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STUDY TITLE: A Phase II Trial of modified FOLFOX-6 Induction Chemotherapy Followed by Esophagectomy and Post-operative Response Based Concurrent Chemoradiotherapy in Patients with Locoregionally Advanced Adenocarcinoma of the Esophagus, Gastro-esophageal Junction, and Gastric Cardia.

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SPONSOR:
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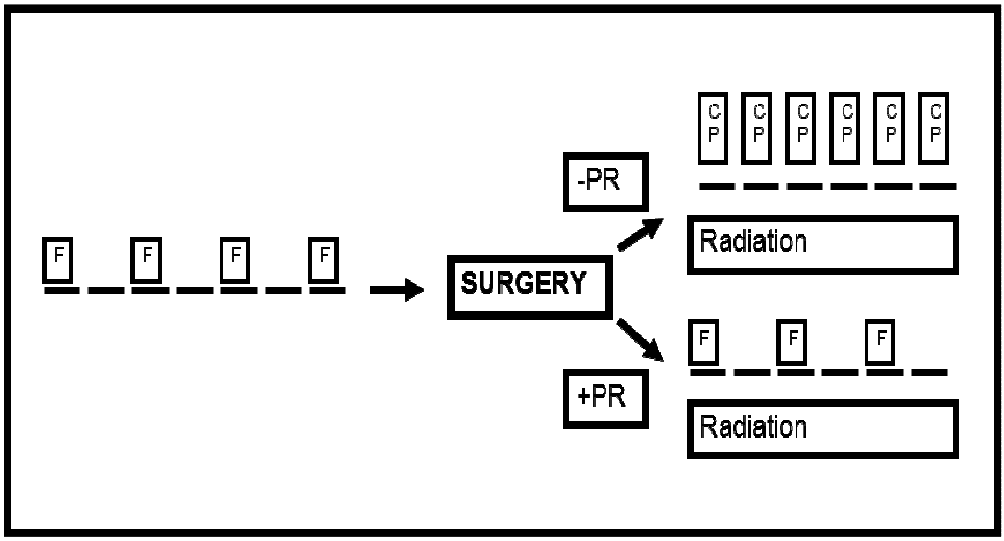
SUPPORT:
Institutional research funding

CHEMOTHERAPY:
Oxaliplatin
5-Flourouracil
Leucovorin
Carboplatin
Paclitaxel

**SCHEMA**
This is a phase II trial in which all patients will receive 4 cycles of induction chemotherapy with modified FOLFOX 6 (mFOLFOX6) followed by surgical resection. Patients who achieve a positive pathologic response (+PR), defined as less than or equal to 50% viable tumor cells remaining in the surgical specimen, will then receive postoperative chemo-radiotherapy with the mFOLFOX6 regimen. Patients who fail to achieve an adequate pathologic response, referred to as a negative pathologic response (-PR) and defined as greater than 50% viable tumor cells remaining in the surgical specimen, will receive postoperative chemo-radiotherapy with weekly carboplatin and paclitaxel. Patients who develop metastatic disease prior to surgery will be removed from the protocol and treated at the discretion of the primary oncologist. Patients who have locoregional disease only after induction therapy but do not undergo surgery should receive chemoradiotherapy with carboplatin and paclitaxel if medically appropriate as determined by the primary oncologist.




**F** = Modified FOLFOX 6, **C** = Carboplatin, **P** = Paclitaxel, **PR** = pathologic response

**Pre-treatment evaluation**

All required pre-treatment investigations will be completed within 6 weeks of the initiation of therapy (day 1, cycle 1).

**mFOLFOX6**
**Oxaliplatin** 85 mg/m2 over 2 hours on day 1
**Leucovorin** 400 mg/m2 over 2 hours administered simultaneously with oxaliplatin on day 1. If drug availability is limited, may administer leucovorin 100mg total dose or substitute levo-leucovorin at 200mg/m2.
**5-fluorouracil** 400 mg/m2 IV push over 2-4 minutes on day one immediately after completion of leucovorin.
**5-fluorouracil** 2400 mg/m2 continuous IV infusion over 44 hours (window 42-48 hours) days 1-3.
Regimen administered every 14 days

**Pre-operative evaluation & Surgery**
All patients will be evaluated and restaged approximately 3-4 weeks from the completion of induction therapy. Surgery will be scheduled for 1-2 weeks later (See section 6.0 for complete details).

**Pathologic response**
A positive pathologic response (+PR) will be defined as ≤ 50% residual tumor cells remaining relative to residual mucin pools and scarring. A negative pathologic response (-PR) will be defined as >50% residual tumor cells remaining relative to residual mucin pools and scarring (see text for full pathologic response assessment).

**Adjuvant chemoradiotherapy**
Post-operative chemoradiotherapy will start between 6-12 weeks from the date of surgery. Patients with a pathologic response will receive mFOLFOX6 chemotherapy concurrent with radiotherapy. Patients who do not achieve a pathologic response will receive carboplatin and paclitaxel concurrent with radiotherapy. Patients who have locoregional disease only after induction therapy but do not undergo surgery should receive chemoradiotherapy with carboplatin and paclitaxel if medically appropriate as determined by the primary oncologist.

**Adjuvant Carboplatin / Paclitaxel**
**Paclitaxel =** 50 mg/m2 IV over 1 hour on days 1, 8, 15, 22, 29, and 36.
**Carboplatin** = (AUC = 2) IV over 30 minutes on days 1, 8, 15, 22, 29, and 36.
Chemotherapy will be given only during radiotherapy.

**Adjuvant mFOLFOX6**
Refer to above for regimen. Administered every 2 weeks for 3 cycles concurrent with radiotherapy on days 1, 15, and 29.

**Adjuvant Radiotherapy**
50.4 Gy/1.8 Gy per fraction/ 28 days

**Note:** The treatment schema above is an outline for therapy. Please refer to Treatment Plan and Dose Delays / Dose Modification, in sections 6 and 7 respectively, for details regarding therapy management.

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## 1.0 INTRODUCTION

1.1 Locoregionally advanced adenocarcinoma of the distal esophagus, gastroesophageal junction, and gastric cardia.

The incidence of adenocarcinoma (ACA) of the esophagus (E) and gastroesophageal junction (GEJ) has increased dramatically over the last four decades and is now the predominant histology of esophageal cancer. While there are several known risk factors for this disease, no effective screening method has been established. Most patients present with solid dysphagia which is associated with locoregionally advanced disease. The outcomes for these patients are relatively poor. Surgery alone cures a minority of patients, with 5 year overall survival rates between 10 and 40%.

Various perioperative therapies have been employed in an attempt to improve upon surgical outcomes. A current standard of care for this disease is preoperative chemoradiotherapy followed by surgical resection. Van Hagen et al. reported results from a randomized phase III study in 2012 comparing preoperative chemoradiotherapy to surgery alone (1). In this trial, patients randomized to chemoradiotherapy received 41Gy with concurrent weekly carboplatin and paclitaxel. Preoperative therapy was associated with improved overall survival (5yr OS 47% v 34%, p=0.003). Several other studies over the past 20 years have demonstrated similar results (2,3). Despite the demonstrated survival advantage with this treatment schedule, most patients with locally advanced disease develop distant metastasis and subsequently die. This pattern of failure suggests that further incorporation of an effective systemic therapy could improve outcomes.

Several trials have demonstrated a survival benefit from pre-operative chemotherapy alone for patients with ACA of the E/GEJ. Bancewicz et al. reported results from a randomized phase III trial comparing surgery alone to chemotherapy followed by surgery in patients with esophageal cancer (4). A total of 802 patients were included in this study. Patients randomized to chemotherapy received 2 cycles of cisplatin and 5FU.

Most patients had adenocarcinoma histology. Patients receiving pre-operative chemotherapy had superior overall survival (HR 0.79, p=0.004). Similar results were demonstrated by Ychou et al (5). In this study, patients with ACA of the E and GEJ were randomized to receive 6 cycles of perioperative cisplatin and 5FU or surgery alone. Survival again favored the chemotherapy arm (5yr OS 43% v 34%, HR 0.79, p=0.02).

However, not all studies investigating perioperative chemotherapy have demonstrated a survival benefit in this patient population. Kelsen et al reported results from a randomized phase III trial in which 444 patients with carcinoma of the E/GEJ received either surgery alone or 5 cycles of perioperative chemotherapy employing cisplatin and 5FU (6). Approximately 50% of patients had adenocarcinoma histology. In this study, there was no significant difference in survival outcomes between the two treatment arms.

Postoperative chemoradiotherapy has also been employed in the management of patients with tumors of the GC and GEJ. MacDonald et al. reported results from a large randomized study comparing adjuvant 5FU based chemoradiotherapy to surgery alone in 556 patients with gastric and GEJ ACA (7). Adjuvant chemoradiotherapy was associated with improved survival (5 yr OS 50% v 41%, p= 0.005). This study established adjuvant chemoradiotherapy as the standard of care for patients with resected gastric cancer.

## 1.2 Rationale

We recently completed a single center phase II trial which incorporated two of these treatment paradigms: pre-operative chemotherapy and adjuvant chemoradiotherapy. Patients with ACA of the E/GEJ received induction chemotherapy followed by surgery and post- operative chemoradiotherapy. Induction chemotherapy consisted of three cycles of epirubicin, oxaliplatin, and 5-flourouracil (EOF). After surgery, patients received 50-55Gy in 1.8-2.0 daily fractions with concurrent administration of infusional cisplatin and 5-floururacil during weeks one and four.

This therapy schedule was relatively well tolerated. Sixty patients were enrolled in this trial. Fifty four patients (90%) underwent resection and 48 patients (80%) completed adjuvant chemoradiotherapy. One patient died during induction therapy and 2 patients died of postoperative complications. Unplanned hospitalization occurred in 19% of patients during induction therapy and 18% of patients during adjuvant treatment. The Kaplan-Meier 3 year projected locoregional control (LRC) was 84%, distant metastatic control (DMC) was 44%, relapse free survival (RFS) was 39%, and overall survival (OS) was 42%. DMC, RFS, and OS were strongly and inversely associated with the amount of remaining viable tumor cells at the time of surgical resection. These outcomes are comparable to other tri-modality regimens.

Building on this experience, we now propose to improve upon these outcomes and reduce toxicity by replacing EOF with the modified FOLFOX6 regimen and by administering adjuvant chemoradiotherapy employing a pathologic response adapted approach.

### 1.2.1 Induction mFOLFOX6

Systemic chemotherapy is often employed for palliation of metastatic gastroesophageal cancer. Several cytotoxic agents are available in this disease, of which platinum compounds, the antimetabolite 5-flourouracil, and the taxanes are the most active. Combination chemotherapy is frequently administered given greater response rates and potentially greater overall survival in the metastatic setting. Regimens incorporating 3 drugs are now commonly employed, of which the combination regimen of epirubicin, cisplatin, and continuous infusion 5FU (ECF) is an example. In the perioperative setting, both ECF and CF (Cisplatin / 5FU) have improved survival outcomes for patients with gastroesophageal cancer compared to surgery alone (5,8).

The FOLFOX chemotherapy regimen was initially designed for use in patients with metastatic colorectal cancer. However, in addition to CRC, this regimen is now broadly used to palliate patients with several metastatic gastrointestinal adenocarcinomas, including cancers of pancreatic, biliary and gastroesophageal origin. This regimen consists of oxaliplatin in combination with leucovorin modulated bolus and short term infusional 5FU. Several permutations of this regimen exist, for which the modified FOLFOX6 regimen is the most commonly utilized.

Oxaliplatin has emerged as the preferred platinum agent for use in combination chemotherapy for palliation of metastatic gastroesophageal cancer. In 2011, Montagnani et al. reported the results of a systematic review and meta-analysis comparing cisplatin and oxaliplatin in patients with metastatic or unresectable ACA of the stomach or GEJ (9). Oxaliplatin regimens were associated with improved PFS and OS compared to cisplatin containing regimens (HR PFS 0.88, p=0.02. HR OS 0.88, p=0.04). There did not appear to be any difference in response rates. With the exception of peripheral neuropathy, oxaliplatin was generally found to be less toxic. It was also well tolerated among patients over age 65, especially when administered in a biweekly fashion with concurrent 5FU.

Furthermore, the FOLFOX regimen appears to be as active as three drug combinations like ECF. In 2010, Enzinger et al. reported in abstract form the results of CALGB 80403 (10). This was a randomized phase II trial comparing FOLFOX, irinotecan / cisplatin, and ECF. Each of the various chemotherapy backbones was combined cetuximab. A total of 245 patients enrolled. Both FOLFOX and ECF appeared comparable, whereas the combination of cisplatin and irinotecan was less effective. FOLFOX and ECF both had response rates > 40% (RR ECF 58% v FOLFOX 51%) and similar PFS and median OS [PFS (ECF) 5.6 v (FOLFOX) 5.7 months, median OS (ECF) 10 v (FOLFOX) 10 months). FOLFOX was better tolerated and required less dose modifications (p=0.0009).

Despite several trials testing agents with activity in the metastatic setting, only the combination of oxaliplatin and 5FU (FOLFOX) has demonstrated improved survival outcomes compared to 5FU alone in the adjuvant treatment of colon cancer (11). This is especially pertinent given the recently reported outcomes of CALGB 80101 (12). In this study, presented in abstract form, patients with resected gastric and GEJ ACA were randomized to adjuvant therapy with either bolus leucovorin modulated 5FU before and

after CRT with continuous IV infusion 5FU (arm A) or ECF chemotherapy before and after CRT (arm B). A total of 546 patients were enrolled. Adjuvant therapy with ECF was not associated with improved median OS or DFS [median OS (arm A) 37 v (arm B) 38 months, p=0.8, median DFS (arm A) 30 v (arm B) 28 months]. The 3 year OS was 50% in arm A as opposed to 52% in arm B. Therefore, despite being more active in the metastatic setting, ECF chemotherapy does not appear to be more effective than 5FU alone in the adjuvant setting for GEJ ACA.

These data provide the rationale to investigate the incorporation of the FOLFOX regimen into the perioperative management of gastroesophageal cancer.

### 1.2.2 Pathologic response adapted chemoradiotherapy

Several trials investigating preoperative concurrent chemoradiotherapy in esophageal cancer have demonstrated an association between the pathologic response to therapy and overall survival (1,2,3). We have demonstrated a similar association with the use of preoperative chemotherapy. The percentage of remaining viable cancer cells relative to surrounding fibrosis and acellular mucin pools was inversely related to distant metastatic control, disease free survival, and overall survival in patients receiving induction therapy with EOF followed by surgery and postoperative chemoradiotherapy with cisplatin and 5FU. Patients who demonstrated a robust treatment effect achieved an estimated 3 year overall survival >60%. However, the outcomes for patients without evidence for a pathologic treatment effect were accordingly quite poor. It is this later group of patients for which introduction of an alternative chemotherapy regimen in the adjuvant setting may improve outcomes.

The Taxanes are di-terpene cytotoxic agents produced by plants of the genus Taxus. Taxanes stabilize microtubules thereby impairing normal mitotic spindle function ultimately resulting in chromosomal breakage and inhibition of cell division (13). Commonly employed Taxanes include paclitaxel and docetaxel. These agents have broad therapeutic utility. Taxanes are active both as single agents and as components of combination chemotherapy regimens in gastroesophageal cancer. Docetaxel is also superior to best supportive care in patients with metastatic gastric cancer who have progressed on a platinum / 5FU regimen (14).

The combination of carboplatin and paclitaxel has been administered concurrently with radiotherapy for various diseases including lung cancer. The safety of this regimen has been well demonstrated. The previously described CROSS trial, reported in 2012 by Van Hagen et al., has established this combination chemotherapy regimen as a standard of care in the pre-operative treatment of patients with LRA ACA of the E/GEJ (1). We plan on employing this regimen in the adjuvant setting with concurrent radiotherapy in an attempt to salvage patients who have failed to achieve an adequate pathologic response to induction therapy with the mFOLFOX6 regimen.

Accordingly, patients who have achieved a pathologic response will continue on FOLFOX in the post-operative setting. Conroy et al. reported results of a randomized

phase II study in 2010 comparing CRT with cisplatin and 5FU to the same radiotherapy administered with the FOLFOX4 regimen (15). Patients in this trial were either unresectable or medically inoperable. A total of 97 patients enrolled. The complete endoscopic response rate favored FOLFOX4 (45% v 24%) as did median TTP and OS [(TTP) 15 months v 9 months and (OS) 22 months v 15 months respectively], but in this relatively small phase II trial, none of these results reached statistical significance. Dose modifications were less common in the FOLFOX arm. There was one treatment related death in the FOLFOX arm compared to 4 in the cisplatin / 5FU arm. Neurotoxicity was more common with FOLFOX (24 v 4%).

Conroy et al. later reported results from a subsequent randomized phase III trial again comparing chemoradiotherapy with a FOLFOX regimen to conventional cisplatin and 5FU (16). Eligibility required locally advanced esophageal cancer for which patients either refused surgery or were unresectable / medically inoperable. In this study, the rates of grade 3 and grade 4 toxicity as well as treatment related death were similar in both treatment arms. Overall survival and progression free survival were also similar [Median OS 20.2 months (FOLFOX) v 17.5 months (Cisplatin/5FU), HR=1.06, 95%CI= 0.77-1.46, 3year PFS 18.2 months (FOLFOX) v 17.4 months (Cisplatin/5FU), HR 1.07: 95% CI = 0.80-1.43]. Therefore, chemoradiotherapy employing the FOLFOX regimen appears safe with similar efficacy and toxicity to the more commonly investigated combination of cisplatin and 5FU.

In summary, we propose to improve outcomes by adapting the postoperative chemoradiotherapy to the pathologic response to induction FOLFOX. Patients whom achieve a pathologic response to induction therapy will receive the same chemotherapy post-operatively administered concurrent with adjuvant radiotherapy. Alternatively, patients without an adequate pathologic response, who would be expected to have an inferior survival, will receive adjuvant radiotherapy with concurrent carboplatin and paclitaxel, an alternative regimen with demonstrated activity.

## 2.0 OBJECTIVES:

### 2.1 Primary Objectives:

2.1.1 To assess the ability of response adapted adjuvant chemoradiotherapy to improve the 1 year RFS compared to historical data in patients with >50% remaining viable tumor after induction chemotherapy.

### 2.2 Secondary Objectives:

2.2.1 To determine the rates of symptomatic, endoscopic, and pathologic response to induction chemotherapy.

2.2.2 To determine the rate of R0 resection after induction chemotherapy.

2.2.3 To establish the toxicity profile of this tri-modality regimen.

2.2.4 To assess the recurrence free survival (RFS) and overall survival (OS) of this tri-modality therapy regimen for the entire cohort and in patients who do and do not achieve a pathologic response.

2.2.5 To assess patterns of failure and assess the rates of distant metastatic control (DMC) and locoregional control (LRC) of this tri-modality therapy regimen.

**2.3 Exploratory Objectives:**

2.3.1 Ki-67:

-To evaluate the pattern of Ki-67 expression in patients with LRA esophageal cancer before and after induction chemotherapy.

-To explore the relationship of Ki-67 expression to clinical and pathologic response parameters as well as survival outcomes.

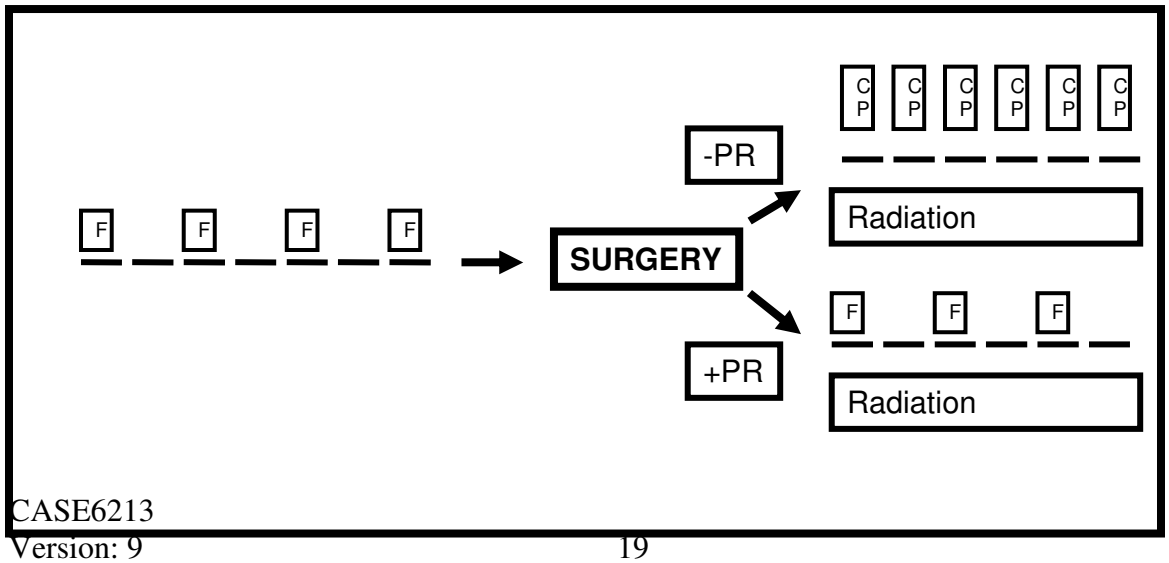
2.3.2 HER2:

-To evaluate the relationship between HER2 overexpression (based on immunohistochemistry) and gene amplification (based on fluorescence in situ hybridization) with clinical and pathologic response parameters and survival outcomes.

## 3.0 STUDY DESIGN

### 3.1 Schema

This is a phase II trial in which all patients will receive 4 cycles of induction chemotherapy with modified FOLFOX 6 (mFOLFOX6) followed by surgical resection. Patients who achieve a positive pathologic response (+PR), defined as less than or equal to 50% viable tumor cells remaining in the surgical specimen, will then receive postoperative chemo-radiotherapy with the mFOLFOX6 regimen. Patients who fail to achieve an adequate pathologic response, referred to as a negative pathologic response (-PR) and defined as greater than 50% viable tumor cells remaining in the surgical specimen, will receive postoperative chemo-radiotherapy with weekly carboplatin and paclitaxel. Patients who develop metastatic disease prior to surgery will be removed from the protocol and treated at the discretion of the primary oncologist. Patients who have locoregional disease only after induction therapy but do not undergo surgery should receive chemoradiotherapy with carboplatin and paclitaxel if medically appropriate as determined by the primary oncologist.



**F** = Modified FOLFOX 6, **C** = Carboplatin, **P** = Paclitaxel, **PR** = pathologic response

## 3.2 Number of Subjects

A total of 33 patients with > 50% viable tumor after induction chemotherapy are required to assess the primary endpoint. We anticipate a total accrual of approximately 66 patients (refer to section 14.0 for statistical rationale).

## 3.3 Replacement of Subjects

All subjects who have received any protocol therapy will be evaluable for study endpoints. Patients who have signed consent but not received therapy will be replaced.

## 3.4 Expected Duration of Study Participation

### 3.4.1 Duration of therapy

Patients will continue study treatment until completion of all planned therapy, death, disease progression, unacceptable toxicity, patient refusal, or the investigator considers it to be in the best interest of the patient.

Patients will be taken off study if they have experienced a serious adverse event or treatment delays resulting in the following:

-A delay between induction therapy cycles of ≥4 weeks (≥6 weeks from initiation of the last cycle).
-A delay between the last dose of induction chemotherapy and surgery >10 weeks.
-A delay > 12 weeks between surgical resection and the initiation of adjuvant chemoradiotherapy.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments. These patients will continue to be followed.

### 3.4.2 Duration of follow-up

Patients will be followed for at least 5 years or until death as outlined in section 11.1.2.

# 4.0 PATIENT SELECTION

## 4.1 Inclusion Criteria

4.1.1 Patients must have a histologic diagnosis of adenocarcinoma of the esophagus, GEJ, or GC based on biopsy material or adequate cytologic exam. Tumors of the GC are defined as originating within 5 cm of the GEJ.

4.1.2 Patients must be clinically staged according to the 7th edition (2010) of the AJCC staging system and must have either clinical T3-4a, or ≥N1 disease. Staging should include upper endoscopy with endoscopic ultrasound and a FDG-PET/CT scan (with diagnostic CT abdomen/pelvis preferred).

4.1.3 Patients must have an ECOG performance status of 0-1.

4.1.4 Patients must have adequate bone marrow function as evidenced by:

a) Absolute neutrophil count ≥ 1,500/µl.

b) Platelet count ≥100,000/µl.

4.1.5 Patients must have adequate renal function as evidenced by:
Serum creatinine (Scr) ≤ 1.5mg/dl. If the Scr > 1.5, patients may still be eligible if the calculated GFR (Cockroft-Gault) is ≥ 40ml/minute.

4.1.6 Patients must have adequate hepatic function as evidenced by:

a) Serum total bilirubin ≤ 1.5X the institutional ULN.

b) Alkaline phosphatase ≤ 3X the institutional ULN.

c) AST/ALT ≤ 3X the institutional ULN.

d) Patients with Gilberts syndrome are eligible provided the total bilirubin is ≤ 3 and the remainder of the liver function tests (ALT, AST, ALK Phos) are within the institutional normal range.

4.1.7 Patients must have a FEV-1 and DLCO > 50% predicted.

4.1.8 Patients or their legal representatives must be able to read, understand, provide and sign informed consent to participate in the trial.

4.1.9 Patients of childbearing potential must agree to use an effective form of contraception during this study and for 90 days following the last dose of chemotherapy. An effective form of contraception is an oral contraceptive or a double barrier method.

4.1.10 Age ≥18 years

## 4.2 Exclusion Criteria

4.2.1 Patients with any other diagnosis except for adenocarcinoma (squamous cell carcinoma, small cell carcinoma, mixed adenosquamous, lymphoma, sarcoma, etc.) will be ineligible.

4.2.2 Patients with evidence of clinical T4b (unresectable) or M1 (distant metastasis) according to the AJCC 2010 staging system will be ineligible.

4.2.3 No prior chemotherapy, radiation therapy, or surgery for this malignancy will be allowed. Prior endoscopic procedures for superficial disease (endoscopic mucosal resection, cryotherapy, photodynamic therapy, etc.) will not exclude a patient. Prior dilatation is also allowed.

4.2.4 Patients with another active malignancy will not be eligible except for:

a) Resected basal cell carcinoma and squamous cell carcinoma of the skin, cervical or prostatic intraepithelial neoplasia, and ductal or lobular carcinoma in situ of the breast.

b) Patients with localized prostate cancer who have received curative intent therapy are also eligible provided:
    1. Surgically treated patients have an undetectable PSA.
    2. Patients treated with brachytherapy have a PSA within the institutional normal range.
    3. Patients who have received pelvic external beam radiotherapy are not eligible.

4.2.5 Patients with a clinically apparent active infection will not be eligible (Please note, an isolated elevation in the white blood cell count, by itself, does not constitute evidence of an infection).

4.2.6 Patients with known hypersensitivity to any component of the chemotherapy regimen will not be eligible.

4.2.7 Patients with a baseline peripheral neuropathy ≥grade 2 will not be eligible.

4.2.8 Patients who are receiving any other concurrent investigational therapy, or who have received investigational therapy within 30 days of the first scheduled day of protocol treatment (investigational therapy as defined as treatment for which there is currently no regulatory authority approved indication) will not be eligible.

4.2.9 Patients who are pregnant or lactating will not be eligible. Pregnant patients are ineligible due to the potential teratogenic effects of cytotoxic chemotherapy and radiotherapy.

4.2.10 Patients with angina, a cardiac ejection fraction <50%, or ischemic heart disease are not eligible.

4.2.11 Patients with any other medical condition, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results, will not be eligible.

4.2.12 Patients with any history of solid organ or bone marrow transplant will not be eligible.

4.2.13 Patients with a known history of infection with hepatitis B or hepatitis C virus (active, previously treated, or both) will not be eligible due to the increased risk of hepatotoxicity and viral reactivation associated with systemic chemotherapy.

4.2.14 Patients with known infection with HIV will not be eligible. HIV infected patients are ineligible because of the increased risk for lethal infections when treated with marrow suppressive therapy.

4.3 Inclusion of Women and Minorities

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

## 5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through the Cleveland Clinic Taussig Cancer Institute and will be provided a study number by the study coordinator.

Allegheny Health System: Site study personnel will complete an eligibility checklist, eligibility coversheet, and registration form for each subject. The eligibility coversheet must be reviewed and signed by 3 different individuals: the primary reviewer (such as a research nurse), a secondary reviewer (another nurse or co-investigator) and a co-investigator or site PI. A registration form must be completed and sent with the eligibility checklist / coversheet. If a subject is ineligible, the checklist will be completed (indicating why the subject was ineligible) and the coversheet will be signed by only one research team member. Within 1 business day of completion the checklist, coversheet, and the registration form must be scanned and sent via secure e-mail to the CCF study coordinator / Primary Investigator. Additionally, Allegheny must provide CCF study coordinator with the following information:

Treating Physician
Enrolling and Treating Nurse

CCF is responsible for registering all subjects – once the eligibility checklist, coversheet, and registration form has been received by CCF, the Primary Investigator or designee (i.e. CCF Co-I) will review this information and sign the registration form. The completed registration form (all signatures obtained) will be sent to Allegheny within 1 business day from the date in which the Sponsor-Investigator or designee (i.e. CCF Co-I) signs the form.

If the patient is registered onto the study (i.e. CCF has approved registration) the CCF study coordinator will enter all on study information for the subject within 2 business days of receiving the eligibility checklist, coversheet, and registration form.

The on study information that must be entered into OnCore is detailed in the data management plan. The study coordinator will document the date in which the eligibility information was received and confirm its completion. Once this has been done, the patient will be put 'on study' in OnCore.

This registration process is also described in the Manual of Operating Procedures (MoOP).

## 6.0 TREATMENT PLAN

All patients will undergo initial screening investigations as outlined in section 11.0 which include a history and physical examination, performance status assessment (ECoG), EGD with EUS, PET/CT (with a diagnostic CT abd/pelvis preferred), PFT (spirometry with DLCO), cardiac stress testing (dobutamine stress echocardiogram preferred), laboratory investigations (CBC and CMP or BMP, HFP), and serum β-HCG (for women of childbearing age). Please refer to section 11.0 (study parameters and calendar).

## 6.1 Induction Chemotherapy

Modified FOLFOX-6:

After completion of staging, informed consent and registration, all patients will receive induction chemotherapy with 4 cycles of the mFOLFOX 6 regimen. Cycles will be administered every 2 weeks (14 days). A window of +/- 2 days is acceptable for administration of chemotherapy. Chemotherapy dose calculation will use actual body weight. The BSA will not be capped..

**Oxaliplatin** 85 mg/m2 over 2 hours on day 1
**Leucovorin** 400 mg/m2 over 2 hours administered simultaneously with oxaliplatin on day 1. If drug availability is limited, may administer leucovorin 100mg total dose or substitute levo-leucovorin at 200mg/m2.
**5-fluorouracil** 400 mg/m2 IV push over 2-4 minutes on day one immediately after completion of leucovorin.
**5-fluorouracil** 2400 mg/m2 continuous IV infusion over 44 hours (window 42-48 hours) days 1-3. Residual chemotherapy will be discarded.

Standard anti-emetics may be employed. Patients will receive 5-FU via a portable infusion pump through an indwelling venous access device.

## 6.2 Restaging and Surgery

### 6.2.1 Restaging

At 3-4 weeks (A window of 2-5 weeks is acceptable and will not be considered a deviation) after discontinuation of 5-fluorouracil, patients will be fully restaged to assure there is no contraindication to surgical resection. Repeat staging will consist of the following studies as outlined in section 11: Dysphagia assessment based on history (defined in section 11.0), PET/CT (with diagnostic CT abdomen/pelvis preferred), EGD with EUS and biopsy, CMP or BMP & HFP, CBC, and CTCs.

### 6.2.2 Surgery

Surgery will be scheduled for approximately one week later (4-5 weeks after completion of induction chemotherapy. A window of 3-7 weeks is acceptable and will not be considered a deviation). Patients will proceed to surgery irrespective of whether there is apparent loco-regional progression after pre-operative chemotherapy unless the disease is felt to be unresectable (cT4b) or there has been interval development of distant metastasis (cM1 disease). It is recommended that potential metastatic disease be biopsied if possible for pathologic confirmation. Patients with biopsy confirmed metastatic disease will be taken off study and treated at the discretion of the physician. Patients with radiographic

abnormalities which are not amenable to biopsy but are felt to represent metastatic disease by the treating physicians will likewise be taken off study. Every attempt to obtain histologic confirmation of metastatic disease should be made. Patients who have locoregional disease only after induction therapy but do not undergo surgery should receive chemoradiotherapy with carboplatin and paclitaxel if medically appropriate as determined by the primary oncologist. Reasons to not receive surgery for locoregional disease include an unresectable primary tumor (T4b), the patient declines surgery, or the patient is felt to be medically inoperable.

The choice of surgical procedure will be at the discretion of the operating physician and will consist of either a trans-thoracic esophagectomy, trans-hiatal esophagectomy, or total gastrectomy with Roux-en-Y esophagojejunostomy depending on the location and extent of the tumor at surgery. An appropriate lymphadenectomy (2-field lymphadenectomy is recommended) will also be performed and immediate reconstruction is anticipated if possible. The goal of surgery is an R0 resection.

### 6.3 Radiotherapy

Radiotherapy will start between 6 and 12 weeks after surgery. If > 12 weeks have elapsed before adjuvant chemoradiotherapy can be administered, patients will be taken off of this study.

Equipment:
Modality- Xrays with nominal energy of 4 MV or greater.

Tumor dose: 50.4 Gy/1.8 Gy per fraction over 28 days; at the discretion of the treating physician, patients with pathologic positive margins may have their total dose increased from 54 Gy to 60 Gy.

Target volume definitions:
Gross target volume (GTV): As patients are being treated in the adjuvant setting there is no GTV.
Clinical Taregt volume (CTV): Treatment will be given to the postoperative esophago-gastric bed and draining regional lymphatic nodal beds. Any known residual disease will be included within the post-operative fields. Unless there is a positive surgical margin, the esophageal anastomosis will not be treated.

Dosimetry: Use of IMRT is not recommended for use in this study. IMRT can be considered on a case by case basis and must be approved by the PI (Dr. Michael McNamara) prior to treatment.

Heterogeneity corrections will be used. A 3-dimensional conformal radiotherapy plan will be generated for each case. A clinical target volume (CTV) and a planning target volume (PTV) will be identified for each case. At the discretion of the treating physician and based on immobilization technique and patient status, the CTV will be expanded by

a margin of at least 1cm to create the PTV and the prescription isodose line will cover ≥ 95 % of the PTV. Dose variation within the PTV may be +/- 7%. Dose volume histogram (DVH) data will be calculated for the treatment plan. For organs at risk (OARs), the mean lung dose (MLD), the volume of lung receiving 20 Gy (V20), doses to heart, kidneys, liver, spinal cord will be documented for each course.

Normal Tissue Constraints: (per RTOG 1010). At the discretion of the treating physician, up to 10% variation in dose-volume constraint objectives is acceptable.
Liver: V30 should be ≤30%
Kidney: V20 should be ≤30%
Heart:Considering whole heart, maximum dose to 0.03cc should be ≤,52 Gy mean dose should be ≤ 32 Gy, and V40 should be ≤ 50%.
Lung: MLD≤20 Gy, V20≤30%
Spinal cord: Maximum dose to 0.03cc of cord is <50 Gy (per RTOG 1010).

Major interruptions in radiation therapy are not acceptable. Every attempt should be made to complete the prescribed course of radiation therapy on schedule.

Mucositis and dysphagia may be significant as a result of this treatment. These toxicities are reversible, and will not serve as an indication for treatment interruption. Appropriate supportive measures will be utilized. All patients are anticipated to have a jejunostomy feeding tube inserted at the time of surgery, which will be kept in place until adjuvant therapy is complete and the patients have recovered sufficiently.

## 6.4 Adjuvant Chemotherapy

### 6.4.1 Carboplatin and Paclitaxel:

Patients with >50% remaining viable tumor (-PR) will receive adjuvant chemoradiotherapy with carboplatin and paclitaxel. Carboplatin and paclitaxel will be given weekly for a maximum of 6 doses concurrent with radiotherapy. Chemotherapy will only be given concurrent with radiotherapy. Chemotherapy will use actual body weight. The BSA will not be capped and there will be no dose adjustments for obese patients.

Please note, a window of +/-2 days of the anticipated cycle interval is acceptable for the administration of chemotherapy

Paclitaxel = 50 mg/m2 IV over 1 hour on days 1, 8, 15, 22, 29, and 36.
Carboplatin = (AUC = 2) IV over 30 minutes on days 1, 8, 15, 22, 29, and 36.

Patients may receive standard premedication for paclitaxel including:
Dexamethasone 20mg IV, Benadryl 25-50mg IV, and famotidine 20mg IV or ranitidine 50mg IV 30-60 minutes immediately prior to chemotherapy.

Carboplatin will be given AFTER the paclitaxel.

Carboplatin dose will be calculated using the Calvert formula:

Carboplatin dose = AUC x (CrCl + 25)

The maximum CrCl used should be 125ml/min. A 24 hour urine collection may be used to better estimate the actual GFR but is not required nor recommended.

The CrCl should be calculated using the Cockroft-Gault equation:

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \text{ (actual weight in kg) } (0.85 \text{ in females only})}{72 \times \text{serum creatinine (mg/dl)}}$$

Note: For subsequent doses, a >10% change in the calculated creatinine clearance, based on the serum creatinine, will warrant a recalculation of the carboplatin dose.

6.4.2 Modified FOLFOX6

Patients with ≤ 50% remaining viable tumor (+ PR) will receive adjuvant chemoradiotherapy with mFOLFOX6. Chemotherapy will only be given concurrent with radiotherapy. FOLFOX will be administered beginning on days 1, 15, and 29. A window of +/- 2 days of the anticipated cycle interval is acceptable for the administration of chemotherapy. The last cycle of FOLFOX chemotherapy can be initiated no later than 3 days prior to the expected radiotherapy completion date (i.e. all chemotherapy must be delivered concurrent with radiotherapy).Chemotherapy dose calculation will use actual body weight. The BSA will not be capped and there will be no dose adjustments for obese patients.

**Oxaliplatin** 85 mg/m2 over 2 hours on day 1.
**Leucovorin** 400 mg/m2 over 2 hours administered simultaneously with oxaliplatin on day 1. If drug availability is limited, may administer leucovorin 100mg total dose or substitute levo-leucovorin at 200mg/m2.
**5-fluorouracil** 400 mg/m2 IV push over 2-4 minutes on day one immediately after completion of leucovorin.
**5-fluorouracil** 2400 mg/m2 continuous IV infusion over 44 hours (window 44-48 hours) days 1-3. Residual chemotherapy will be discarded.

Standard anti-emetics may be employed. Patients will receive 5-FU via a portable infusion pump through an indwelling venous access device

## 6.5 General Concomitant Medications and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, anti-emetics, etc when appropriate.

### 6.5.1 Gastrointestinal toxicity

Nausea / vomiting- standard anti-emetics will be employed at the initiation of treatment. Chemotherapy related nausea and emesis will be aggressively managed at the discretion of the investigator.

Diarrhea- any grade gastrointestinal toxicity is common with 5-fluorouracil. Aggressive pro-active management will be employed to minimize this toxicity. Dose modifications will be incorporated as outlined in section 7. For uncomplicated grade 1 and-2 diarrhea, patients will be instructed to maintain adequate oral hydration and eat frequent small meals if possible. Standard doses of loperamide will be used if necessary. Patients will be instructed to take 4 mg as an initial dose followed by 2 mg every 4 hours or after every unformed stool. The maximum dose of 16 mg per day will be used in this protocol. It is suggested that loperamide be continued until the subject is free from diarrhea for 12 hours. Other agents such as diphenoxylate / atropine (trade name Lomotil) can be used for mild to moderate diarrhea which is not fully controlled with the use of Imodium at the discretion of the investigator.

For more severe diarrhea (grade 3-4) or moderate grade 2 diarrhea with complicating features (severe nausea / vomiting, decreased performance status, fever, neutropenia), IV hydration and hospitalization will be considered. Dose modifications will be employed as previously outlined. Consideration for testing for a coincident Clostridium difficile infection is also recommended in the appropriate clinical context.

Note that diarrhea after an esophagectomy or total gastrectomy is not uncommon, and may be due to multiple factors unrelated to the chemotherapy. Appropriate adjustments in diet or tube feeding should be made in addition to the interventions described above.

Mucositis- No specific prophylactic measures will be employed. Oral cryotherapy is specifically contraindicated given the potential for LPD (described in section 7.1.6) in patients receiving oxaliplatin. Recommendations for patients with established mucositis include atraumatic cleansing and oral rinses with salt & baking soda solution every 4-6 hours. Topical therapy with BMX (equal parts lidocaine / diphenhydramine / aluminum hydroxide) may be employed for patients with > grade 1 symptoms. If necessary, appropriate systemic analgesics will also be prescribed.

### 6.5.2 Neurotoxicity

Peripheral neuropathy- peripheral neuropathies (both motor and sensory) are commonly associated with the use of oxaliplatin as well as paclitaxel. No specific prophylactic measures are recommended as part of this protocol. Patients with established neuropathy will require dose adjustment / modification as outlined in section 7.1.5 (FOLFOX) and 7.3.3 (carboplatin / paclitaxel).

## 6.6 Duration of Therapy

Patients will continue study treatment until completion of all planned therapy, death, disease progression, unacceptable toxicity, patient refusal, or the investigator considers it to be in the best interest of the patient.

The study protocol will also be discontinued for patients who have experienced a serious adverse event or treatment delays resulting in the following:

A delay between induction therapy cycles of ≥4 weeks (≥6 weeks from initiation of the last cycle).

A delay between the last dose of induction chemotherapy and surgery >10 weeks.

A delay between surgical resection and the initiation of adjuvant chemoradiotherapy > 12 weeks.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments. These patients will continue to be followed.

### 6.7 Duration of Follow Up

Patients will be followed for at least 5 years or until death as outlined in section 11.1.2.

## 7.0 DOSE DELAYS / DOSE MODIFICATIONS

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for all treatment related acute toxicity and adverse event reporting unless otherwise specified. CTCAE version 4.0 can be downloaded from http://ctep.info.nih.gov.

Dose reductions beyond those specified in this protocol are not allowed and will be considered protocol violations.

### 7.1 Induction Chemotherapy

Any dose reductions during induction chemotherapy will be permanent and continued throughout subsequent courses of pre-operative treatment. A delay between induction therapy cycles of ≥4 weeks (≥6 weeks from initiation of the last cycle) will require that the induction therapy be discontinued and the patient proceed to surgery. These patients will be removed from the study protocol. These patients will continue to be followed.

For patients who receive post-operative FOLFOX chemoradiotherapy, all dose reductions / modifications established during pre-operative therapy will apply for adjuvant therapy as well. Please refer to post-operative chemoradiotherapy dose modifications for specific details.

Dose Level Definitions: Pre-operative chemotherapy

| Agents | Level 0 | Level -1 | Level -2 |
|---|---|---|---|
| Oxaliplatin | 85mg/m2 | 68mg/m2 | 51mg/m2 |
| Bolus 5-FU | 400mg/m2 | 320mg/m2 | 240mg/m2 |
| Infusional 5-FU | 2400mg/m2 | 1920mg/m2 | 1440mg/m2 |

Leucovorin dose will not be modified for toxicity. Leucovorin will not be given without concurrent administration of 5-FU.

### 7.1.1 Hematologic toxicity: Pre-operative chemotherapy

Hematologic toxicity parameters are based on the CBC on the day of treatment, or within 48 hours of the day of therapy.

Erythropoietic stimulating agents will not be allowed.

White blood cell growth factor (Filgrastim / Pegfilgrastim) support may be used at the discretion of the treating physician during induction therapy but will not be allowed during the post-operative concurrent chemoradiotherapy.

If a treatment delay is required due to hematologic toxicity, a CBC will be repeated weekly.

For cycle 1 of induction chemotherapy, the CBC must meet eligibility criteria for the protocol. For cycles 2-4 of induction chemotherapy, the ANC must be ≥ 1,200 and the platelet count must be ≥ 75,000 for treatment to proceed. Unless otherwise specified, a dose level reduction applies for all agents (Oxaliplatin, bolus 5-FU, and infusional 5-FU) in the regimen except for leucovorin.

ANC <1200: Delay FOLFOX and check CBC weekly and resume therapy when the ANC is ≥ 1200. If therapy is delayed for 1 week, resume at the same dose level and add Filgrastim / pegfilgrastim. If therapy is delayed > 1 week, reduce one dose level and add Filgrastim / pegfilgrastim. For subsequent cycles of therapy, if the ANC is <1200, delay FOLFOX and check the CBC weekly. Resume therapy when the ANC is ≥ 1200 with another dose level reduction. If therapy is held ≥ 4 weeks, the patient will proceed to surgery and will be taken off the study.

Febrile Neutropenia: Check the CBC weekly and Resume therapy once the ANC is ≥ 1200. FN will require one dose level reduction and the addition of filgrastim / pegfilgrastim. If therapy is held ≥ 4 weeks, the patient will proceed to surgery and will be taken off the study.

A second occurrence of Febrile neutropenia despite appropriate dose modification and growth factor support will require cessation of induction therapy. Once the patient has recovered, he / she will go to surgery. In that event, in the adjuvant setting, carboplatin and paclitaxel will be administered regardless of pathologic response.

Plt < 75,000: Delay FOLFOX and check a CBC weekly and resume therapy when the platelet count is ≥ 75,000. If therapy is held for 1 week, resume at the same dose level. If two consecutive cycles of therapy are held for 1 week or if therapy is held for > 1 week, resume with one dose level reduction. For subsequent cycles of therapy, if the platelets are < 75,000, delay FOLFOX and check a CBC weekly. Resume therapy when the platelet count is ≥ 75,000 with one dose level reduction. If therapy is held ≥ 4 weeks, the patient will proceed to surgery and will be taken off the study.

Dose reductions below level -2 are not allowed and will require discontinuation of induction therapy. In that event, patients will proceed directly to surgery and receive carboplatin and paclitaxel in the adjuvant setting regardless of pathologic response.

### 7.1.2 Gastrointestinal toxicity

Diarrhea ≥ grade 2 requires that FOLFOX be held until diarrhea < grade 2 and institution of supportive measures with subsequent cycles. If diarrhea occurs despite maximum supportive care (as outlined in this protocol), the following dose reductions / modifications are required.

Grade 1 diarrhea: Continue FOLFOX without modification.
Grade 2 diarrhea: Delay FOLFOX and reevaluate weekly. Resume therapy when ≤ grade 1 and reduce 5-FU one dose level.
Grade 3 diarrhea: Delay FOLFOX and reevaluate weekly. Resume therapy when ≤ grade 1 and reduce oxaliplatin and 5-FU one dose level.
Grade 4 diarrhea: If patients experience grade 4 diarrhea despite appropriate supportive care, induction therapy will be stopped and the patient will proceed to surgery once they have recovered sufficiently. In that event, in the adjuvant setting, carboplatin and paclitaxel will be administered regardless of pathologic response.

### 7.1.3 Mucositis

Treatment will be delayed if ≥ grade 2 mucositis is present on the day of therapy. Patients will be reevaluated weekly and therapy will resume when grade ≤ 1.

Grade 1-2 mucositis at any point during therapy will not affect subsequent FOLFOX dosing.
Grade 3 mucositis at any point during therapy will require one dose level reduction in 5-FU only.
Grade 4 mucositis during therapy will require that induction therapy be stopped and the patient proceed to surgery once they have recovered sufficiently. In that event, in the adjuvant setting, carboplatin and paclitaxel will be administered regardless of pathologic response.

### 7.1.4 Nausea / Vomiting

Treatment will NOT be held for chemotherapy related nausea and / or emesis.

Grade 1-3 nausea / emesis at any point during therapy will not require dose modification but may lead to hospitalization for antiemetic control

Grade 4 nausea / emesis at any point during therapy despite appropriate prophylactic and supportive management will require that induction therapy will be stopped and the patient will proceed to surgery once they have recovered sufficiently. In that event, in the adjuvant setting, carboplatin and paclitaxel will be administered regardless of pathologic response

### 7.1.5 Neurotoxicity

Oxaliplatin neurotoxicity will be graded according to the Oxaliplatin-Specific Neurotoxicity Scale

| | |
|---|---|
| Grade 1 | Parasthesias/dysesthesias of short duration that resolve prior to subsequent cycles |
| Grade 2 | Parasthesias/dysesthesias interfering with function, but not with ADLs |
| Grade 3 | Parasthesias/dysesthesias with pain or functional impairment interfering with ADLs |
| Grade 4 | Parasthesias/dysesthesias that are disabling |

Grade 1 neurotoxicity will not require dose modification
Grade 2 neurotoxicity that is not persistent (< grade 2 at the time of treatment) will not require dose modification
Grade 2 neurotoxicity which persists to the time of treatment will require one dose level reduction of oxaliplatin
Grade 3 neurotoxicity which is ≤ grade 2 at the time of treatment will require one dose level reduction of oxaliplatin
Grade 3 neurotoxicity which is persistent or any grade 4 neurotoxicity will require discontinuation of oxaliplatin. Induction chemotherapy will proceed with 5-FU and leucovorin alone. In that event, in the adjuvant setting, patients will receive chemoradiotherapy with 5-FU and leucovorin alone regardless of the pathologic response to therapy

### 7.1.6 Laryngopharyngeal dysesthesia

Laryngopharyngeal dysesthesia (LPD) is an acute neurotoxicity associated with oxaliplatin and often precipitated by exposure to cold. LPD is characterized by the sensation of dyspnea and difficulty swallowing without objective evidence of either. It must be distinguished from platinum hypersensitivity (PH) reactions. PH is suggested by the presence of true bronchospasm and laryngospasm often associated with hypoxemia. Patients with LPD are typically hemodynamically stable with the exception of mild

tachycardia. Hypotension suggests PH. PH can further be distinguished from LPD by the presence of hives/rash sometimes with pruritis.

If a patient develops symptoms consistent with LPD, the oxaliplatin infusion should be held until the diagnosis is confirmed. Consideration should then be given to the administration of anxiolytics. The patient should be observed in the clinic until symptoms resolve. If the diagnosis is confirmed and the symptoms resolve, the oxaliplatin infusion can be completed at 1/3 the initial rate of infusion. Since LPD is often associated with the rate of oxaliplatin infusion, subsequent doses of oxaliplatin should therefore be given over 6 hours. Dose reduction is not required. Premedication with steroids or anti-histamines are not helpful in the prevention of LPD.

While LPD is typically seen during or shortly after the administration of oxaliplatin, patients will be instructed to avoid cold beverages within the first 48 hours of administration and to exercise caution throughout treatment.

### 7.1.7 Allergic reactions

Oxaliplatin, like other platinum drugs, is associated with a significant risk of hypersensitivity reactions, typically after multiple doses of therapy. Symptoms include, but are not limited to, dyspnea with laryngospasm and / or bronchospasm, hypotension, hypoxia, hives, and pruritis. Pretreatment with steroids and anti-histamines may be helpful in some patients but are not sufficiently adequate to allow retreatment of patients who have developed grade 3-4 hypersensitivity reactions.

For patients who have experienced a grade 1-2 platinum hypersensitivity reaction, subsequent cycles of FOLFOX (including adjuvant chemo-radiotherapy if applicable) will require premedication with the following regimen:
Dexamethasone 20mg PO 12 and 6 hours prior to oxaliplatin infusion.
Dexamethasone 20mg IV, diphenhydramine 50mg IV, and either ranitidine 50mg IV or famotidine 20mg IV 30-60 minutes immediately prior to oxaliplatin infusion.

If patients develop a recurrent hypersentivity reaction (any grade) despite these measures, or any Grade 3-4 hypersensitivity reaction, oxaliplatin will be discontinued and chemotherapy will continue with 5-FU alone. Patients who require discontinuation of oxaliplatin due to hypersensitivity in the preoperative setting will receive adjvant CRT with 5-FU and leucovorin alone regardless of the pathologic response.

Patients experiencing a hypersentivity reaction will be managed in the usual fashion per institutional protocol.

### 7.1.8 Pulmonary fibrosis

In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea, or new radiographic pulmonary infiltrates, all treatment should be held until further

investigation suggests an alternative etiology or oxaliplatin interstitial fibrosis has been excluded. Patients who develop oxaliplatin related lung injury will be taken off study.

### 7.1.9 Palmer-Plantar erythema (Hand-Foot syndrome)

The development of ≥ grade 2 palmer-plantar erythema will require that any remaining 5-FU be discontinued and all therapy held until ≤ grade 1. 5-FU will then be reintroduced at one dose level reduction.

### 7.1.10 Cardiovascular toxicity

The development of any grade 5-FU related cardiac toxicity will require urgent discontinuation of any remaining 5-FU. Manifestations of 5-FU cardiotoxicity include chest pain / angina, myocardial infarction, and arrhythmia. Rechallenge with 5-FU is not permitted. If patients develop 5-FU related cardiotoxicity during preoperative therapy, they will proceed to surgery if medically appropriate and they will receive carboplatin and paclitaxel in the adjuvant setting regardless of pathologic response.

### 7.1.11 Other non-hematologic toxicity

All other non-hematologic grade 3 toxicity related to FOLFOX will require induction therapy to be held until ≤ grade 1. FOLFOX may then resume with one dose level reduction.

All other Grade 4 non-hematologic toxicity will mandate discontinuation of induction chemotherapy. The patient may proceed to surgery if medically appropriate and will receive carboplatin and paclitaxel in the adjuvant setting regardless of pathologic response.

## 7.2 Adjuvant Chemoradiotherapy

Dose Level Definitions: carboplatin and paclitaxel post-operative chemoradiotherapy.

| Agents | Level 0 | Level -1 | Level -2 |
|---|---|---|---|
| Carboplatin | AUC 2.0 | AUC 1.6 | AUC 1.2 |
| Paclitaxel | 50mg/m2 | 40mg/m2 | 30mg/m2 |

Dose Level Definitions: Post-operative FOLFOX chemoradiotherapy.

| Agents | Level 0 | Level -1 | Level -2 |
|---|---|---|---|
| Oxaliplatin | 85mg/m2 | 68mg/m2 | 51mg/m2 |
| Bolus 5-FU | 400mg/m2 | 320mg/m2 | 240mg/m2 |
| Infusional 5-FU | 2400mg/m2 | 1920mg/m2 | 1440mg/m2 |

Leucovorin dose will not be modified for toxicity. Leucovorin will not be given without concurrent administration of 5-FU.

All dose modifications during adjuvant chemoradiotherapy will be permanent. No dose escalation is permitted.

For patients who receive post-operative (adjuvant) FOLFOX based chemoradiotherapy, all dose modifications / reductions established during pre-operative therapy will be continued in the post-operative setting.

No growth factor therapy will be allowed during adjuvant chemoradiotherapy. Patients receiving post-operative FOLFOX who required filgrastim / Pegfilgrastim for neutropenic fever will start adjuvant therapy without growth factor support and one dose level reduction. If patients have already had two dose level reductions during induction chemotherapy and required growth factor support for febrile neutropenia, FOLFOX cycle length will extended to 21 days. Patients would therefore receive only two cycles of chemotherapy with radiation. Otherwise, dose level reductions below Level -2 are not allowed. Chemotherapy will be stopped and patients will continue radiotherapy

For patients who received filgrastim / pegfilgrastim for indications other than neutropenic fever, all dose modifications / reductions during pre-operative chemotherapy will be continued during post-operative chemoradiotherapy. No further dose reductions / modifications will be required for initiation of post-operative therapy.

Chemotherapy will only be administered during Radiotherapy. Missed doses will not be made up after the completion of radiotherapy. For patients on FOLFOX, the last cycle of chemotherapy can be initiated no later than 3 days prior to the expected radiotherapy completion date (i.e. all chemotherapy must be delivered concurrent with radiotherapy).

Chemotherapy will start within 24 hours of initiating radiotherapy during week 1.

Post-operative radiotherapy should begin on a Monday if possible, but should not start after Wednesday.

### 7.3 Carboplatin and Paclitaxel Post-operative Chemoradiotherapy

#### 7.3.1 Hematologic toxicity (carboplatin / paclitaxel)

Dose modifications are based on the CBC from the day of expected treatment or within 48 hours prior. If therapy is held for hematologic toxicity, a CBC will be rechecked weekly.

If the patient experiences multiple toxicities, dose level reductions / modifications will be based on the worst toxicity.

Dose level reductions below Level -2 are not allowed. Chemotherapy will be stopped and patients will continue radiotherapy.

ANC $\geq$ 1200: No dose adjustment.

ANC <1200: Hold chemotherapy and check the CBC weekly. Resume when the ANC is ≥ 1200. If therapy was delayed for 1 week, resume at the same dose level. If therapy is held > 1 week or two consecutive cycles are delayed, reduce one dose level carboplatin / paclitaxel.

Febrile neutropenia = Hold therapy and check the CBC weekly. Resume when the ANC is ≥ 1200 with one dose level reduction of carboplatin and paclitaxel. A second occurrence of Febrile neutropenia despite appropriate dose modification will result in the discontinuation of chemotherapy. Radiotherapy will be completed.

Plt <100,000: Delay therapy until the platelet count ≥ 100,000 and resume at the same dose level. If two consecutive cycles of therapy are delayed for a platelet count of < 100,000 or a single cycle is delayed > 1 week, one dose level reduction is required.

### 7.3.2 Gastrointestinal toxicity (carboplatin / paclitaxel)

Diarrhea ≥ grade 2 requires that chemotherapy be held until diarrhea < grade 2 and institution of supportive measures with subsequent cycles. If diarrhea occurs despite maximum supportive care (as outlined in this protocol), the following dose reductions / modifications are required.

Grade 1 diarrhea: Continue chemotherapy without modification.
Grade 2-3 diarrhea: Delay chemotherapy and reevaluate weekly. Resume therapy when ≤ grade 1 and reduce one dose level.
Grade 4 diarrhea: If patients experience grade 4 diarrhea despite appropriate supportive care, chemotherapy will be discontinued. Radiotherapy will be completed.

### 7.3.3 Neurotoxicity- peripheral neuropathy (carboplatin / paclitaxel)

Grade 1 neurotoxicity will not require dose modification
Grade 2 neurotoxicity that is not persistent (< grade 2 at the time of treatment) will not require dose modification
Grade 2 neurotoxicity which persists to the time of treatment will require one dose level reduction of carboplatin and paclitaxel
Grade 3 neurotoxicity which is ≤ grade 2 at the time of treatment will require one dose level reduction of carboplatin and paclitaxel
Grade 3 neurotoxicity which is persistent or any grade 4 neurotoxicity will require discontinuation of chemotherapy. Radiotherapy will be completed

### 7.3.4 Allergic reactions (carboplatin / paclitaxel)

Both carboplatin and paclitaxel are known to be associated with systemic infusion reactions and anaphylaxis. Standard premedication will be given as prophylaxis throughout chemoradiotherapy with carboplatin and paclitaxel. All patients will receive

dexamethasone 20mg IV, Benadryl 25-50mg IV, and famotidine 20mg IV or ranitidine 50mg IV 30-60 minutes immediately prior to chemotherapy.

Grade 1-2 infusion reactions / hypersensitivity: The infusion will be temporarily held and the patient will be examined. Chemotherapy can be resumed at the discretion of the treating physician provided the patient has returned to baseline and is asymptomatic. Mild infusion reactions will require that patients receive dexamethasone 20mg PO 12 and 6 hours prior to chemotherapy with subsequent cycles of therapy in addition to the standard premedications.

Chemotherapy will be discontinued in patients who develop a recurrent infusion reaction of any grade despite these premedications. Radiotherapy will be completed.

Grade 3-4 infusion reaction / hypersensitivity: Requires appropriate immediate therapy and will result in discontinuation of chemotherapy. Radiotherapy will be completed.

### 7.3.5 Other non-hematologic toxicity

All other non-hematologic grade 3 toxicity related to carboplatin and paclitaxel will require induction therapy to be held until ≤ grade 1. Chemotherapy may then resume with one dose level reduction.

All other Grade 4 non-hematologic toxicity will require the discontinuation of chemotherapy. Radiotherapy will be completed.

## 7.4 FOLFOX Post-operative Chemoradiotherapy

FOLFOX dose reductions / modifications during post-operative chemoradiotherapy are the exact same as those listed above for induction chemotherapy with the exception of hematologic toxicity, which is outlined below. Dose reductions / modifications that were required during pre-operative induction will be maintained during the post-operative adjuvant therapy.

Dose level reductions below Level -2 are not allowed. Chemotherapy will be stopped and patients will continue radiotherapy.

Management of diarrhea, mucositis, chemotherapy related nausea and vomiting, LPD, neurotoxicity, allergic reactions, palmer-plantar erythema, pulmonary fibrosis, and cardiovascular toxicity is the exact same as listed for induction chemotherapy, with the following exceptions:

Grade 4 diarrhea, mucositis, or chemotherapy related nausea and vomiting will require chemotherapy be discontinued. Radiotherapy should be completed.

Persistent Grade 3 or any Grade 4 neurotoxicity will require discontinuation of Oxaliplatin. Radiotherapy with concurrent 5FU will be completed.

Grade 3/4 or recurrent platinum hypersensitivity reactions will require discontinuation of Oxaliplatin. Radiotherapy with concurrent 5FU will be completed.

Pulmonary fibrosis (as defined in section 7.1.8): Both radiotherapy and chemotherapy will be discontinued. The patient will remain on study.

### 7.4.1 Hematologic toxicity

Hematologic toxicity parameters are based on the CBC from the day of treatment, or within 48 hours of the day of therapy. Erythropoietic stimulating agents will not be allowed. White blood cell growth factor (Filgrastim / Pegfilgrastim) support may not be used during chemoradiotherapy.

ANC ≥ 1200: No dose adjustment

ANC <1200: Hold chemotherapy and check the CBC weekly. Resume when the ANC is ≥ 1200. If therapy is delayed one week, resume without dose modification. If therapy is held > 1 week or two consecutive cycles are delayed,reduce one dose level FOLFOX.

Febrile Neutropenia: Hold therapy and recheck the CBC weekly. Resume when the ANC is ≥ 1200 with one dose level reduction of FOLFOX. A second occurrence of Febrile neutropenia despite appropriate dose modification will require discontinuation of further chemotherapy. Radiotherapy will be completed.

Plt < 100,000: Delay FOLFOX and recheck the CBC weekly. Resume when the platelet count is ≥ 100,000. If therapy is delayed one week, resume without dose modification. If two consecutive cycles of therapy are delayed for a platelet count < 100,000 or a single cycle is delayed > 1 week, one dose level reduction is required.

## 7.5 Radiotherapy

Radiation treatment will be interrupted for grade 4 in-field toxicity and will not be resumed until resolution to ≤ grade 2. Examples of potential in-field toxicity include:

- radiation pneumonitis
- pleuritis
- pericarditis
- inflammation ulceration of esophagus (esophagitis)
- neoesophagus (gastritis, etc).

Aggressive supportive care is encouraged throughout the course of radiotherapy. Every attempt should be made to complete treatment despite acute toxicity.

Radiotherapy will be permanently discontinued in patients who experience a treatment interruption lasting ≥ 4 weeks. Patients will remain on study. Chemotherapy will only

be given concurrent with radiotherapy in the adjuvant setting and therefore, will also be discontinued.

## 8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with the observed AEs (Sections 8.3 and 8.4). The treatment period is considered to begin with signing of the informed consent document and lasts up to 30 days from the end of therapy.

The clinical course of each event during the treatment period will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. If an event is related to treatment or participation, follow-up is not required once it is determined to be a chronic, stable, and an ongoing condition.

Serious adverse events that are still ongoing at the end of the treatment period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the treatment period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

### 8.1 Adverse Events and Potential Risks

#### 8.1.1 Carboplatin

The most common side effects are myelosuppression (dose related) nausea and vomiting, hepatic toxicity, electrolyte imbalance (hypomagnesemia, hypocalcemia, hyponatremia), peripheral neuropathy, fatigue, allergic reactions, and renal insufficiency.

Please refer to the manufacturers package insert for further information.

#### 8.1.2 5-Flourouracil

Gastrointestinal and hematopoietic toxicity are common with 5-FU. Mucositis, diarrhea, anorexia, and nausea are the most frequent gastrointestinal side effects. Granulocytopenia, anemia, and thrombocytopenia may occur. Other toxicities include Hand-Foot syndrome, alopecia, and photosensitivity dermatitis. Ocular toxicity including tear duct stenosis, photophobia, and conjunctivitis is uncommon. Neurologic toxicity is also uncommon, but may manifest as confusion, headache, or an acute cerebellar syndrome.

Chest pain as a result of myocardial ischemia secondary to coronary vasospasm is a rare but notable toxicity which requires urgent medical attention and discontinuation of further 5-FU administration. Patients with dihydropyrimidine dehydrogenase (DPD) deficiency may experience significant, life threatening gastrointestinal and hematologic toxicity.

Please refer to the manufacturers package insert for further information.

### 8.1.3 Leucovorin

Allergic / anaphylactic reactions have been described with this agent but are uncommon. Leucovorin may enhance the toxicity of 5-Flourouracil when given concomitantly.

Please refer to the manufacturers package insert for further information.

### 8.1.4 Oxaliplatin

The most common side effects include fatigue, nausea, diarrhea, vomiting, anorexia, anemia, thrombocytopenia, leukopenia, and peripheral neuropathy. Less common toxicities include laryngopharyngeal dysesthesia (LPD) and hypersensitivity reactions.

Please refer to the manufacturers package insert for further information.

### 8.1.5 Paclitaxel

Myelosuppression, peripheral neuropathy, alopecia, myalgias and arthralgiasis, and nausea and vomiting are the most common toxicities associated with paclitaxel. Fatigue and anorexia are also frequently noted. Acute allergic / anaphylactoid reactions can be serious and necessitate premedication. Other toxicities include stomatitis, mucositis, pharyngitis, increased liver function tests with possible hepatic failure, arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, alterations of taste, seizures, mood swings, sensation of flashing lights; blurred vision, scintillating scotoma, Stevens-Johnson Syndrome, rash, pruritus, infiltration (erythema, induration, tenderness, rarely ulceration) and radiation recall reactions.

Please refer to the manufacturers package insert for further information.

## 8.2 Definitions

### 8.2.1 Adverse events

An adverse event (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research (a); the collection of identifiable private information in the research (b); an underlying disease, disorder, or condition of the subject (c); and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject (d). In general, adverse events that are at least partially the result of (a) or (b) would be

considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

External adverse events are adverse events experienced by subjects enrolled in multi-center clinical trials at sites other than the sites over which the Institutional Review Board (IRB) has jurisdiction.

Internal adverse events are adverse events experienced by subjects enrolled at the sites under the IRBs jurisdiction for either multicenter or single-center research projects

8.2.2 The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with event as opposed to threat to a patient's life or functioning (i.e., moderate to severe or life-threatening). Based on the National Cancer Institute guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events

Grades 1 are mild adverse events (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance).

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; noninvasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death

8.2.3 Serious adverse events

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

-Results in death
-Is a life-threatening adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

-Requires inpatient hospitalization or prolongation of existing hospitalization. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as serious, unless at least one of the following expectations is met:

-The admission results in a hospital stay of less than 12 hours or
-The admission is preplanned (i.e., elective or scheduled surgery arranged prior to the start of the study) or
-The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during a hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authority is specifically require a more stringent definition, the local regulation takes precedent.

-Results in persistent or significant disability/incapacity. The definition of disability is a substantial disruption of a person's ability to conduct normal lifes functions

-Is a congenital anomaly/birth affect.

-Is an important medical event. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.2.4 Expectedness

Adverse events can be Expected or Unexpected

An expected adverse event is and events the previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the investigator brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

### 8.2.5 Attribution

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

Definite - The AE is clearly related to the study drug
Probable - The AE is likely related to the study drug.
Possible - The AE may be related to the study drug.
Unlikely - The AE is a doubtfully related to the study drug.
Unrelated - The AE is clearly not related to the study drug.

## 8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subjects participation in the study. The clinical course of each event will be followed up until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. If the event is related to the study treatment or participation, follow-up is not required once it has been determined to be a chronic, stable, and an ongoing condition.

The investigator is responsible for assuring that all adverse events observed or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subjects case report form, subjects medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:
-Description of the event
-Date of onset and resolution
-Grade of toxicity
-Attribution of relatedness to the investigational agent
-Action taken as a result of the event
-Outcome of the event

In this study, descriptions and grading scale is found in the NCI common terminology criteria for adverse events (CTCAE) version of 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

## 8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to the Cleveland Clinic IRB and local IRB (Allegheny) per IRB policy.

## 8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that all serious adverse events are reported to the Case Comprehensive Cancer Centers data safety toxicity committee.

## 9.0 PHARMCEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this study can be found in section 8.0.

### 9.1.1 Carboplatin

**Chemical Name**

Platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-*O*,*O'*]-, (*SP*-4-2).

**Other Names**

Paraplatin®

**Classification**

Antineoplastic. Alkylating agent.

**Molecular Formula**

C(6)H(12)N(2)O(4)Pt

**Mode of Action**

Carboplatin is a cisplatin analog with similar antineoplastic activity, but with a different adverse effect profile than cisplatin. Carboplatin has a carboxycyclobutane moiety replacing the chloride atoms on cisplatin. The major antineoplastic mechanism of action for carboplatin is the production of crosslinks within and between strands of deoxyribonucleic acid (DNA). Normal DNA synthesis is inhibited by this disruption of cellular DNA conformation.

**Metabolism**

Carboplatin is predominately excreted in the urine. Minimal hepatic metabolism occurs.

**Product description**

Carboplatin is available as 50mg, 150mg, and 450mg individual vials.

**Solution preparation**

Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:
Vial Strength Diluent Volume
50 mg 5 ml
150 mg 15 ml
450 mg 45 ml
These dilutions all produce a carboplatin concentration of 10 mg/ml.

**Storage requirements**

Carboplatin for injection should be protected from light and stored at controlled room temperature, 15 to 30 degrees centigrade (59 to 86 degrees Fahrenheit).

**Stability**

Unopened vials of PARAPLATIN are stable for the life indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light. When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.

**Route of administration**

Carboplatin is administered intravenously over 30 mintues after paclitaxel. Aluminum reacts with carboplatin to form an inactive precipitate; therefore, intravenous sets and needles containing aluminum which may come in contact with carboplatin should not be used.

Prior aminoglycoside therapy may potentiate carboplatin-induced renal toxicity

**Drug Procurement**

Carboplatin is commercially available in the United States. The cost of this agent will be the subjects responsibility.

### 9.1.2 5-Flourouracil

**Chemical Name**

5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione.

**Other Names**

Adrucil®

**Classification**

Antineoplastic. Antimetabolite.

**Molecular Formula**

C(4)H(3)FN(2)O(2)

**Mode of Action**

5-Flourouracil belongs to the class of agents referred to as antimetabolites. Its principle mechanism of action is thought to be inhibition of the enzyme Thymidylate Synthase (TS). Decreased activity of TS results in thymidine depletion and a subsequent reduction in the synthesis of DNA. TS inhibition accounts for the S-phase specificity of cytotoxicity. Other metabolites of 5-FU may incorporate into DNA and RNA, destabilizing these molecules and interfering with DNA repair.

**Metabolism**

5-Flourouracil is predominately metabolized by the liver.

**Product description**

5-Flourouracil is available as follows: 500mg/10ml vial, 1000 mg/20 ml, 2500mg/50ml vial, and 5000mg/100ml vial.

**Solution preparation**

Reconstitution is not required. The product should be visually inspected for particulate material. If precipitation has occurred as a result of exposure to cold temperature, 5-FU should be heated to 140 degrees farenheit and shaken vigorously to allow dissolution. 5-Flourouracil may be dispensed in a syringe or dilute in 50-1000 mL 0.9% normal saline or dextrose 5% water for infusion.

**Storage requirements**

5-Flourouracil should be stored at room temperature and protected from light.

**Stability**

Solutions of 5-FU are stable for 7 days when stored at 37°C and several weeks when stored at 25°C.

**Route of administration**

5-Flourouracil will be administered as an intravenous push over 2-4 minutes followed by a continuous IV infusion over 44 hours delivered via a portable infusion pump. All patients will require an implantable venous access catheter.

**Drug Procurement**

5-Flourouracil is commercially available. The cost of this agent will be the subjects responsibility.

### 9.1.3 Leucovorin

**Chemical Name**

Calcium N -[p -[[[(6RS)-2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl]methyl]amino]benzoyl]-L-glutamate(1:1).

**Other Names**

Folinic acid

**Classification**

Chemotherapy modulating agent. Antidote.

**Molecular Formula**

C(20)H(21)CaN(7)O(7)

**Mode of Action**

Leucovorin enhances the therapeutic and toxic effects of flouropyrimidines. Leucovorin is converted to 5, 10-methylenetetrahydrofolate, which acts to stabilize the binding of the 5-Flourouracil metabolite, 5-Fluorodeoxyuridine monophosphate, to thymidylate synthase, thereby augmenting inhibition of this enzyme.

**Metabolism**

Leucovorin is predominately metabolized by the liver.

**Product description**

Leucovorin calcium is supplied as a single use 50mg, 100mg, 200mg, 350mg, and 500mg sterile lyophilized powder.

**Solution preparation**

Powder for injection can be reconstituted using bacteriostatc water for injection U.S.P or sterile water for injection. Dilute in 100-1000 mL NS, D5W for infusion. When doses >10 mg/$m^2$ are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

Leucovorin should not be mixed in the same infusion as 5-FU, as these agents may precipitate.

**Storage requirements**

Lyophilized powder should be stored at room temperature and protected from light.

**Stability**

When reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion. When reconstituted with Bacteriostatic Water for Injection, USP, the solution can be refrigerated and stored for up to 7 days. The final parenteral admixture is stable for 24 hours at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

**Route of administration**

Leucovorin is administered intravenously over 2 hours concurrent with oxaliplatin. Longer infusion schedules over 6 hours are permissible in the setting of oxaliplatin dose modification. Due to the calcium content, Leucovorin solutions should never be administered at a rate greater than 160mg/minute.

**Drug Procurement**

Leucovorin is commercially available. The cost of this agent will be the subjects responsibility.

### 9.1.4 Oxaliplatin

**Chemical Name**

cis-[(1R,2R)-1,2-cyclohexanediamine-N,N'][oxalate(2-)-O,O'] platinum

**Other Names**

Eloxatin®

**Classification**

Antineoplastic. Alkylating agent.

**Molecular Formula**

C(8)H(14)N(2)O(4)Pt

**Mode of Action**

The principle mechanism of anti-neoplastic activity is attributed to the formation of inter- and intra-strand DNA / platinum cross-links. This results in inhibition of DNA replication, transcription, and induction of apoptosis. Cytotoxicity is cell cycle nonspecific.

**Metabolism**

Oxaliplatin undergoes non-enzymatic conversion forming several active and inactive derivatives. There is no evidence for cytochrome P450 mediated oxaliplatin metabolism. The predominant mechanism of elimination is renal excretion.

**Product description**

Sterile, preservative-free Lyophilized powder for reconstitution is supplied as 50mg and 100mg vials.

**Solution preparation**

Oxaliplatin is reconstituted by adding 10ml (for the 50mg vial) or 20ml (for the 100mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. The reconstituted solution must be further diluted in an infusion solution of 250-500 ml of 5% dextrose injection, USP. Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions. Do not use needles or administration sets containing aluminum during preparation.

**Storage requirements**

Powder may be stored at room temperature under normal lighting conditions.

**Stability**

Reconstituted solution in original vial may be stored for up to 24 hours under refrigeration [2-8 degrees C (36-46 degrees F)]. Final solution for infusion should be immediately administered but can be kept for up to 6 hours at room temperature.

**Route of administration**

Oxaliplatin will be given IV over 2 hours in this study. Infusion time may be increased to 6 hours as outlined above. Flush infusion line with $D_5W$ prior to administration of any concomitant medication.

**Drug Procurement**

Oxaliplatin is commercially available. The cost of this agent will be the subjects responsibility.

### 9.1.5 Paclitaxel

**Chemical Name**

5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine

**Other Names**

Taxol®

**Classification**

Antineoplastic. Antimicrotubule agent.

**Molecular Formula**

C(47)H(51)NO(14)

**Mode of Action:**
Paclitaxel stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for mitotic cellular functions.

**Metabolism**

Paclitaxel is predominately metabolized by the cytochrome P450 enzymes CYP2C8 and CYP3A4.

**Product description**

Paclitaxel is supplied as a clear to slightly yellow viscous solution intended for reconstitution. Paclitaxel is available in 30mg/5ml, 100mg/16.7ml, 150 mg/25ml, and 300mg/50ml multidose vials. Each mL of solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

**Solution preparation**

Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer'sInjection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter. Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter should not be used.

**Storage requirements**

Store intact vials at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

**Stability**

Unopened vials of paclitaxel are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions diluted for infusion in $D_5W$ and NS are stable for up to 3 days at room temperature (25°C).

**Route of administration**

Paclitaxel is administered intravenously over 1 hour before carboplatin.

**Drug Procurement**

Paclitaxel is commercially available. The cost of this agent will be the subjects responsibility.

## 10.0 EXPLORATORY CORRELATIVE STUDIES

### 10.1 Ki67 Expression in Locally Advanced Esophageal Adenocarcinoma

10.1.1 Background

The Ki67 antibody was first discovered in the early 1980s by researchers in Kiel, Germany. While the exact function of Ki67 remains undefined, it appears to be necessary for cellular replication. Ki67 is a nuclear protein which is expressed during all phases of the cell cycle (G1, S, G2, M) but is absent during quiescence (Go). Ki67 therefore serves as a marker of proliferation (17).

Over the past two decades, Ki67 expression has been investigated in various malignancies, including cancers of the breast, prostate, colon, and rectum. While the data are inconsistent and sometimes conflicting, increased Ki67 expression appears to have prognostic utility. For example, Stuart-Harris et al. reported results from a systematic review and meta-analysis evaluating various proliferation markers with respect to survival outcomes in patients with early breast cancer (18). In this study, Ki67 overexpression was associated with diminished OS and DFS by univariate and multivariate analysis (HR OS 1.73, HR DFS 1.84).

Ki67 expression has also been explored as a predictive marker for response to treatment in studies investigating neoadjuvant therapy. Von Minckwitz et al. evaluated the ability of Ki67 and other biomarkers to predict for a pathologic complete response to pre-operative therapy (19). Patients were randomized to receive chemotherapy with 4 cycles of dose dense doxorubicin and docetaxel with or without concurrent tamoxifen. While Ki67 expression did not correlate with pathologic complete response rates, patients with low Ki67 expression appeared to respond preferentially to tamoxifen.

In contrast to these results, Carlomagno et al. reported results from a phase II study investigating the ability of various biomarkers to predict for pathologic response after preoperative chemoradiotherapy in patients with rectal cancer (20). In this study, 46 patients received pre-operative chemoradiotherapy with 5FU and oxaliplatin. Ki67 expression in >30% of cells on the initial biopsy specimen was associated with a favorable pathologic response. Furthermore, pathologic response correlated with disease free survival.

Similar results were seen in a retrospective study reported by Fasching et al (21). Ki67 expression in core biopsy specimens was investigated prior to the administration of pre-operative chemotherapy in patients with early breast cancer. In this study, high Ki67 expression prior to initiation of pre-operative therapy was an independent predictor of pCR (OR 3.5, p=0.01) and OS (HR 8.1, p=0.0001).

Andrade et al. reported results from a retrospective analysis investigating several biomarkers in patients with rectal cancer who again received pre-operative therapy (22). In contrast to the previously mentioned studies, Ki67 expression was evaluated in the surgical specimen after pre-operative chemoradiotherapy. Patients with <50% of cells expressing Ki67 were felt to have a low proliferative index (LPI). Patients with a LPI after pre-operative chemoradiotherapy had superior overall survival compared to patients with an elevated Ki67 expression (p=0.041).

10.1.2 Rationale for Analysis

It appears that elevated Ki67 expression at the time of diagnosis may predict for pathologic response to neoadjuvant chemotherapy. Furthermore, increased expression of Ki67 after pre-operative chemotherapy may be indicative of aggressive tumor biology and may be associated with inferior survival outcomes. We plan to prospectively analyze Ki67 expression on tumor specimens before and after pre-operative chemotherapy and correlate these findings with clinical and pathologic response parameters as well as survival outcomes

10.1.3 Collection of specimens

Biopsy / surgical material for Ki67 evaluation will be obtained from the following procedures:

1) Pre-treatment staging upper endoscopy.
2) Surgical resection specimen.

10.1.4 Handling of specimens

Biopsy material / surgical pathology will be handled per institutional protocol.

10.1.5 Laboratory

Biopsy specimens / surgical pathology will be processed in the Cleveland Clinic laboratory per institutional protocol.

## 10.2 HER2 Gene Amplification and Protein Overexpression in Locally Advanced Esophageal Adenocarcinoma

10.2.1 Background

The human epidermal growth factor receptor 2 (HER2) is a trans-membrane glycoprotein receptor with cytoplasmic tyrosine kinase activity. It belongs to the ErbB family, which is comprised of ErbB1 (EGFR), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). Ligand binding to inactive ErbB monomers stimulates the formation of homo / hetero-dimers between ErbB members leading to auto-phosphorylation and subsequent signal

transduction through various signaling cascades including the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. While HER2 lacks binding affinity for the EGFR family of ligands, it is the preferred hetero-dimeric binding partner for other members of the ErbB family. Ligand binding and subsequent signal transduction through the ErbB family of receptor tyrosine kinases results in augmented cellular proliferation and survival and influences differentiation and apoptosis (23).

HER2 gene amplification by fluorescence in situ hybridization (FISH) and / or protein overexpression by immunohistochemistry (IHC) has been demonstrated in various malignancies, including breast, gastric, and ovarian cancer (23). In breast cancer, HER2 gene amplification or protein overexpression offers both prognostic and predictive information, identifying a small group of tumors with aggressive biology that are often more responsive to monoclonal antibodies and small molecule tyrosine kinase inhibitors which target the HER2 oncoprotein.

Approximately 20% of patients with gastric cancer demonstrate either HER2 overexpression or gene amplification (referred to as HER2 positive) (23). Many of these patients appear to obtain benefit from the addition of trastuzumab to standard chemotherapy in the metastatic setting. The trastuzumab for gastric cancer (ToGA) trial was a multinational, randomized, phase III, open label study comparing the combination of cisplatin and capecitabine (or 5-fluorouracil) with or without the addition of trastuzumab in HER2 positive patients with gastric and GEJ adenocarcinoma (24). Patients received 6 cycles of chemotherapy administered every 3 weeks. Patients in the investigational arm received trastuzumab concurrently with chemotherapy and then as maintenance every 3 weeks until they developed progressive disease. The primary endpoint of the study, overall survival, favored treatment with trastuzumab. Patients randomized to the trastuzumab arm had a median overall survival of 13.8 months compared to 11.1 months in patients who received chemotherapy alone (HR 0.74, 95% CI 0.60-0.91, p=0.0046). In a post hoc analysis, patients with higher levels of HER2 protein expression appeared to obtain greater benefit with the addition of trastuzumab compared to HER2 positive patients with lower levels of expression. Patients who were HER2 IHC 3+ or HER2 IHC 2+ / FISH amplified (high HER2 expression) were compared to patients who were FISH amplified but only IHC 0-1+ (low HER2 expression). Patients with high HER2 expression obtained a median overall survival of 16.0 months compared to 11.8 months in patients with low levels of expression (HR 0.65, 95% CI 0.51-0.83). This study, reported by Bang et al in 2010, established a new standard of care for patients with HER2 positive gastric cancer. While a treatment effect could not be excluded in patients with gastroesophageal junction adenocarcinomas, they represented only 20% of subjects in the investigational arm. Therefore, it remains unclear if we can extrapolate these results to patients with adenocarcinoma of the GEJ and distal esophagus.

It also remains unclear whether HER2 overexpression or gene amplification is a prognostic factor in patients with gastroesophageal adenocarcinoma. Phillips et al. recently reported the results of a retrospective analysis exploring the relationship between clinicopathologic features, survival outcomes and HER2 status (25). Pathologic specimens from 156 patients enrolled in 2 prospective phase II studies of perioperative chemoradiotherapy for locoregionally advanced adenocarcinoma of the esophagus and GEJ were examined. Twenty three percent of the specimens analyzed were found to be HER2 positive. With the exception that HER2 positive tumors were more likely to be poorly differentiated when compared to HER2 negative disease ($p<0.001$), there was no association between clinicopathologic features and HER2 status. Furthermore, there was no difference in survival outcomes or local control between HER2 positive and HER2 negative subjects.

Similar results were reported by Janjigian et al. in 2012 (26). This study was a retrospective review of 381 patients enrolled in 6 prospective studies of first line chemotherapy (without trastuzumab) for metastatic gastroesophageal adenocarcinoma. In this study, 20% of patients were found to be HER2 positive. HER2 positive patients were more likely to have intestinal histology and liver metastasis when compared to HER2 negative patients. However, on multivariate analysis, HER2 did not emerge as an independent predictor of overall or disease free survival.

In contrast to these findings, Chan et al. reported results of a systematic review and meta-analysis in 2012 which suggested that HER2 overexpression or gene amplification is associated with an inferior survival in patients with operable esophageal cancer (27). This study evaluated 14 trials and included 1464 patients with locoregional esophageal SCC and ACA. Various perioperative management strategies were employed, but notably only one trial utilized preoperative chemoradiotherapy. The overall 5 year mortality was higher in HER2 positive patients [OR 1.43 (95% CI 1.04-1.95) p=0.03]. HER2 was found to be a poor prognostic factor in both esophageal SCC and ACA.

10.2.2 Rationale for Analysis

HER2 gene amplification or protein overexpression serves as a predictive marker in patients with gastric cancer for response to trastuzumab. Unlike in breast cancer, it remains unclear if HER2 also provides prognostic information for patients with locoregionally advanced gastroesophageal adenocarcinoma. We plan to investigate the association between HER2 status and clinical and pathologic response parameters and survival outcomes in patients with LRA ACA of the DE and GEJ. We will evaluate HER2 protein expression by IHC and gene amplification by FISH.

10.2.3 Collection of specimens

Biopsy material for HER2 evaluation will occur as part of the initial upper endoscopy with endoscopic ultrasound. Specimens from the surgical resection specimen will also be evaluated for HER2 expression by IHC and gene amplification by FISH.

10.2.4 Handling of specimens

Biopsy material / surgical specimens will be handled per institutional protocol.

10.2.5 Laboratory

HER2 evaluation by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) will be performed in the Cleveland Clinic laboratory per institutional protocol.

## 11.0 STUDY PARAMETERS AND CALENDAR:

### 11.1 Study Parameters

The following studies and evaluations will be obtained and recorded as part of this investigational protocol:

Informed consent
History and physical examinations
Performance status assessment (ECOG)
EGD with EUS and biopsy
PET/CT (with diagnostic CT abdomen/pelvis preferred)
CT Chest /abdomen / pelvis with contrast
PFT (spirometry with DLCO)
Cardiac stress testing (dobutamine stress echocardiogram preferred)
BMP (basic metabolic panel)
HFP (hepatic function panel)
CMP (complete metabolic panel)
CBC
Ki67 (exploratory study)
HER2 by IHC and FISH (exploratory study)
Dysphagia assessment (see section 12.2)
β-HCG (in women of child bearing potential)

#### 11.1.1 Screening evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤ 42 days (6 weeks) prior to administration of protocol therapy.

Informed consent
History and physical exam
Performance status (ECOG)
EGD / EUS

PET / CT (with diagnostic CT abdomen / pelvis preferred)
PFT (Spirometry with DLCO)
Cardiac stress test (dobutamine stress echocardiogram preferred)
CBC
BMP and HFP (a CMP may substitute for BMP and HFP)
Serum β-HCG in women of childbearing potential
Correlative study- Ki67 IHC and HER2 FISH / IHC will be performed on initial biopsy specimens after enrollment.

### 11.1.2 Treatment period

**Pre-operative chemotherapy**
All subjects will receive 4 cycles of mFOLFOX6, administered every 14 days. Chemotherapy can be administered within +/- 2 days of the 14 day cycle.

Cycle 1 / Day 1
H & P, Performance status (ECOG)
Dysphagia evaluation
BMP, CBC
Please note all studies / evaluations may be performed within 1 week prior to starting protocol therapy.

Cycle 2 / Day 1
H & P, Performance status (ECOG)
BMP, CBC
Please note all studies / evaluations may be performed within 48 hours prior to C2/D1

Cycle 3 / Day 1
H & P, Performance status (ECOG)
BMP, CBC
Dysphagia evaluation
Please note all studies / evaluations may be performed within 48 hours prior to C3/D1

Cycle 4 / Day 1
H & P, Performance status (ECOG)
BMP, CBC
Please note all studies / evaluations may be performed within 48 hours prior to C4/D1

**Pre-operative assessment**
Approximately 3-4 weeks (a window of 2-5 weeks is acceptable and will not be considered a deviation) after the completion of chemotherapy, all subjects will undergo a pre-operative evaluation including the following:

H & P, Performance status (ECOG)
Dysphagia evaluation

CBC
BMP, HFP (a CMP may be substituted for a BMP and HFP)
EGD/EUS
PET/CT (PET/CT with diagnostic CT abdomen/pelvis is preferred) OR CT chest / abdomen / pelvis with IV/oral contrast

**Surgical Pathology**
In addition to standard pathologic evaluation, including assessment of residual tumor viability, the following exploratory studies will be obtained: Ki67 IHC and HER2 FISH / IHC.

**Post-operative assessment**
Approximately 4-6 weeks (a window of 3-8 weeks is acceptable and will not be considered a deviation) after surgery, all subjects will be evaluated prior to initiating post-operative chemoradiotherapy. Review of the pathologic data will be performed and the post-operative chemoradiotherapy regimen will be identified. In addition, all subjects will undergo the following:

H & P, Performance status (ECOG)
CBC
HFP, BMP (a CMP may be substituted for a BMP and HFP)

**Post-operative chemoradiotherapy**
All subjects will initiate adjuvant chemoradiotherapy between 6 – 12 weeks post-operatively. All patients receiving adjuvant therapy will be seen and evaluated weekly during chemoradiotherapy. FOLFOX cycle length is 14 days. Carboplatin and paclitaxel is administered in one 36 day cycle on chemotherapy days 1, 8, 15, 22, 29, and 36. Chemotherapy will only be administered if radiotherapy is ongoing. Please note all chemotherapy can be given within a window of +/- 2 days of the anticipated cycle interval. All subjects will undergo at least the following weekly assessments:

Weekly post-operative adjuvant therapy assessments
H & P, Performance status (ECOG)
CBC, BMP
Please note all assessments / evaluations may be performed within 48 hours prior to scheduled chemotherapy

**Post-therapy follow up**
Follow-up visits after completion of therapy are recommended approximately every 3 months for the first 2 years. After 2 years from the completion of therapy, follow-up visits are recommended every 4-6 months for a total of 5 years. After 5 years, annual follow-up visits are recommended but not required.

H & P, Performance status (ECOG)
CBC, BMP, HFP, and CT scans are not mandatory but should be performed based on symptoms at the discretion of the investigator

## 11.2 Calendar

Pretreatment testing will be performed within the 6 weeks (42 days) of initiation of cycle 1 / day 1.

| | Pre-treatment evaluation | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Pre-operative evaluation | Surgery | Post-operative evaluation | Weekly Adjuvant CRT | Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|
| H & P | X | X | X | X | X | X | | X | X | X |
| Written Informed consent | X | | | | | | | | | |
| ECOG /performance status | X | X | X | X | X | X | | X | X | X |
| Dysphagia assessment | | X | | X | | X | | | | |
| Cardiac Stress Test (dobutamine echo preferred) | X | | | | | | | | | |
| PFT with DLCO | X | | | | | | | | | |
| CT C/A/P | | | | | | X• | | | | |
| PET/CT (with diagnostic CT abd/pelvis preferred) | X | | | | | X | | | | |
| EGD / EUS | X | | | | | X | | | | |
| BMP | X | X | X | X | X | X | | X | X | |
| HFP | X | | | | | X | | X | | |
| CBC w diff | X | X | X | X | X | X | | X | X | |
| Pregnancy test | X•• | | | | | | | | | |
| Ki67 | X | | | | | | X | | | |
| HER2 | X | | | | | | X | | | |

(•) = A PET/CT (with diagnostic CT of the abdomen/pelvis) is preferred. However, in the event a PET/CT cannot be obtained, a CT chest / abdomen / pelvis may suffice.
(••) = For women of child bearing potential.
NOTE: A CMP may substitute for the combination of a BMP and HFP.

NOTE: Chemotherapy can be administered within a window of +/- 2 days of the anticipated cycle interval.

## 12.0 MEASUREMENT OF EFFECT

### 12.1 Definitions of Resection

R0 resection is defined as the resection of all gross and microscopic tumor, i.e. absence of tumor at the inked margins of resection.

R1 resection is defined as microscopic involvement at the inked margins of resection.

R2 resections is defined as gross residual disease

### 12.2 Response Criteria

12.2.1 Symptomatic response

Dysphagia: Dysphagia will be assessed throughout treatment. Dysphagia response is defined as improvement in dysphagia by ≥ 1 grade from pretreatment baseline. Severity / grade of dysphagia will be recorded during pre-operative chemotherapy on day 1 / cycle 1, day 1 / cycle 3, and at the pre-operative medical oncology physician visit, scheduled at the time of pre-operative re-staging.

Dysphagia will be assessed as follows:

Level 1: No dysphagia. Dose not require dietary modification
Level 2: Minimal dysphagia - able to swallow liquids and most solid foods, experiencing occasional difficulty. Diet is modified
Level 3: Moderate dysphagia - able to swallow liquids and very soft foods.
Level 4: Severe dysphagia - unable to swallow liquids or solids. Requires an enteral feeding tube or parenteral nutritional support

12.2.2 Dysphagia response will be recorded as follows:

Complete response = complete resolution of dysphagia to level 1 which remains stable until surgery
Partial response = improvement in dysphagia by ≥ 1 level without complete resolution of symptoms during pre-operative chemotherapy which remains stable until surgery
Stable disease = no change in dysphagia
Progressive disease = worsening dysphagia ≥ one level during pre-operative chemotherapy without transient benefit
Transient response = improvement in dysphagia by ≥ 1 level by day 1 / cycle 3 with return to baseline grade or worse at pre-operative evaluation

12.2.3 Endoscopic response

EGD with endoscopic ultrasound is required for initial staging and will be repeated prior to surgery. The primary role of repeat endoscopy is to ensure resectability. However, endoscopic response rate will be recorded as follows:

Complete response = no residual abnormality (cyT0N0-Stage 0)
Partial response = any improvement in the clinically determined T or N stage (without reciprocal deterioration in T or N) when compared to the pretreatment clinical stage as assessed by EGD/EUS.
Stable disease = no change in the clinical T or N stage when compared to the pretreatment assessment.
Progressive disease = any increase in the T or N stage (irrespective of any reciprocal improvement in the T or N stage) when compared to the pretreatment clinical stage as assessed by EGD/EUS.

Note: Locoregional progressive disease will not preclude surgical intervention provided the disease remains potentially resectable at re-evaluation (i.e. no cT4b or cM1 disease). Patients with evidence for distant metastases will be considered inoperable.

Note: Clinical response (symptomatic / endoscopic) will not be used to determine post-operative adjuvant therapy.

12.2.4 Pathologic response

Pathologic response of the primary tumor will be reported as the treatment effect. The treatment effect estimates the amount of residual viable tumor relative to residual mucin pools or scarring. The relative extent of invasion of both viable tumor cells and acellular mucin pools / scarring will also be reported along with final pathologic stage.

Treatment effect will be quantified and described as follows:
Complete pathologic response (pCR) = No residual cancer cells
Major pathologic response (pMjR) = 1-25% residual cancer cells
Intermediate pathologic response (pIR) = 26-50% residual cancer cells
Minor pathologic response (pMnR)= 51-75% residual cancer cells
No pathologic response (pSD) = >75% residual cancer cells

Positive pathologic response (+PR) = complete, major, and intermediate pathologic response.

Negative pathologic response (-PR) = minor or no pathologic response.

Patients who have achieved a complete, major, or intermediate pathologic response (≤50% viable tumor), referred to as a positive pathologic response (+PR), will continue to be treated with FOLFOX during the adjuvant period concurrent with radiotherapy.

Patients with a minor (pMnR) or no (pSD) pathologic response (>50% viable tumor), referred to a negative pathologic response (-PR), will receive adjuvant chemoradiotherapy with carboplatin and paclitaxel.

### 12.3 **Survival**

Overall survival is defined as the length of time from starting treatment until death due to any cause. Recurrence free survival will be defined as the time from starting treatment until first recurrence or death from any cause.

### 12.4 **Patterns of Failure**

Sites of first recurrence will be defined as loco-regional, distant, or combined (loco-regional and distant). Locoregional failure is recurrent disease in the radiotherapy field. Distant failure is recurrent disease outside of the radiotherapy field.

## 13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

### 13.1 **Data Reporting**

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

### 13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

#### 13.2.1 Written informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and

adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject data protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center / Cleveland Clinic Cancer Institute supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.6 Data safety and monitoring plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations

## 14.0 STATISTICAL CONSIDERATIONS

In our prior phase II protocol, investigating induction chemotherapy followed by surgery and adjuvant chemoradiotherapy, exploratory analysis demonstrated an association between the percentage of viable tumor at the time of esophagectomy and survival outcomes. More specifically, both overall survival (OS) and recurrence free survival

(RFS) were superior in patients with ≤ 50% viable tumor compared to patients with >50% viable disease [OS (p=0.020; log rank test), RFS (p=0.002; log rank test)]. The one year RFS was 93% in patients with ≤ 50% viability and 49% in patients with > 50% viability. Our hypothesis is that we will improve RFS in patients with greater than 50% tumor viability after induction chemotherapy by employing an alternative adjuvant chemotherapy regimen, while maintaining a similar RFS to the prior study in patients with ≤ 50% tumor viability. Specifically, if our current pathologic response based approach is effective, we would anticipate an improvement in one year RFS from 50% to ≥ 65% in patients who have > 50% viable tumor after induction chemotherapy. Thirty-three patients with > 50% viable tumor will be required to test this hypothesis using a one sided test with 5% significance and 80% power assuming this trial will take 3 years to accrue and an additional 2 years of follow-up. Therefore, this study will accrue patients until we acquire 33 subjects with greater than 50% viable tumor. Based on our prior phase II protocol, we anticipate that approximately 50% of patients treated according to this protocol will have > 50% viable tumor after induction therapy. Therefore, we anticipate a total accrual of approximately 66 patients. We also expect that patients with ≤ 50% viable tumor after induction therapy will have a RFS similar to our prior study. Therefore, study size calculations are based on expected differences in RFS among those with > 50% viable tumor.

In addition to RFS comparisons between the current and prior studies by tumor viability, OS and RFS will be compared between patients with ≤50% and >50% viable tumor using the log-rank test. Outcomes will be calculated relative to the start of therapy. Cox proportional hazards analysis will be used to estimate the hazard ratio for OS and RFS for patients with >50% viable tumor relative to those with ≤50%. If there are a sufficient number of events, multivariable Cox analysis will be done to adjust for other prognostic factors.

Symptomatic, endoscopic, and pathologic response will be estimated using exact 95% confidence intervals, as will R0 resections and toxicities. Kaplan-Meier analysis will be used to estimate local and distant recurrence (patterns of failure).

The correlative studies are considered only exploratory. Ki-67 expression will be described as mean and standard deviation or median and range, as appropriate. Change in Ki-67 expression before and after induction chemotherapy will be assessed using either the paired t-test or Wilcoxon signed rank test. HER2 overexpression will be described as frequency counts and percentages. The prognostic effect of KI-67 and HER2 overexpression on pathologic response will be assessed with logistic regression analysis, and the prognostic effect on OS and RFS with Cox proportional hazards analysis.

Data will be analyzed using SAS® software (SAS Institute, Inc., Cary, NC). Unless otherwise noted, all statistical tests will be two-sided, and $p \leq 0.05$ will be used to indicate statistical significance.

**REFERENCES**


1) Van Hagen P, Hulshof MCCM, Van Lanschot JJB, et al.: Preoperative chemoradiotherpay for esophageal or junctional cancer. N Eng J Med 2012, 366:2074-2084.

2) Walsh TN, Noonan N, Hollywood D, et al.: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Eng J Med 1996, 335:462-467.

3) Tepper J, Krasna MJ, Niedzwiecki D, et al.: Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008, 26:1086-1092.

4) Bancewicz J, Clark PI, Smith D, Donnelly RJ, et al.: Surgical resection with or withour preoperative chemotherapy in esophageal cancer: a randomized control trial. The Lancet 2002, 359:1727-33.

5) Ychou M, Boige V, Pignon J, et al.: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011, 29:1715-1721.

6) Kelsen DP, Ginsberg R, Pajak TF, et al.: Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998:1979-84.

7) Macdonald JS, Smalley SR, Benedetti J, et al.: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Eng J Med 2001, 345:725-30.

8) Cunningham D, Allum WH, Stenning SP, et al.: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Eng J Med 2006, 335;11-20.

9) Montagnani F, Turrisi G, Marinozzi C, et al,: Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2011, 14;50-55.

10) Enzinger PC, Burtness B, Hollis D, et al.: CALGB 80403/ECOG 1206: A randomized phase II study or three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. J Clin Oncol (Meeting Abstracts) May 2010 vol. 28 no. 15_suppl 4006.

11) Andre T, Boni C, Mounedji-Boudiaf L, et al.: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Eng J Med 2004, 350:2343-51.

12) Fuchs CS, Tepper JE, Niedzwiecki D, et al.: Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: intergroup trial CALGB 80101. J Clin Oncol (meeting abstracts) May 2011 vol. 29 no. 15_suppl 4003.

13) "Taxol [package insert]. Bristol-Myers Squibb Company: 2011. Princeton, NJ 08543 USA. http://packageinserts.bms.com/pi/pi_taxol.pdf

14) Ford H, Marshall A, Wadsley J, et al. Cougar-02: a randomized phase III study of docetaxel versus active symptom control in advanced esophagogastric carcinoma (abstract). J Clin Oncol 30: 2012 (suppl 34: abstr LBA4).

15) Conroy T, Yataghene Y, Etienne PL, et al,: Phase II randomized trial of chemoradiotherpay with Folfox4 or cisplatin plus fluorouracil in esophageal cancer. British Journal of Cancer 2010, 103:1349-1355

16) Conroy T, Galais MP, Raoul JL, et al.: Phase III randomized trial of definitive chemoradiotherapy (CRT) with FOLFOX or cisplatin and fluorouracil in esophageal cancer (EC): final results of the PRODIGE 5/ACCORD 17 trial.

17) Yerushalmi R, Woods R, Ravdin PM, et al.: Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 2010, 11:174-83.

18) Stuart-Harris R, Caldas C, Pinder SE, et al.: Proliferation markers and survival in early breast cancer: a systematic review and meta-analysis of 85 studies in 32,825 patients. The Breast 2008, 17:323-34.

19) Von Minckwitz G, Sinn HP, Raab G, et al.: Clinical response after two cycles compared to HER2, Ki-67,p53, and bcl-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast. Breast Cancer Research 2008, 10:R30.

20) Carlomagno C, Pepe S, D'Armiento FP, et al.: Predictive factors of complete response to neoadjuvant chemoradiotherapy in patients with rectal cancer. Oncology 2010, 78:369-75.

21) Fasching PA, Heusinger K, Haeberle L, et al.: Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011, 11:486.

22) Andrade NR, Oshima CTF, Gomes TS, et al.: Immunoexpression of Ki-67 and p53 in rectal cancer tissue after treatment with neoadjuvant chemoradiation. J Gastrointest Canc 2011, 42:34-39.

23) Almhanna K, Meredith KL, Hoffe S, et al. Targeting the human epidermal growth factor receptor 2 in esophageal cancer. Cancer Control 2013, 20:11-16.

24) Bang Y, Van Cutsem E, Feyereislova A, et al,: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancer 2010, 376:687-697.

25) Phillips BE, Tubbs RR, Rice TW, et al.: Clinicopathologic features and treatment outcomes of patients with human epidermal growth factor receptor 2- positive adenocarcinoma of the esophagus and gastroesophageal junction. Diseases of the Esophagus 2013, 26:299-304.

26) Janjigian YY, Werner D, Pauligk C, et al.: Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA international collaborative analysis. Annals of Onocology 2012, 23:2656-62.

27) Chan DSY, Twine CP, Lewis WG: Systematic review and meta-analysis of the influence of HER2 expression and amplification in operable oesophageal cancer. J Gastrointest Surg 2012, 16:1821-29.

## APPENDIX

## PERFORMANCE STATUS CRITERIA*

| ECOG Performance Status Scale | |
|---|---|
| **Grade** | **Descriptions** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 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). |
| 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. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |

| | |
|---|---|
| 5 | Dead. |

*Karnofsky performance status can be converted to ECOG using the following scale:
ECOG 0 = Karnofsky = 90-100
ECOG 1 = Karnofsky = 70-80
ECOG 2 = Karnofsky = 50-60
ECOG 3 = Karnofsky = 30-40
ECOG 4 = Karnofsky = 10-20
ECOG 5 = Karnofsky = 0

**SUMMARY OF CHANGES v8 01/16/2018**

| Protocol Date | Section | Change |
|---|---|---|
| 01/1618 | schema | Added schema is an outline and to refer to treatment plan for details |
| 01/16/18 | 6.3 | Added IMRT is allowed on a case by case bases |
| 01/16/18 | 6.3 | Removed, No radiation dose or schedule modification will be allowed on this protocol. Every attempt should be made to complete the prescribed course of radiation therapy on schedule. |
| 01/16/18 | 7.3.4 | Changed, Benadryl to 25-50 mg IV |
| 01/16/18 | | Protocol version changed to 8. Protocol date changed to 01/16/2018 on page 1 and the footer |