, 24 months; at the time of other blood draws)

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1. OBJECTIVES

1.1 Study Design

This is a single-arm pilot study of the neoadjuvant administration of the FOLFIRINOX regimen and pre-operative radiation therapy followed by surgery in patients with locally-advanced (T 3/4 or N+) gastric or gastroesophageal (GE)-junction cancer.

1.2 Primary Objective

To determine the FOLFIRINOX completion rate of neoadjuvant chemotherapy followed by chemoradiation delivered in the pre-operative or definitive setting to patients with gastric and GE junction cancers.

1.3 Secondary Objectives

1) To describe the toxicities of neoadjuvant FOLFIRINOX and chemoradiation given to patients with gastric and GE junction cancers
2) To investigate the clinical response rate of patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation
3) To investigate the pathologic complete response rate at time of surgery in patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation.
4) To investigate the progression-free survival (PFS) of patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation
5) To investigate the overall survival (OS) at 5 years of patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation
6) To investigate the relationship between tissue, cell and plasma biomarkers and response rate in patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation
7) To investigate quality of life, symptom burden, mood, and nutrition in patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation.
8) To investigate utilization of health services (emergency room, hospital and intensive care unit) in patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation.

2. BACKGROUND

2.1 Gastric and GE junction cancers

Gastric cancer is a lethal disease. While the incidence has been decreasing (Siegel 2017), it

remains a major cause of cancer related death in the United States. The high death rate is related to late presentation in Western countries, where the majority of patients present with locally advanced or metastatic disease (Agboola), which portends a poor prognosis. Surgery remains the mainstay of therapy, with cure being only feasible if the disease is completely extirpated. Numerous standards of care exist to improve upon surgery alone including perioperative chemotherapy, postoperative chemotherapy, and postoperative chemoradiation.

2.2 Study Agents

2.2.1 5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis. It is systemically metabolized, with the enzyme dihydropyrimidine dehydrogenase (DPD) being rate-limiting.

It forms the backbone of treatment for most gastrointestinal malignancies, and is a crucial component of the FOLFIRINOX regimen, in which it is administered as a 400 mg/m2 bolus, followed by a 2400 mg/m2 46-hour infusion. Initial dose of 5-FU may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.2.2 Oxaliplatin

Oxaliplatin is a platinum compound classified with the alkylating agents. Its mechanism of action is via intra-strand cross-linking, thereby inhibiting DNA replication and transcription. In the FOLFIRINOX regimen it is administered as an 85 mg/m2 infusion over 2 hours. Initial dose of oxaliplatin may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.2.3 Irinotecan

Irinotecan is a camptothecin topoisomerase I inhibitor commonly used in gastrointestinal malignancies. In the FOLFIRINOX regimen it is delivered as a 180 mg/m2 infusion over 90 minutes on Day 1 of treatment. Initial dose of Irinotecan may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.2.4 Leucovorin

Leucovorin is a reduced folate which, when combined with 5-FU, augments 5-FU cytotoxicity by increasing the inhibition of thymidylate synthase (TS) by the 5-FU active metabolite FdUMP. It is well-tolerated but can be associated with allergic reactions (rash, urticaria, anaphylaxis) and is contraindicated in patients with B12 deficiency and pernicious anemia.

2.2.5 Paclitaxel

Paclitaxel is a cyclodecane isolated form the bark of the Pacific yew tree Taxus brevifolia. Palitaxel binds to tubulin and inhibits the diassembly of microtubules, thereby resulting in the inhibition of cell division.

2.2.6 Carboplatin

Carboplatin is a second-generation platinum compound with a broad spectrum of anti-neoplastic properties. It contains a platinum atom complexed with two ammonia groups and a cyclobutane-dicarboxyl residue. This agent is activated intracellularly to form reactive platinum complexes that bind to nucleophilic groups such as GC-rich sites in DNA, thereby inducing intrastrand and interstrand DNA cross-links, as well as DNA-protein cross-links. These carboplatin-induced DNA and protein effects result in apoptosis and cell growth inhibition.

2.2.7 Radiation Therapy

Proton Beam Radiation Therapy

There have been unprecedented efforts in radiation oncology to develop and use sophisticated, conformal photon techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. Toward this end, many advances have been made and examples of new developments include Tomotherapy and intensity modulated photon therapy. At the same time, heavy charged-particle programs, particularly those for proton therapy, have been developed. Proton therapy dose distributions are superior to those of photon therapy and this provides the potential to further improve clinical outcomes. Several institutions have committed to build dedicated proton therapy centers such as the Francis H. Burr Proton Therapy Center (FHBPTC) at the Massachusetts General Hospital (MGH) and the Loma Linda University Medical Center proton therapy facility. Several more proton therapy centers are in the final planning stage.

The Advantages of Protons for Delivery of Conformal Therapy

Characteristics of Proton Beams

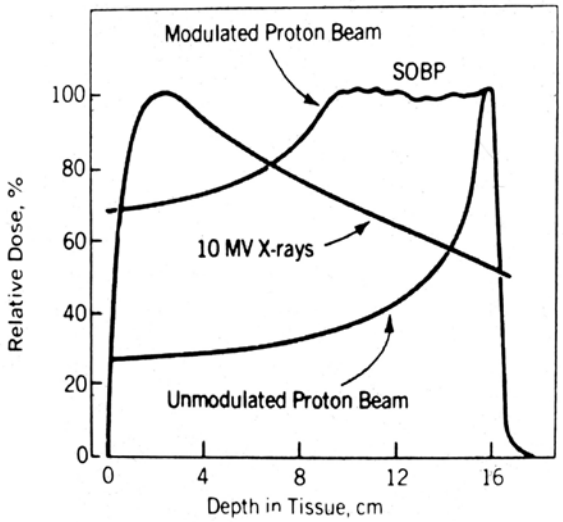

Figure 1. Proton (Bragg peak and modulated Peak) and 10 MV depth dose curves.

The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (see Figure 1). Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) known as the Bragg peak (see the curve labeled "unmodulated proton beam" in Figure 1). In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.

The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP). This is shown in Figure 1 as the “modulated proton beam”.

For comparison, Figure 1 also shows the depth-dose curve for a 10 MV x-ray beam, an x-ray

energy commonly used to treat deep seated tumors. Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, and then falls off exponentially to lower doses at the treatment depth. A clinical comparison of single-beam proton and photon beams is shown in Figure 2 where a single posterior beam is used for the treatment of the spinal axis in the treatment of medulloblastoma. Note that, for the photon treatment, the heart, mediastinum, esophagus, lung and spinal cord are irradiated by the treatment beam whereas for the proton treatment, the beam stops abruptly distal to the target volume and there is no irradiation of the tissues and organs distal to the target volume.

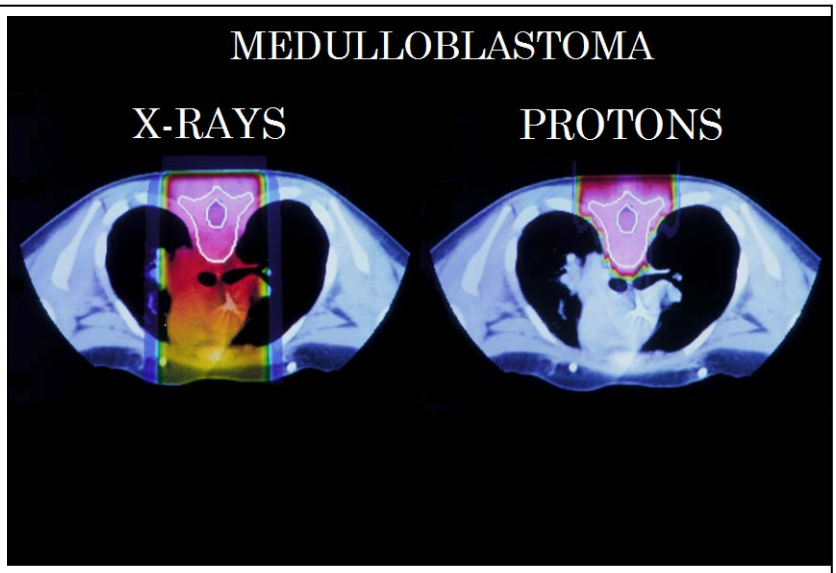

Figure 2. Posterior, single-beam treatment of the spinal axis

In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems, proton therapy capabilities are equivalent to those for state-of-the-art, conformal therapy using x-rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

Intensity Modulated Radiation Therapy

Intensity-modulated x-ray therapy (IMXT) – the use of x-ray beams each of which is purposely made non-uniform over its cross-section – provides a new degree of freedom in treatment delivery and can lead to more conformal dose distributions. Protons, too, can be used in an intensity modulated mode (IMPT) similar to that for photons and, in an additional degree of freedom, are also made non-uniform in depth. The advantage that single beams of protons have over single beams of x-rays, which is maintained when multiple cross-firing beams of uniform intensity are employed, is similarly maintained when intensity modulation is employed.

In IMXT, the dose can be made to conform to the target volume while avoiding selected adjacent sensitive structures (although the dose uniformity within the target volume is strongly influenced by such selective avoidance and is often of undesirable magnitude). However, IMXT does not reduce the integrated dose delivered outside the target volume (as compared to standard conformal photon therapy); it only, in general, spreads that energy out over a larger volume. In our treatment planning intercomparisons (in nasopharynx, paranasal sinus, lung and Ewing's sarcoma) we have found that the integral dose for IMPT is a factor of two (on the average) less than for IMXT. Moreover, whatever improvement IMXT achieves over standard conformal x-ray therapy, a comparable improvement is achieved when IMPT is compared to standard conformal proton therapy.

Figure 3: Paranasal sinus tumor treated with IMPT (left) and IMXT (right). Dose difference distribution below.

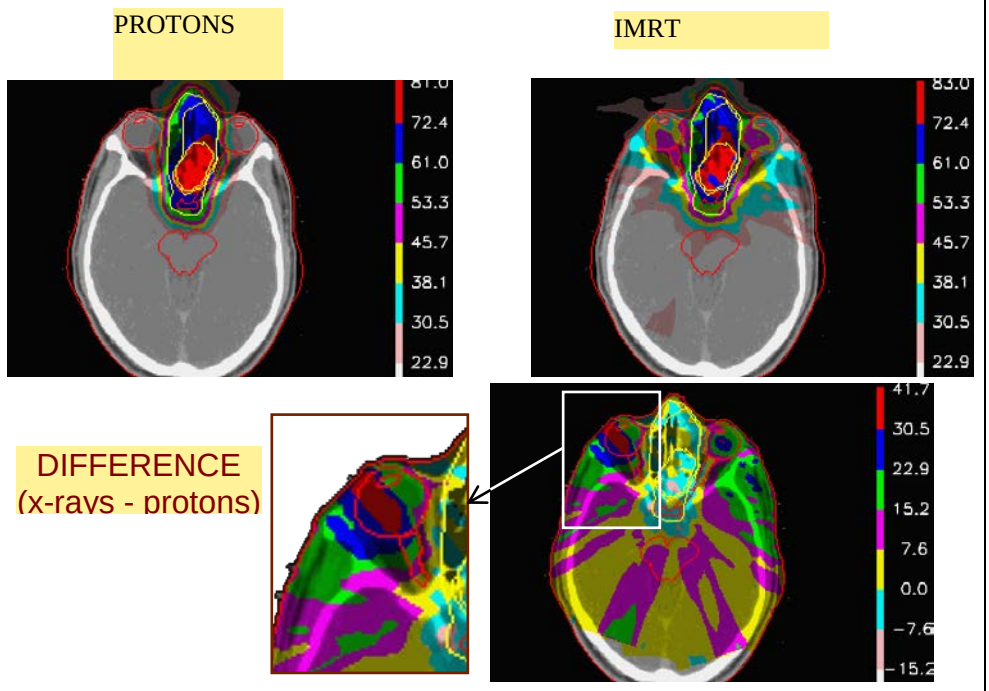

Figure 3 demonstrates the above points. It is a comparison of two IMRT plans, one with x-rays and one with protons, designed to treat a paranasal sinus tumor (with three target volumes receiving 76, 66, and 56 Gy, respectively). The two plans were subject to identical dose constraints on normal tissues. The proton dose distribution (left) is clearly excellent; the photon distribution on the right is also very good. However, the presentation of the dose in the top panels does not adequately reveal the significant differences between the two distributions. The lower panels show the dose difference between the plans. X-rays deliver an additional "bath" of from 5 to 15 Gy throughout the brain and, in the region of the right eye (which is magnified in the lower left), up to 40 Gy more than the protons. (The constraint on the right eye's retina was 50 Gy; had it been reduced, x-rays could certainly have reduced the dose in that region – but at the price of increased dose elsewhere and, perhaps, of greater non-uniformity of dose in the target volumes.)

2.3 Rationale

Chemotherapy and chemoradiation both have defined roles in the management of esophagogastric cancers. In patients with esophagogastric junction (GE junction) and esophageal cancer, neoadjuvant chemoradiation has been established as the standard of care. In the setting of inoperable esophageal/GE junction cancers, chemoradiation produces long term control in some patients. Patients with node positive gastric cancer similarily benefit from multi-agent chemotherapy and chemoradiation.

2.3.1 Neoadjuvant chemoradiation in resectable GE junction adenocarcinoma

A phase III trial called the CROSS trial (van Hagen) randomized patients with T1-3 or N+ esophageal or GE junction cancer to neoadjuvant chemoradiation followed by surgery, versus surgery alone. Patients randomized to chemoradiation received 41.4 Gy with weekly carboplatin and paclitaxel. pCR was achieved in 29% of patients receiving chemoradiation. Patients with adenocarcinoma achieved a pCR rate of 23%, compared with 49% for squamous cell carcinoma. Overall survival at 5 years was improved from 34% to 47% ($p<0.001$). There was no increased risk of postoperative mortality with neoadjuvant chemoradiation ($P=0.85$)

2.3.2 Definitive chemoradiation in inoperable GE junction adenocarcinoma

Many patients will have unresectable cancer due to either unresectable tumor (T4 disease or extensive nodal involvement) or medical comorbidities. Chemoradiation was established as optimal therapy based on Radiation Therapy Oncology Group (RTOG) 8501, which randomized patients between 64 Gy of radiation alone or 50 Gy of chemoradiation with cisplatin and 5-FU. 5-year overall survival improved with the addition of chemotherapy from 0% to 27% ($P<0.0001$) (Cooper). However, at two years, 45% of patients experienced a local recurrence.

To decrease this risk of local failure, a follow up trial was conducted by the US Intergroup (INT 0123) to determine if dose escalation could reduce the risk of local recurrence (Minsky). Patients with inoperable esophageal cancer were randomized to 50.4 Gy or 64.8 Gy with concurrent cisplatin/5-FU. There was no improvement in local control or overall survival.

Because of the high rate of toxicity seen with cisplatin and 5-FU, a randomized trial was conducted comparing radiation to 50 Gy with either cisplatin/5-FU or FOLFOX (Conroy) in patients with inoperable esophageal or GE junction cancer. This study showed equivalent overall survival between the two regimens but markedly lower early and toxic death rate.

2.3.3 Chemotherapy and chemoradiation in resectable gastric cancer

Multiple standards of care exist for adjuvant therapy in resected, locally advanced gastric cancer. The development of both chemoradiation and chemotherapy-alone adjuvant approaches highlights the two competing risks of recurrence in patients with locally advanced gastric cancer: locoregional recurrence and metastatic recurrence. In the US, the high rates of locoregional failure observed after surgery alone led to the design of Intergroup 0116 (Smalley), in which patients with margin-negative gastrectomy were randomized to observation or post-operative

chemoradiation with 5-fluorouracil (5FU), sandwiched between three cycles of Mayo Clinic schedule 5-FU. This study demonstrated a survival benefit of ~10% directly related to an improvement in locoregional control, but no difference in rates of distant metastases. Despite these results, significant skepticism remained regarding the impact of this trial outside the United States as over half the patients had an insufficient, D0, lymphadenectomy. In Europe, the MAGIC study evaluated peri-operative chemotherapy with epirubicin, cisplatin and 5-FU (ECF) versus surgery alone (Chua). Patients receiving chemotherapy received three cycles before and after surgery. Similarly, this study demonstrated a survival benefit of ~ 10%, though this time due to a substantial improvement in distant metastases.

To evaluate the role of radiation in patients receiving chemotherapy after a D2 lymph node dissection, the ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial randomized patients between capecitabine and cisplatin (XP) for 6 cycles vs. XP for 2 cycles, followed by chemoradiation with capecitabine to 45 Gy, followed by XP for 2 more cycles (XP/XRT/XP) (Lee). 458 patients were randomized between the two arms. Patients were generally high risk, with >85% enrolled having node (+) disease. Over half the patients had diffuse type disease, as opposed to intestinal type. As expected from this high-volume surgical center, all patients had a D2 dissection, with a median of 40 lymph nodes evaluated in both arms. With a median follow up of 53.2 months, the 3-year DFS was 78.2% in the XP/XRT/XP arm compared to 74.2% in the XP arm (p=0.0862). While this difference did not reach statistical significance, the node-positive patients appeared to derive benefit from the addition of radiation, with a 3-year DFS was 77.5 % in the XP/XRT/XP arm compared to 72.3% in the XP arm (p=0.0365). Interestingly, locoregional recurrence was quite low in both arms (4.8% in XP/XRT/XP arm vs. 8.3% in XP arm; p=0.3533).

2.3.4 Neoadjuvant FOLFIRINOX and Chemoradiation

A study of preoperative chemotherapy and chemoradiation for localized gastric and gastroesophageal junction adenocarcinoma (LGCA) was conducted (Elimova). Patients with LGCA with baseline endoscopic ultrasound (eus) T2-T3 any N, M0 (M stage by laparoscopy and imaging) were eligible. Patients received 4 or fewer doses of oxaliplatin and infusional 5-FU every 2 weeks then oxaliplatin and infusional 5-FU with 45 Gy of conformal radiation in 25 fractions. 5-6 weeks after chemoradiation, patients underwent an attempted D2 dissection and were followed. Between February 2004 and November 2010, a total of 58 patients were enrolled. Most patients were men (66%) and had clinical stage IIIA cancer (52%). 14% (95%CI: 6%, 25%) of patients achieved a pathologic CR. With a median follow-up of 37.4 months, the median survival was 39.4 (95%CI: 27.6, NR) months. 72% of patients proceeded to surgery and 86% of these had an R0 resection. The 5-year OS for patients who had surgery was 56%. 44.8% of patients experienced grade 3 and/or 4 toxicities (commonly, fatigue, anorexia and insomnia) due to induction chemotherapy. 58.6% experienced grade 3 and/or 4 toxicities due to chemoradiation (commonly, fatigue, myelosuppression, vomiting, and dysphagia). No treatment-related death occurred.

The 5-yr OS for all patients treated on this study was 44% and the 5-year Progression Free Survival (PFS) was 42%. Our data show that if LGCA patients can complete the described therapeutic strategy (i.e., including surgery), their outcome may be excellent.

2.4 Correlative Studies Background

Preclinical and clinical work in the Steele Labs and elsewhere has identified the plasma and tissue hepatocyte growth factor (HGF), carbon anhydrase IX (CAIX), stromal-derived factor 1 alpha (SDF1α) as candidate biomarkers of response or resistance to various therapies, but their role after proton beam radiation therapy in gastric cancer is unknown. Based on findings from preliminary studies, we propose here to evaluate the baseline and changes in blood circulating protein biomarkers and circulating and tumor-infiltrating immune cells to explore potential associations between the changes in these biomarkers and resistance to treatment in this disease. These biomarkers will be monitored from baseline throughout FOLFIRINOX therapy, before and after chemoradiation, after surgical resection, and at time of disease progression. In exploratory studies, we will evaluate several other cytokines using multiplex protein array (Meso-Scale Discovery, Inc.).

Circulating cell populations will be evaluated by fluorescence-based flow cytometry. Protein concentration in plasma will be measured using ELISA kits for HGF, CAIX, and SDF-1 (RnD Systems) and MSD multiplex kits for cytokines (Human ProInflammatory Panel 1 V-PLEX™ Plus IFN-γ, IL-1β, IL-10, IL-12 p70, IL-13, IL-2, IL-4, IL-6, IL-8, TNF-α; Meso-Scale Discovery #K15049G-1), and vascular growth factors (Human Angiogenesis Panel 1 V-PLEX Kit: bFGF, Flt-1, PlGF, sTie-2, VEGF, VEGF-C, VEGF-D; Meso-Scale Discovery #K15190D-1). These techniques have been used in the Steele Lab for over 15 years to evaluate patients' samples.

In gastric cancer, mutations of interest do not occur randomly, but rather a relatively small number of well-characterized mutations comprise the majority of activating mutations. Other genes of interest already mentioned include APC, CTNNB1 (β-catenin), Braf, PTEN, and PIK3CA. Our institution uses an adaptation of SNaPSHOT (Applied Biosystems) as our clinical method of determining KRAS mutational status in tumors, as described by Dias-Santagata, et al. This testing is routinely done on all newly diagnosed GI cancer patients.

2.5 Patient-Reported Outcomes Background

Studying patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to better understand their disease- and treatment-related outcomes. Patients' symptom burden and QOL are better indicators of their treatment tolerability than clinician-reported toxicity monitoring. Combining objective endpoints, such as response rate, with subjective patient-reported outcomes has become increasingly important in determining efficacy, toxicity, and safety and for allowing comparisons across treatment arms (Edgerly). Additionally, evaluating patient-reported measures may help highlight patients' difficulties with treatment adherence by demonstrating additional side effects and toxicities of therapy (Berry). Increased attention to patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to improve their quality of care (Oberguggenberger, Meyers). Thus, we aim to describe QOL, symptom burden and mood in this study population to help us better identify the side effects and challenges faced by patients with gastric cancer.

We will use the EORTC QLQ-C30, a validated instrument designed for prospective clinical trials that evaluates five functions (physical, role, cognitive, emotional, and social), and nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties) to measure QOL (Aaronson). The EORTC QLQ-STO22 is a 22-item gastric cancer site-specific supplemental module to augment the QLQ-C30 to enhance the sensitivity and specificity for gastric cancer QOL measures (Blazeby). We will use the Edmonton Symptom Assessment System-revised (ESAS-r) to measure symptoms, which has been previously validated in patients with advanced cancer (Watanabe). The ESAS-r consists of ten items assessing pain, fatigue, drowsiness, nausea, anorexia, dyspnea, depression, anxiety, well-being, and a free-response item. We will include constipation as the free-response item. The ten items are scored on a scale of 0-10 (0 reflecting no reported presence of the symptom and 10 reflecting the worst possible severity of the symptom). We will instruct patients that items are to be rated based on the previous 24-hour period. We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety (Zigmond). The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week. The questionnaire consists of a four-point item response format that quantifies the degree to which participants experience a particular emotion. Scores on each subscale range from 0 to 21, with a cutoff of 8 or greater denoting clinically significant depression or anxiety symptoms.

We will use the Mini-Nutritional Assessment (MNA) to assess nutrition (Cohendy, Kaiser). The MNA has been established as one of the most valid and most frequently used nutritional screening tools.

2.6 Health Care Utilization Background

As oncologists strive to improve care quality and lower health care costs, their focus has turned to reducing avoidable admissions and decreasing hospital length of stay (LOS) for patients with cancer (Earle, Sadot). Patients with gastric cancer often experience symptoms related to the cancer itself or the therapies used to treat it (Crippa). Symptom management for these patients may necessitate frequent clinic visits, surgical interventions, and ultimately admissions to the hospital. Avoiding unnecessary hospitalizations is an area needing improvement for patients with cancer, but a better understanding of health care utilization is necessary in order to develop future interventions (Brooks). Thus, we propose to collect data on study participants' health care utilization including hospital admissions, intensive care unit stays and emergency room visits. Similar to measuring patient-reported outcomes, assessing health care utilization will help us better understand study patients' experience with their cancer treatment and the differences between the two treatment regimens.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria in order to be eligible to participate in the study:

3.1.1 Histologically or cytologically confirmed T 3/4 or N+ (> 1 cm in size or FDG avid) gastric or gastroesophageal (GE) junction cancer. Diagnosis must be confirmed by a DF/HCC institution pathology department prior to registration.

3.1.2 Age 18 years or older. There will be no upper age restriction.

3.1.3 ECOG performance status ≤ 1

3.1.4 Life expectancy of greater than 3 months

3.1.5 Participants must have adequate organ and marrow function as defined below:

– absolute neutrophil count	≥ 1,500 cells/mm3
– platelets	≥ 75,000 cells/mm3
– total bilirubin	≤ 1.5 x upper limit of normal, or, for patients who have undergone biliary stenting, total bilirubin of ≤ 2 or two down trending values.
– AST(SGOT)	≤ 2.5 × upper limit of normal
– ALT (SGPT)	≤ 2.5 x upper limit of normal
– creatinine	≤ 1.5 mg/dL, or
– creatinine clearance	≥ 30 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.6 The effects of both radiation therapy and the chemotherapy agents used in this trial are known to be teratogenic. Therefore, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation plus 30 days from the last date of study drug administration. 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.

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

3.2 Exclusion Criteria

Participants who fulfill any of the following criteria will be excluded from the study:

3.2.1 Evidence of metastatic disease as determined by chest CT scan, abdomen/pelvis CT scan (or MRI with gadolinium and/or manganese) within six weeks of study entry. Distant nodal disease is allowed if it is in the radiation port.

3.2.2 Any prior chemotherapy, targeted/biologic therapy, or radiation for treatment of the participant's gastric or GE junction cancer.

3.2.3 Receipt of chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.4 Treatment of other invasive carcinomas within the last five years with greater than 5% risk of recurrence at time of eligibility screening. Carcinoma in-situ and basal cell carcinoma/ squamous cell carcinoma of the skin are allowed.

3.2.5 Receipt of any other investigational agents within 4 weeks preceding the start of study treatment.

3.2.6 Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator), such as significant cardiac or pulmonary morbidity (e.g. congestive heart failure, symptomatic coronary artery disease and/or cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months, or ongoing infection as manifested by fever.

3.2.7 History of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance or drug intake.

3.2.8 Pregnant women are excluded from this study because radiation therapy and the chemotherapy agents to be used have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued while the mother is receiving protocol therapy.

3.2.9 Major surgery, excluding laparoscopy, within 4 weeks of the start of study treatment, without complete recovery.

3.2.10 No concurrent administration of cimetidine (as it can decrease the clearance of 5-FU). Another H2-blocker or proton pump inhibitor may be substituted before study entry.

3.2.11 Known, existing uncontrolled coagulopathy.

3.2.12 Prior systemic fluoropyrimidine therapy (unless given in an adjuvant setting and at least six months earlier). Prior topical fluoropyrimidine use is allowed.

3.2.13 Known hypersensitivity to 5-fluorouracil or known DPD deficiency.

3.2.14 History of allergic reaction(s) attributed to compounds of similar chemical or biologic composition to 5-fluorouracil, irinotecan, or oxaliplatin.

3.3 Inclusion of Women and Minorities

We do not expect the eligibility criteria to over- or under-represent women, minorities, or under-

represented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis and will include administration of the FOLFIRINOX regimen (with dose modifications for those 65 years old or older) followed by proton or photon radiation therapy concurrent with paclitaxel and carboplatin.

Expected toxicities and potential risks as well as dose modifications for FOLFIRINOX and ChemoRadiation are described in Section 6 (Expected Toxicities and Dosing Delays/ Dose Modification).

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Pre-Treatment Criteria

Prior to study enrollment, participants must undergo the following evaluations:

- Chest CT and abdominal-pelvic CT (or MRI) with intravenous contrast within 42 days of enrollment.
- Physical exam within 14 days of enrollment

- Lab studies (CBC with diff, Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase, and a urine or serum HCG for women of childbearing potential) within 14 days of enrollment

Evaluations obtained to confirm study eligibility may be used as pre-treatment evaluations provided that they are done within the above timeframes.

Staging laparoscopy is NOT required prior to study treatment because participants will receive systemic chemotherapy at doses equivalent to that received by patients who have documented Stage IV disease.

The mutational analysis (SNaPSHOT panel) requires a paraffin-embedded block or ten unstained slides from the untreated biopsy specimen that were obtained at the time of endoscopy or diagnostic biopsy. Participants without sufficient material for SNaPSHOT will NOT be excluded from the study as this constitutes a secondary, exploratory aim of the study.

5.2 Agent Administration

A cycle will be two weeks (14 days) long, with FOLFIRINOX administered on days 1-3. Participants will receive up to 8 two-week cycles (for a total of 16 weeks) of FOLFIRINOX chemotherapy. Cycle adjustments of +7 / -1 days may be made at the discretion of the treating physician. A break in therapy of up to one week for restaging after 4 cycles is allowed.

The order of FOLFIRINOX administration is as follows:

1. Oxaliplatin
2. Leucovorin (may be given concurrently with Oxaliplatin or following Oxaliplatin)
3. Irinotecan
4. 5-Fluorouracil

Paclitaxel and Carboplatin will be given concurrently with radiation therapy weekly (+/- 1 day).

All treatments should be administered according to institutional standard of care. All dose adjustments should be made as outlined in section 6.2. Additional dose modifications can be made at the discretion of the treating medical oncologist but the reason for these modifications must be documented in the medical record.

5.2.1 Oxaliplatin

Oxaliplatin will be administered as a dose of 85 mg/m2 by intravenous infusion over 120 minutes except for patients with an initial platelet count between 75,000 and 100,000 who will be treated at an Oxaliplatin dose of 65 mg/m2. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia. Patients requiring oxaliplatin desensitization may continue on study as long as the institution has procedures in place for desensitization. Oxaliplatin should be administered on day 1 of each cycle, followed by or concurrent with leucovorin and prior to irinotecan.

Oxaliplatin is unstable in the presence of chloride 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.

5.2.2 Leucovorin

For all patients, Leucovorin (400 mg/m2) will be diluted with 5% dextrose and administered by IV infusion over 2 hours. It may either be given after oxaliplatin, or concurrently. If given concurrently, use separate containers with a Y-type administration set. There are no adjustments of leucovorin. Even if the bolus 5-FU dose is not given, the leucovorin dose should be administered.

5.2.3 Irinotecan

For patients less than 65 years old, Irinotecan will be initially administered as an initial dose of 180 mg/m2 by intravenous infusion over 90 minutes. For patients aged 65 years or older, the Irinotecan will initially be administered as an initial dose of 150 mg/m2 by intravenous infusion over 90 minutes.

5.2.4 5-Fluorouracil

For patients less than 65 years old, 5-FU will be initially administered as a bolus dose of 400 mg/m2 IV push per institutional standard on day one, followed by a 1200 mg/m^2/day dose by continuous infusion via an ambulatory infusion pump for the subsequent 46 hours. For patients 65 years or older, the bolus 5-FU will not be given. For patients who have a platelet count between 75,000 and 100,000 at the time of registration, the 5-FU bolus should be initially administered as a bolus of 200 mg/m2 (DL-1).5-FU administration will occur after irinotecan. 5-FU is not a vesicant or irritant.

5.2.5 Paclitaxel

Paclitaxel will be given concurrent with radiation therapy. It may be administered before or after radiation. Paclitaxel 50 mg/m^2 will be administered as an IV infusion over 30-60 minutes, weekly (+/- 1 day). Paclitaxel dose does not need to be recalculated for weight changes ≤ 10% of the participant's total body weight. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors. Nothing else is to be infused through the line through which paclitaxel is administered.

Prior to the first dosage of paclitaxel, participants will be premedicated with dexamethasone 20 mg (or an equivalent agent) orally the night before and 20 mg either orally or intravenously on the morning of paclitaxel administration. On the morning of the first paclitaxel administration: if dexamethasone is given intravenously, administer 30 minutes prior to paclitaxel administration; if dexamethasone is given orally, administer 1-3 hours prior to paclitaxel administration. Also prior to the first dosage of paclitaxel, patients will be premedicated with diphenhydramine, 50 mg intravenously, and famotidine (or other H2 blocker), 20 mg intravenously. If no allergic

reactions occur, then subsequent dosages of premedications with dexamethasone, diphenhydramine, and H2 blockers may be reduced at the investigator's discretion.

Patients must be attended by medical personnel for the first 15 minutes of infusion and then have blood pressure checked every 15 minutes for 1 hour, then as needed. Medications for acute management of anaphylaxis should be readily available in the location where the patient is being treated.

All dose adjustments are to be made at the discretion of the treating medical oncologist.

5.2.6 Carboplatin

Carboplatin will be given concurrent with radiation therapy. It may be administered before or after radiation on a dosing day. Carboplatin dose will be area under the curve (AUC) = 2 over one hour, weekly (+/- 1 day). The dose of carboplatin is calculated as follows (using the Calvert formula based on creatinine clearance):

Total dose (mg) = Target AUC (in mg/mL per min) x (Estimated GFR + 25)

The GFR should not exceed 125 ml/min. If the calculated GFR based on the Calvert formula is greater than 125 ml/min, a GFR of 125 ml/min should be used. The maximum carboplatin dose for an AUC = 2 should not exceed 300 mg.

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets that contain aluminum may not be used with this agent. Carboplatin will be administered after paclitaxel. Patients will receive appropriate antiemetics and supplemental hydration as per institutional standard.

All dose adjustments are to be made at the discretion of the treating medical oncologist.

5.3 Radiation Therapy

5.3.1 Simulation and Planning

Tumor volume will be defined on the basis of CT and MRI imaging findings and operative notes and findings. The primary tumor and any clinically enlarged lymph nodes will be treated with a margin of nodal coverage outlined below.

Total dose will be prescribed to the 95 to 100% isodose line based on coverage. The prescribed dose to the PTV is 4500 cGy delivered in 180 cGy/day over 25 fractions. For GE junction tumors, a 540 cGy boost may be included to the GTV + 1 cm. A dose painted boost to involved vasculature is permitted to a total dose of 30 Gy. Radiation treatment assignment will be based on resource availability at the time of radiation planning.

Patients will be simulated supine. Intravenous and oral contrast will be administered per standard department protocol. 4-D CT simulation will be obtained for treatment planning to ascertain the

extent of tumor motion.

The Gross Tumor Volume (GTV) is defined as the gross primary tumor and any lymph nodes enlarged over 1 cm during simulation using contrast given during CT or MRI. For participants with diffuse-type gastric cancer, where the GTV cannot be visualized, the entire stomach will be identified as the GTV. Areas of involved adenopathy should be carefully depicted and their geographic relationship to the primary lesion should be accurately defined on planning images.

When the GTV can be clearly identified, the clinical target volume (CTV) will include a longitudinal mucosal margin that extends 3.5-4 cm proximally and distally to the GTV. When the GTV cannot be identified, the entire stomach will need to be treated.

All grossly involved lymph nodes should have a 5 mm CTV expansion. The following nodal volumes should be covered:

Nodal Coverage (all tumors)
Celiac nodes
Gastrohepatic nodes

GE junction tumors and cardia tumors:
Paraesophageal nodes 4 cm proximal to the GTV
Splenic nodes may be considered

Distal tumors:
Porta hepatis
Peripancreatic nodes may be considered

The Planning Target Volume (PTV) will be customized based on 4D CT scan. Generally, 0.5 cm expansion will be used, except for superiorly/inferiorly where 0.7 cm will be used.

Computerized dosimetry is required if more than two fields are used. All fields must be simulated using a machine that duplicates the geometry of the actual treatment machine. Patient contours and isodose plots are required. Isodose plots must account for the effect of all treated fields, including any blocking used.

5.3.2 Treatment

Radiation treatment will begin within 4 weeks after the completion of FOLFIRINOX.

All radiation treatment will be given at the Francis H. Burr Proton Therapy Center or the Clark Center for Radiation Oncology at MGH. Film or digital images will be taken prior to each treatment in accordance with the Department of Radiation Oncology's standard practice for all patients. These images are used to verify the position of the patient and the aperture. These digital images are permanently stored electronically for each patient.

Radiation treatment may start on any day that the center is functioning. If the proton center is

unexpectedly not functioning for 1 or 2 days, these fractions may be made up the following week. However, if the proton center is not functioning for longer than 2 days, patients may receive photon radiation for the remaining fractions. If radiation therapy start is delayed beyond 4 weeks after completion of FOLFIRINOX due to toxicity, the patient will proceed to radiation therapy on study at the discretion of the treating investigator.

Treatments will be delivered 5 days/week excluding hospital holidays or closed for other emergencies. Patients are encouraged to not eat for 4 hours prior to treatment, and not drink for two hours prior to treatment. For protons, passively scattered protons and pencil beam protons are both permitted. For photons, 3D photons and IMRT are both permitted.

5.3.3 Target Dose Constraints

The prescribed dose to the PTV is 4500 cGy delivered in 180 cGy/day over 25 fractions. For GE junction tumors, a 540 cGy boost may be included to the GTV + 1 cm.

The dose to 99% of the PTV must be at least 93% of the prescribed dose, and a contiguous volume of no more than 2cc inside the PTV may exceed 20% of the prescribed dose.

Calculations will take into account the effects of tissue heterogeneity. Planning will be performed using an approved dose calculation algorithm. Approved algorithms include convolution superposition, collapsed cone convolution, and Monte Carlo.

5.3.4 Normal Tissue Dose Constraints

The normal structures to be contoured will depend on the level of the esophagus involved, but can include left and right lungs, heart, brachial plexus, left and right kidneys, liver, small intestine, and spinal cord. The dose to normal tissues must be kept within parameters described below:

1. Lungs
    a. $V_{20Gy} \leq 20\%$
    b. and $V_{30Gy} \leq 15\%$
    c. and $V_{40Gy} \leq 10\%$
    d. $V_{10Gy} \leq 40\%$
2. Cord
    a. Max $\leq$ 4500 cGy
3. Bowel
    a. Max bowel dose < Max PTV dose
    b. and $D_{05} \leq 4500$ cGy
4. Heart
    a. $V_{30Gy} \leq 30\%$ (closer to 20% preferred)

b. Mean < 3000 cGy

5. Left Kidney, Right Kidney (evaluate each one separately):

   No more than 33% of the volume can receive 1800 cGy

6. Liver
   a. $V_{20Gy} \leq 30$ %
   b. $V_{30Gy} \leq 20$
   c. Mean <2500 cGy

Treatment planning should be adjusted for decreased renal function based on an elevated serum creatinine, a history of unilateral or bilateral renal disease, and abnormalities in baseline laboratory or radiographic studies. Additional studies to assess renal function will be performed as needed. For protons, passively scattered protons and pencil beam protons are both permitted. For photons, 3D photons and IMRT are both permitted.

5.4 Other Modalities and Procedures

5.4.1 Surgery

Surgery will be performed five weeks after chemoradiation. Patients who do not proceed to surgery will remain in active follow up.

5.4.2 Pathology

Processing the specimen and pathology will be reported according to the AJCC Cancer Staging Manual, 6th Edition. Recorded on permanent section will be: tumor size, degree of differentiation (well, moderate, poor), lymph node status, and margin status.

5.4.3 Chemotherapy

Patients may receive adjuvant chemotherapy after surgery at the discretion of the treating investigator. Adjuvant chemotherapy is not considered part of protocol treatment. If there is no evidence of metastatic progression in the pre-operative and intra-operative assessment, then four additional months of therapy with the FOLFIRINOX regimen will be the recommended standard.

If adjuvant chemotherapy is administered, at minimum, administration of FOLFIRINOX therapy will be contingent on participant meeting original inclusion criteria (lab parameters and performance status). Physicians may opt to provide FOLFOX or FOLFIRI in the postoperative setting, with the full FOLFIRINOX regimen administered only when the patient can tolerate this therapy. If there is evidence of progression, patients will be withdrawn from the study and, as per NCCN guidelines, proceed to second-line therapy. Appropriate dose reductions and modifications can be made at the discretion of the treating physician.

5.5 General Concomitant Medication and Supportive Care Guidelines

Prophylactic administration of G-CSF (Neulasta) should be completed per institutional guidelines with each cycle of FOLFIRINOX at the discretion of the treating provider, due to the high rate of neutropenia typically experienced by patients receiving this regimen. G-CSF should be administered 24-48 hours after discontinuation of infusional 5-fluorouracil.

Participants should receive full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics, etc. when appropriate. Erythropoietin is allowed.

No other cytotoxic therapy or radiotherapy may be used during therapy.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

5.7 Duration of Follow Up

Study participants will be in active follow-up after completion of neoadjuvant treatment until 5 years post surgery, except in the case of documented progression, at which time they will be followed for survival only. Participants who do not undergo surgery will be followed for 5 years post completion of neoadjuvent treatment. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study and the date the participant was removed must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

When possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used including anti-emetics, anti-diarrheals, etc.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting.

6.1.1 FOLFIRINOX Regimen

Expected hematologic adverse events associated with the FOLFIRINOX regimen include neutropenia, febrile neutropenia, anemia, and thrombocytopenia.

Anticipated non-hematologic adverse events associated with the FOLFIRINOX regimen include fatigue, nausea, diarrhea, peripheral neuropathy, elevated ALT, vomiting, alopecia (grade 2) and infection without neutropenia.

6.1.2 5-FU

In addition to the above, 5-FU is also known to cause poor appetite, taste changes, stomatitis (usually 5-8 days after treatment initiation), loss of nails, hyperpigmentation, photosensitivity, maculopapular rash, palmar-plantar erythrodysesthesias (in many patients receiving continuous infusion), cerebral ataxia (rare), myocardial infarction, angina, asymptomatic S-T changes, excessive lacrimation and, rarely, tear duct stenosis.

6.1.3 Oxaliplatin

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. 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 region. 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 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 paresthesias, dysesthesias, and hypothesia. Abnormalities in momioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin. Various agents have been used to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, Mg+, Ca++). Calcium and magnesium infusions appear to be beneficial in preventing neurotoxicity. Generalized pain, cough and headache have been observed.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is moderately emetogenic), constipation 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, dysphagia) 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.

6.1.4 Irinotecan

Virtually all phase I and II studies of irinotecan have reported neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after irinotecan administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, weight loss, insomnia, headache, chills, skin rash, flatulence, flushing of the face during infusion and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of 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, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Occasionally, abnormalities of hepatic enzymes, or thrombocytopenia have been observed.

6.1.5 Radiation Therapy

The most common toxicities of radiation therapy are fatigue, nausea, abdominal pain, diarrhea, indigestion, vomiting, weight loss, lymphocytopenia, and anorexia. Other toxicities may include radiation fibrosis if surgery is delayed too long, skin redness and irritation, esophagitis, gastritis, pneumonitis, elevated liver function tests, skin damage, GI bleed and bowel perforation.

Much less common toxicities could include liver damage, kidney damage, and late secondary malignancies.

6.1.6 Paclitaxel

The most common toxicities of paclitaxel include myelosuppression, nausea, diarrhea, vomiting, abdominal pain, peripheral neuropathy, severe anaphylactic reactions, alopecia, fatigue, arthralgia, myalgia, infiltration (induration, tenderness, rarely ulceration), irritation to the injection site, mucositis.

6.1.7 Carboplatin

Myelosuppression is a common toxicity with carboplatin. Thrombocytopenia, neutropenia, leukopenia, and anemia are common but typically resolve by day 28 when carboplatin is given as a single agent.

Hypersensitivity to carboplatin has been reported in 2% of patients. Symptoms include rash, urticariaThe reactions can be managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Peripheral neuropathies have been observed in 4% of patients, with mild paresthesia being the most common. Nausea and vomiting are common but usually resolve within 24 hours and also respond to anti-emetics. Other gastrointestinal events include diarrhea and constipation. Pain, asthenia, and alopecia, taste changes, abnormal magnesium levels, infection and central neurotoxicityhave also been reported.

6.2 Dose Modifications for Toxicities

6.2.1 FOLFIRINOX Dose Modifications

The table below indicates potential dose levels for each of the agents for which dose modifications will be allowed. Dose adjustments of each agent may be made independently, based on the specific types of toxicities observed. Only those agents specified in the sections below should be dose-reduced.

Participants who require multiple dose reductions during a cycle for grade 2 toxicity may, at the discretion of the treating physician, begin the following cycle at one dose level higher than the current dose reduction. If dose reduction beyond dose level -3 is required for any agent, that agent will be discontinued.

Agent*	Oxaliplatin	5-FU Bolus	5-FU Infusion (per 46-48 hours)	Irinotecan
Initial Dose	85 mg/m2	400 mg/m2	2400 mg/m2	180 mg/m2
Level –1	65 mg/m2	320 mg/m2	1920 mg/m2	150 mg/m2
Level –2	50 mg/m2	270 mg/m2	1600 mg/m2	120 mg/m2
Level –3	40 mg/m2	230 mg/m2	1360 mg/m2	100 mg/m2

Leucovorin dose is always 400 mg/m2, IV, given prior to the infusion of 5-FU. If any infusion of 5-FU is to be skipped, leucovorin will also be skipped. Initial doses may be reduced, if necessary, at treating physician’s discretion.

If a patient has undergone biliary stent placement prior to enrollment, the following treatment guidelines will apply for Cycles 1 and 2. If ALT and AST are elevated at 2.5 x the upper limit of normal or higher at time of study enrollment, but demonstrate two consecutive down-trending values, the patient should begin treatment without Irinotecan, or with dose-reduced Irinotecan if clinically indicated. The agents 5-FU and Oxaliplatin may be given during Cycle 1 with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated above 2.0 mg/dl at time of enrollment, the patient may begin Cycle 1 with full dose 5-FU and Oxaliplatin, with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated between the upper limit of normal and 2.0 mg/dl at time of enrollment, the patient may receive full dose 5-FU and Oxaliplatin, with dose-reduced Irinotecan. Irinotecan may be increased to full dose in the first or second cycle if laboratory values permit.

6.2.1.1 Hematologic Toxicities

The following dose modifications are based on toxicity demonstrated during a mid-cycle visit and/or at the time of laboratory assessment for planned administration of the next cycle of therapy (for example on the planned day of administration of Cycle 2 Day 1 after completing the 14-day period constituting Cycle 1.)

Hematologic Toxicity on the Day of Treatment (D1)	**Action**	**Oxaliplatin**	**Irinotecan**	**5-FU Bolus (Leucovorin follows protocol for 5FU bolus)**	**5-FU Continuous Infusion**
Neutropenia G2 (ANC 1500-1000) – all patients should have Neulasta support per institutional guidelines	HOLD ALL THERAPY	Hold until ANC >=1500, resume without dose reduction	Hold until ANC >=1500, resume without dose reduction	Hold until ANC >=1500, resume @permanent DL-1	Hold until ANC >=1500, resume without dose reduction
Neutropenia G3-4, Febrile neutropenia (ANC 1000-500, <500)	HOLD ALL THERAPY, Supportive care and antibiotics per institutional guidelines	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved	Hold until ANC >=1500, resume @ permanent DL-2 level once resolved	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved
Thrombocytopenia (PLT <100K – 75K)	Treat with DR Oxaliplatin	Treat at permanent DL -1	No reduction	Treat at permanent DL-1	No reduction
Thrombocytopenia G2 (75K – 50K)	HOLD ALL THERAPY	Hold until resolved to >75K, resume at permanent DL-1	Hold until resolved to >75K, no reduction	Hold until resolved to >75K, No reduction	Hold until resolved to >75K, No reduction
Thrombocytopenia G3-4 (50K – 25K, <25K)	HOLD ALL THERAPY	Hold until resolved to >75K. Resume @ permanent DL-1 if resolved in 1 week, permanent DL -2 if >1 week	Hold until resolved to >75K. Resume @ permanent DL-1.	Hold until resolved to >75K Resume @ permanent DL-1.	Hold until resolved to >75K Resume @ permanent DL-1.

		to resolve			

6.2.1.2 Non-hematologic Toxicities

Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1.0 mg IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

Late diarrhea (e.g., developing more than 24 hours after irinotecan) should be managed with loperamide. The following dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle): For **grade 2 diarrhea**, reduce 5-FU and irinotecan one dose level for the next cycle, and for all cycles thereafter. Oxaliplatin is not dose reduced. For **grade 3 or 4 diarrhea**, eliminate bolus 5-FU and dose reduce 5-FU and irinotecan by one dose level for the next cycle and for all cycles thereafter.

The following dose modifications are based on the grade of mucositis seen for any day after Day 1 in any cycle. For **grade 2 mucositis**, reduce 5-FU one dose level for the remainder of the cycle and for all cycles thereafter. For **grade 3 and 4 mucositis**, eliminate bolus 5-FU for the next cycle and all cycles thereafter. Dose-reduce infusional 5-FU and irinotecan by one dose level for the next cycle and all cycles thereafter.

The following dose modifications are based on the grade of nausea and vomiting occurring during a cycle (i.e., after Day 1 in any cycle). For grade **3 or 4 nausea or vomiting** despite maximal antiemetic therapy, reduce all agents in the FOLFIRINOX regimen by one dose level for the next cycle and for all cycles thereafter.

Oxaliplatin may cause sensory neuropathies. Use this Scale for Sensory Neuropathies Associated with Oxaliplatin Symptoms:

Grade 1	Paresthesias/dysesthesias* of short duration that resolve and do not interfere with function.
Grade 2	Paresthesias/dysesthesias* interfering with function, but not in activities of daily living (ADL)
Grade 3	Paresthesias/dysesthesias* with pain or with functional impairment that also interfere with ADL.
Grade 4	Persistent paresthesias/dysesthesias* that are disabling or life threatening.
* May be cold induced	

For **grade 2 neurotoxicity** persisting between treatments, reduce oxaliplatin by one dose level for the next cycle and for all subsequent cycles. For **grade 3 neurotoxicity** that resolves to grade 2 between treatments, reduce oxaliplatin by one dose level for the next cycle and for all

subsequent cycles.

For **recurrent grade 3 neurotoxicity** resolving to grade 2 between treatments, reduce oxaliplatin by one additional dose level for the next cycle and for subsequent cycles. Oxaliplatin will not be reduced beyond level –3. If further dose reduction is required for neurotoxicity, oxaliplatin will be discontinued. Participants should continue to receive other protocol therapy.

For **grade 3 neurotoxicity** persisting between treatments, discontinue oxaliplatin. Participants should continue to receive other protocol therapy. For **grade 4 neurotoxicity**, discontinue oxaliplatin. Participants should continue to receive other protocol therapy.

For **pharyngo-laryngeal dysesthesia,** increase the duration of oxaliplatin infusion to 6 hours for all subsequent treatments.

Extravasation of oxaliplatin has been associated with necrosis. If extravasation is suspected, the infusion should be stopped and the drug administered at another site. Extravasation may be treated according to institutional guidelines.

For all other grade 3 non-hematologic toxicities, decrease each drug by one dose level for the next cycle.

For all other grade 4 non-hematologic toxicities, discontinue the FOLFIRINOX chemotherapy.

6.2.2 Radiation Therapy

Radiation therapy will be held for Grade 3 or 4 nausea that is not well-controlled with anti-emetic support, until nausea resolves to Grade 2 or less. It will then be resumed at same dose.

Radiation therapy will be held for ANC < 500 mcL or Platelets < 50,000 mcL. Resume radiation therapy when ANC > 500 and Platelets > 50,000.

6.2.3 Paclitaxel and Carboplatin

Dose reductions of paclitaxel and carboplatin are permanent.

Dose levels for paclitaxel are as follows:

Weekly Paclitaxel Dose	50 mg/m^2
Dose Level -1	40 mg/m^2
Dose Level -2	30 mg/m^2
Dose Level -3	20 mg/m^2

There will be no dose level reductions below a weekly dose of 20 mg/m^2

Dose levels for carboplatin are as follows:

Weekly Carboplatin Dose	AUC = 2
Dose Level -1	AUC = 1.5
Dose Level -2	AUC = 1.0
Dose Level -3	AUC = 0.5

There will be no dose level reductions below a weekly dose AUC = 0.5.

6.2.4 Hematologic Toxicities

The dose of paclitaxel and carboplatin will be modified according to blood counts within 72 hours of the day of treatment as shown in the table below.

Treatment Day Blood Counts			Modification
ANC		Platelet Count	
≥ 1,000 mcL	AND	> 75,000 mcL	Full dosage paclitaxel and carboplatin.
500-999 mcL	OR	50,000-75,000 mcL	Hold carboplatin and paclitaxel. Recheck CBC weekly. When ANC > 1,000 and Plt > 75,000, resume paclitaxel at 1 dose level reduction and carboplatin at 1 dose level reduction.
< 500 mcL	OR	< 50,000 mcL	Hold carboplatin, paclitaxel; Recheck CBC weekly. When ANC >1,000 and Plt > 75,000 resume paclitaxel and carboplatin and reduce both by 1 dose level.

Participants who experience 4 episodes of ANC < 500 or Platelets < 50, 000 may complete radiation but will not receive additional carboplatin or paclitaxel.

6.2.5 Non-hematologic Toxicities

Nonhematologic adverse events that require dose reduction of paclitaxel or carboplatin include treatment-related diarrhea, mucositis, esophagitis, gastritis, nausea/vomiting/dehydration despite adequate treatment with anti-emetic therapy, and treatment-related pulmonary toxicity. The dose of paclitaxel and carboplatin will be modified for these non-hematologic events as shown in the table below.

Toxicity	**Grade**	**Agent**	**Modification**

1st Episode Grade 3 or 4	≥ grade 3	Carboplatin Paclitaxel	Hold until ≤ grade 2; resume, dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level
2nd Episode	≥ grade 3	Carboplatin Paclitaxel	Hold until ≤ grade 2; resume dose, reducing carboplatin by 1 dose level and paclitaxel by 1 dose level
3rd Episode	≥ grade 3	Carboplatin Paclitaxel	Discontinue carboplatin and paclitaxel.
Paclitaxel infusion-related reaction	≥ grade 4	Paclitaxel	Discontinue paclitaxel. Carboplatin and radiation may be continued.
Carboplatin infusion-related reaction	≥ grade 4	Carboplatin	Discontinue carboplatin. Paclitaxel and radiation may be continued.

7. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

All serious adverse events (SAE) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form.

This includes events meeting the criteria outlined in Section 7.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Ted Hong, MD, PI
Tel. 617-726-6050
Fax. 617-726-3603
Tshong1@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

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.

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or

- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

For the purposes of this study, the following grade 4 toxicities are expected in the setting of dehydration, diarrhea or reduced oral intake and will not require expedited serious adverse event reporting: low magnesium, low potassium, and low phosphorus. The following grade 4 toxicities are expected and will not require expedited serious adverse event reporting: low white blood cell count, neutropenia, and low lymphocyte count.

7.1.3 Expectedness

Adverse events can be expected or unexpected

7.1.3.1 Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk. Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

7.1.3.2 Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

7.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

7.2 Expedited Serious Adverse Event Reporting

Investigators **must** report to the overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must **also** be reported in routine study data submissions. All Adverse Events that occur through 30 days after the last dose of study drug will be recorded in the protocol-specific case report forms.

7.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this study can be found in Section 6.1.

8.1 5-Flurouracil (5-FU, fluorouracil, “Adrucil”)

Please refer to the package insert for complete product information.

8.1.1 Form

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

8.1.2 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.

8.1.3 Compatibility

5-FU should not be mixed in the same solution with most parenteral antiemetics.

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.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of 5-FU in a self-contained and protective environment.

8.1.5 Availability

5-FU is commercially available.

8.1.6 Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath. Bolus injections are prepared using undiluted drug. 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 antiemetics.

8.2 Oxaliplatin (Eloxatin)

Full information regarding oxaliplatin is available on the package insert.

8.2.1 Form

Oxaliplatin is an aqueous solution in vials containing 50mg in 100mg at a concentration of 5mg/mL.

8.2.2 Storage and Stability

Vials of Oxaliplatin do not contain any preservatives and they are intended for single use. 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.

8.2.3 Compatibility

Oxaplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line.

8.2.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of Oxaliplatin in a self-contained and protective environment.

8.2.5 Availability

Oxaliplatin is commercially available.

8.2.6 Preparation

The calculated dose of oxaliplatin should be diluted for infusion with 250mL to 500mL 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.

8.3 Irinotecan (CPT-11, Camptosar)

Full information regarding Irinotecan is available on the package insert.

8.3.1 Form

Irinotecan is available as a 20 mg/mL solution in 2mL and 5mL vials.

8.3.2 Storage and Stability

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

8.3.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal Irinotecan in a self-contained and protective environment.

8.3.4 Availability

Irinotecan is commercially available.

8.3.5 Preparation

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

8.4 Leucovorin

Please refer to the package insert for complete Leucovorin product information.

8.4.1 Form

Leucovorin is available in 50mg, 100mg, 350mg vials for reconstitution.

8.4.2 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with Bacteriostatic Water for Injection (BWI) are stable for at least 7 days at room temperature.

8.4.3 Availability

Leucovorin is commercially available.

8.4.4 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 Rungers solution.

8.5 Paclitaxel

Refer to the package insert for additional information.

8.5.1 Form

Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation.

A sterile solution concentrate, 6 mg/ml in 5 ml vials *(*30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use.

8.5.2 Storage and Stability

Paclitaxel vials should be stored between 20°-25°C (68°-77°F). Properly prepared solutions (0.3 – 1.2 mg/mL) are physically and chemically stable for 27 hours at ambient temperature (27^0 C).

8.5.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of Paclitaxel in a self-contained and protective environment.

8.5.4 Availability

Paclitaxel is commercially available.

8.5.5 Preparation

Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D_5W, USP, in glass or polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the intravenous fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

8.6 Carboplatin

Refer to the package insert for additional information.

8.6.1 Form

Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.

8.6.2 Storage and Stability

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30˚C or 59-86˚F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

8.6.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of Carboplatin in a self-contained and protective environment.

8.6.4 Availability

Carboplatin is commercially available.

8.6.5 Preparation

When available, prediluted vials of carboplatin should be utilized. Otherwise, the preparation of carboplatin should proceed as described below:

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL:

Vial size	Diluent volume
50 mg	5mL
150 mg	15 mL
450 mg	45 mL

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Blood Based Correlatives

9.1.1 Rationale

This study will incorporate blood based assessments of circulating tumor DNA (ctDNA) and plasma protein and circulating cell biomarkers. These analyses will provide systemic measures of tumor response, mechanism of action, and will serve as a potential predictor of residual disease after surgery and increased likelihood of recurrence.

9.1.2 Procedures

Peripheral blood will be collected serially throughout study treatment as specified in the study calendar. 30mL of blood will be collected at each time point into two 10mL Streck cfDNA and 1

EDTA fixative tubes.

The two 10mL Streck cfDNA tubes will be centrifuged to separate cell pellet from plasma, and each component will be aliquoted and frozen for subsequent analysis. Blood samples in Streck cfDNA tubes can be shipped at room temperature (within 5 days of draw) to:

Corcoran Laboratory
Massachusetts General Hospital Cancer Center
149 13th St, Room 7330
Charlestown, MA 02129

The EDTA tube with the blood sample will be shipped in wet ice within 2 hours of drawing for further processing at Steele Laboratories at MGH. The tube of blood should be placed in a sealable container and placed in a box with the necessary information. The box should be marked Biohazard.

The blood will be delivered to:

Dr. Dan Duda
Attn: Mrs. Anna Khachatryan/Mrs. Julia Kahn
Steele Laboratories
Cox-734, 100 Blossom Street
Tel: 617-724-1352/3
Fax: 617-724-5841
Pager: 14082

Samples to measure circulating biomarkers will be collected at the following time points:

- Pretreatment, prior to the start of FOLFIRINOX therapy
- Cycle 1, Day 8 of FOLFIRINOX therapy
- Restaging after Cycle 4 of FOLFIRINOX therapy
- Restaging after Cycle 8 of FOLFIRINOX therapy
- After chemoradiation OR pre-operatively
- One month after completion of therapy (surgery or neoadjuvent treatment)
- Within two weeks of disease progression (radiologic)

9.1.3 Analyses

Serial blood draws will be analyzed as follows:

Serial monitoring of tumor burden and residual disease by circulating tumor DNA analysis.

Cell free DNA will be isolated from serial plasma aliquots. For each patient, one to two specific clonal mutations identified by exome sequencing of tumor tissue (above) will be used to track circulating tumor DNA (ctDNA) levels throughout treatment using custom mutation-specific droplet digital PCR probes as a personalized measure of tumor burden. This method will allow accurate monitoring of the response of overall tumor burden to treatment and can be correlated

with radiologic endpoints. The presence of detectable ctDNA one month after surgery (or at subsequent time points) will be evaluated as a means of detecting minimal residual disease post-operatively and will be correlated with recurrence.

In addition, based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating proteins and circulating immune cells throughout the treatment course to explore potential associations between the changes in these biomarkers and resistance to treatment and survival outcomes. Plasma will be separated from the cellular fraction, aliquoted and stored at <–70ºC until the end of the study. At that point, we will evaluate several cytokines using multiplex protein array (Meso-Scale Discovery, Inc.) and single analyte ELISA kits (RnD Systems) using the CLIA-certified Clinical Correlative Studies Core of the Steele Laboratories. Circulating immune cells will be enumerated and phenotyped by flow cytometric analysis in fresh samples, using the same Core, and using published protocols.

9.1.4 Potential risks to patients

These studies will involve peripheral blood draw only. Peripheral blood draws do involve a small risk of patient discomfort, bruising, or puncture site infection, but these risks are minimal. Furthermore, correlative blood draws will be performed at the same time as patients are having routine clinical blood laboratory assessments during study treatment, and thus will not involve any additional peripheral venipuncture.

9.2 Correlative Studies: SNaPshot analysis

Mutational analysis will be performed by tumor SNaPSHOT for the mutations listed in section 2.4. Paraffin-embedded block or ten unstained slides will be used from the untreated biopsy specimen obtained at the time of upper endoscopy or initial diagnostic biopsy. Analysis will be performed as described by Dias-Santagata at the Translational Research Laboratory at MGH.

9.3 Patient-reported outcomes

QOL (EORTC QLQ-C30, version 3.0 and the EORTC STO22), symptoms (ESAS-r), mood (HADS), and nutrition (MNA) will be assessed at time of informed consent prior to neoadjuvant therapy; day 1 of cycles 2, 4, 6, 8 of neoadjuvant chemotherapy; on day 1 and every 2 weeks during chemoradiotherapy and during post-op follow up.

9.4 Health care utilization

Hospital admissions, emergency department (ED) visits, intensive care use and palliative care consultation will be monitored and recorded for each patient throughout the study.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans must be done ≤ 6 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of

the next cycle of therapy.

All pre-study assessments must be performed prior to administration of any study medication, unless otherwise noted. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted. All follow up assessments may be performed +/- 21 days of the protocol-specified date.

	Baseline	Day 1 of each cycle of FOLFIRINOX	Restaging	During ChemoRT	Post-op F/U (11)	Progression
Informed consent	X					
History	X					
Physical Examination	X	X	X	X (8)	X	X
Vital Signs and performance status	X			X (8)	X	
Height/Weight	X			X (9)		
Toxicity Assessment		X	X	X (8)	X	X
CBC/plts/diff	X (2)	X	X	X (10)	X	X
Serum chemistries (1)	X (2)	X	X	X (10)	X	X
CEA/CA19-9	X (2)	X (15)	X	X (15)	X	
Creatinine clearance calculation (Cockroft Gault)	X	X (6)		X (10)		
Pregnancy test (3)	X (2)					
CT (or MRI) of chest, abdomen, pelvis	X		X (7)		X	X
Tumor SNaPshot (4) OPTIONAL	X				X	
Correlative Studies (5) OPTIONAL	X	X	X	X	X	X
Patient-reported outcomes (EORTC, ESAS, HADS, MNA)	X	X (12)		X (13)	X (14)	X

(1) Serum chemistries include: Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bili, Alk Phos
(2) Pre-study laboratories are to be obtained with 14 days of study entry.
(3) For women of child-bearing potential
(4) Tumor SNaPshot will be done once for each participant; either on the pre-treatment biopsy specimen (if available) or on the resected tumor specimen.
(5) Peripheral blood for correlative studies will be obtained with clinical labs at pretreatment, Cycle 1 Day 8 of FOLFIRINOX, at restaging visits, after chemoradiation therapy (pre-operatively), 1 month after completion of therapy (surgery or neoadjuvent treatment) and within two weeks of radiographic progression (these blood draws are optional).
(6) Creatinine clearance to be done on Day 1 of Cycles 1, 3, 5 and 7 of FOLFIRINOX.
(7) CT/MRI to be done at baseline, after first week of Cycle 4 of FOLFIRINOX, after the first week of the last cycle of FOLFIRINOX, 3-4 weeks after chemoradiation.
(8) To be done weekly during ChemoRT
(9) Height and weight should be measured at the start of ChemoRT.
(10) On Days 1, 8 and 15 of ChemoRT.
(11) Post-op follow up schedule is as follows. For years 1 and 2 follow up will be visit and labs at least every 3 months, scans at least every 6 months, For year 3, visit and labs will be at least every 3 months and scans will be at least every 12 months. For years 4 and 5 visit and labs will be at least every 6 months and scans will be at least every 12 months. For patients with R0, R1 and R2 resections, the first post-op CT scan, visit and labs are 3-8 weeks postoperatively. All follow up assessments may be performed +/-21 days of the protocol-specified date. Participants who do not undergo surgery will be followed per the schedule above for 5 years post completion of neoadjuvant treatment
(12) Patient-reported outcomes will be assessed on day 1 of cycles 2, 4, 6, and 8.
(13) Patient-reported outcomes will be assessed on day 1 and every 2 weeks during chemoradiotherapy.
(14) Patient-reported outcomes will be assessed per the post-op follow schedule outlined above, 11.
(15) Tumor markers (CEA and CA19-9) to be assessed on Day 1 of Cycles 2, 4, 6, and 8 of FOLFIRINOX; Day 1 and Day 29 of ChemoRT; and 1 month after completion of therapy (surgery or neoadjuvant treatment).

11. MEASUREMENT OF EFFECT

11.1 Completion

The primary endpoint is the completion of induction chemotherapy with FOLFIRINOX in combination with chemoradiation.

11.2 Evaluation of Response

11.2.1 Clinical Response

For the purposes of this study, participants should be re-evaluated for response as outlined in

section 10.

Response to therapy and/or progression after induction chemotherapy with FOLFIRINOX and after chemoradiation will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) committee (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. In the event that CT staging cannot be utilized, restaging MRI will be the substitute modality.

Objective clinical response is defined as a best overall response of CR or PR according to RECIST v1.1. The best overall response is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment until progression (per RECIST v1.1), or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or the discontinuation from the study, whichever occurs first. The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

11.2.2 Pathological Response

All patients will undergo a full pathological review of their surgical specimen according to the AJCC Staging Classification, 6th. Initial gross evaluation and identification of resection margins will be performed jointly by the surgeon and the pathologist. Pathological complete response will be defined as the absence of any viable tumor cells within the pathologic specimen.

11.2.3 Progression-free Survival

Progression-free survival (PFS) is defined as the time from the date of first dosing to the first documentation of radiographic disease progression (per RECIST v1.1) or death due to any cause, whichever occurs first. Subjects who are alive with no documented progressive disease by the data cutoff date for PFS analysis will be censored at the date of their last evaluable disease assessment.

11.2.4 Overall Survival

Overall survival (OS) is defined as the time from the date of first dosing until death due to any cause. If there is no death reported for a subject by the data cut-off date for overall survival analysis, OS will be censored at the last known alive date.

11.3 Toxicity

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Acute and late toxicities will be scored using Common Toxicity Criteria (CTCAE) version 4.03.

Toxicities will be noted and recorded in protocol-specific case reports from the time of first dose of protocol therapy until 5 years after the end of protocol therapy.

11.4 Definitions

11.4.1 Evaluable for Target Disease response

Only those participants who have measurable disease present at baseline, have received at least four cycles of FOLFIRINOX, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.4.2 Evaluable Non-Target Disease Response.

Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.4.3 Measurable disease

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 (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm).

11.4.4 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

11.4.5 Target lesion

The primary tumor is the target lesion.

11.4.6 Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5

target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.5 Method for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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.

CT scan. The RECIST guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. CT scans should be performed with contiguous cuts in slice thickness of 5mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scan. Magnetic resonance imaging of the chest and abdomen is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations.

11.5.1 Evaluation of Response by RECIST v. 1.1

11.5.1.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. 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 the diameters of target lesions, taking as reference the baseline sum diameters.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.5.1.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor

marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. Unequivocal progression of existing non-target lesions will be defined as the 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. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.5.1.3 Appearance of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.5.1.4 Evaluation of Overall Response

The best overall response is the best 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). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Overall Response at a Single Timepoint by RECIST V1.1

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
Complete response	Complete response	No	Complete response

No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Non-complete response/ non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable[b]	No	Partial response
.Stable disease	Non-progressive disease and not evaluable[b]	No	Stable disease
.Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response/ non-progressive disease	No	Non complete response/non-progressive disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline
[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 Adverse Events Reporting Requirements.

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint of the pilot study is completion of induction chemotherapy comprising 8 cycles of FOLFIRINOX followed by 5 weeks of chemoradiation. A total of 25 patients with locally advanced gastric or gastroesophageal junction cancer will be enrolled and treated. If at least 18 of them were to complete the treatment plan specified in the protocol (**5.2-5.3**), it will be considered as feasible in the management of resectable and borderline resectable tumors. The decision rule is associated with 89% power for declaring success if FOLFIRINOX in combination with chemoradiation were associated with an underlying completion rate of 80%. In contrast, the probability of type 1 error is only 15% if 60% of patients were truly able to complete the intended therapy.

13.2 Sample Size, Accrual Rate and Study Duration

The accrual duration is projected to be about 2 years to enroll a total of 25 patients with locally advanced gastric or gastroesophageal junction cancer. The follow-up schedule will extend up to 5 years post-operatively for late effects, progression, survival and patient-reported outcomes.

13.3 Stratification Factors

No stratification of patient enrollment.

13.4 Interim Monitoring Plan

Not applicable.

13.5 Analysis of Primary Endpoint

The completion rate of chemotherapy in combination with chemoradiation will be estimated with a 95% confidence interval of maximal width +/-20% based on the exact binomial distribution.

13.6 Analysis of Secondary Endpoints

- Toxicity associated with neoadjuvant FOLFIRINOX and chemoradiation will be summarized by category and grade according to the CTCAE version 4.0 (**7.1**).
- Clinical response will be assessed using RECIST criteria (**11.2.1**) after 4 and 8 cycles of FOLFIRINOX as well as 3-4 weeks following chemoradiation. The rate of objective clinical response to induction FOLFIRINOX and chemoradiation will be reported as the proportion of eligible patients starting protocol therapy who achieve a complete or partial response as the best overall response.
- Pathologic response will determined by a full pathological review of the surgical specimen according to the AJCC classification (**11.2.2**). The rate of pathologic complete response at surgery following FOLFIRINOX and chemoradiation will be reported as the proportion of eligible patients who start protocol therapy. The denominator will include patients who are not resected due to discontinuation of chemotherapy or chemoradiation, disease progression or early death.
- Progression-free survival (PFS) is defined as the duration from the first date of protocol therapy to the earliest date of disease progression per RECIST criteria or death due to any cause. PFS time will be censored at the date of last follow-up for patients still alive with no documentation of progressive disease. The PFS rate will be estimated using the Kaplan-Meier method with 95% confidence intervals based on the complementary log-log transformation.
- Overall survival (OS) is defined as the duration from the first date of protocol therapy to the date of death due to any cause and will be censored at the date of last follow-up for patients still alive. The OS rate will be estimated using the Kaplan-Meier method with 95% confidence intervals based on the complementary log-log transformation
- To investigate the relationship between tissue, cell and plasma biomarkers and response rate in patients with gastric and GE junction cancers treated with neoadjuvant FOLFIRINOX and chemoradiation.
- Mutational analysis will be available from the routine testing of patients with GI patients that includes KRAS and the majority of activating mutations. Association of specific genotype and clinical response to chemotherapy and chemoradiation will be analyzed using Fisher's exact test.
- Peripheral blood will be collected at serial timepoints **(9.1.3**) between baseline and one month post-operatively and also at disease progression. ctDNA levels of one or two specific clonal mutations identified by exome sequencing of tumor tissue will be used as a personalized measure of tumor burden and correlated with clinical response. The detectable level of post-operative ctDNA will be evaluated as a measure of minimal residual disease to determine the association with progression following surgery. Plasma proteins, ctyokines and circulating immune cells at baseline as well as changes during and after treatment will be analyzed as biomarkers of response and resistance. ctDNA and

biomarker data will be analyzed primarily using standard methods for graphical and descriptive statistics to identify potential trends and associations. Analyses will be exploratory and hypothesis-generating due to the optional biospecimen collection.

- Patient-reported outcomes will be reported using descriptive statistics to summarize QOL (EORTC QLQ-C30 and STO22), symptom burden (ESAS-r), mood (HADS), and nutrition (MNA) at each timepoint. Changes in QOL and symptom burden during neoadjuvant therapy may be analyzed by repeated measures ANOVA. The HADS subscales will be used with a cutoff of 7 to estimate the proportion of patients with depressive and anxiety symptoms at each timepoint. The MNA tool to estimate the proportion of patients with abnormal nutritional status. The dichotomous outcomes may be analyzed by McNemar's test to assess changes between paired timepoints.
- Health care utilization will be assessed using descriptive statistics to summarize hospital admissions, intensive care unit stays, emergency department visits and palliative care use during the course of protocol participation. Patient subgroups may be compared using standard for two-sample methods, such as the Wilcoxon rank-sum test and Fisher's exact test.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All enrolled patients who receive any protocol therapy will be evaluated for toxicity from the time the first dose is administered.

13.7.2 Evaluation of the Primary Endpoint

All enrolled patients who receive any protocol therapy will be evaluable for analysis of the completion rate, including those who do not proceed to chemoradiation due to early progression or toxicity.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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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.