ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A021302

IMPACT OF EARLY FDG-PET DIRECTED INTERVENTION ON PREOPERATIVE THERAPY FOR LOCALLY ADVANCED GASTRIC CANCER: A RANDOM ASSIGNMENT PHASE II STUDY

NCI-supplied agent(s): NONE
Industry-supplied agent(s): NONE
Commercial agent(s): Epirubicin, Oxaliplatin, Cisplatin, Capecitabine, 5-Flurouracil (5-FU), Docetaxel, Irinotecan
IND Exempt Study

ClinicalTrials.gov Identifier: NCT02485834

Study Chair
Manish A. Shah MD
Weill Medical College of Cornell University

[redacted]

Surgical Oncology Co-chair
[redacted]

RT and Community Oncology Co-chair
[redacted]

GI Correlative Science Co-Chair
[redacted]

GI Committee Co-Chairs
[redacted]

Imaging Committee Co-Chairs
[redacted]

Primary Statistician
[redacted]

Secondary Statistician
[redacted]

Protocol Coordinator
[redacted]

Data Manager
[redacted]

ECOG Co-Chair
[redacted]

SWOG Co-Chair
[redacted]

NRG Co-Chair
[redacted]

Participating Organizations:
ALLIANCE / Alliance for Clinical Trials in Oncology (lead), ECOG/ACRIN / ECOG-ACRIN Cancer Research Group, SWOG / SWOG, NRG / NRG Oncology

Study Resources:

Expedited Adverse Event Reporting [redacted]	**Medidata Rave® iMedidata portal** [redacted]
OPEN (Oncology Patient Enrollment Network) [redacted]	**Biospecimen Management System** [redacted]

Protocol Contacts:

A021302 Nursing Contact [redacted]

A021302 Pharmacy Contact [redacted]

Alliance Biorepository at Ohio State [redacted]

Imaging Core Lab at IROC Ohio [redacted]

Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, & (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Regulatory Affairs Manager [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Ohio State University [redacted]
Questions regarding RT QA Data Requirements and Submission	IROC Rhode Island QA Center [redacted]

Document History	**Effective Date:**		
Pre-Activation	07/01/15	Update 03	04/15/2016
Activation	08/01/15	Update 04	XX/XX/2016
Update 01	11/01/15		
Update 02	03/15/2016		

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via: **ONLINE**: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) **EMAIL**: [redacted] (regulatory documentation only) **FAX**: [redacted] **MAIL**: [redacted] For regulatory questions call the CTSU Regulatory Help Desk at [redacted]	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted].	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., patient eligibility or treatment-related) see Protocol Contacts, Page 2		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org.		

IMPACT OF EARLY FDG-PET DIRECTED INTERVENTION ON PREOPERATIVE THERAPY FOR LOCALLY ADVANCED GASTRIC CANCER: A RANDOM ASSIGNMENT PHASE II STUDY

Pre-Registration (Step 0) Eligibility Criteria (see Section 3.2)

Histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II, III)

Pre-treatment clinical stage of T3-4NanyM0 or TanyNpositiveM0 as determined by laparoscopy, CT scan (or PET/CT), or endoscopic ultrasound (histologic confirmation of lymph involvement not required).

Patients can have measurable or non-measurable disease.

Patients must be eligible for curative intent surgical resection.

Required Initial Laboratory Values	
Absolute neutrophil count (ANC)	$\geq 1500/mm^3$
Platelet Count	$\geq 100,000/mm^3$
Creatinine	$\leq$ 1.5 x ULN
Total Bilirubin	$\leq$ 1.5 x ULN
Alkaline Phosphatase	$\leq$ 2.5 x ULN
AST / ALT	$\leq$ 2.5 x ULN

Patients must have an FDG avid tumor(s), which are defined as a primary tumor with an increased uptake in the region of the tumor that has an SUV of > 5.0 or a tumor:liver ratio of > 1.5.

No prior history of Congestive heart failure (NYHA class I to IV) or known DPD deficiency

No current grade 2, 3, or 4 of neuropathy or known hypersensitivity to oxaliplatin and cisplatin, capecitabine and 5-flurouracil, docetaxel or irinotecan

Not pregnant and not nursing. Women of childbearing potential only, a negative serum pregnancy test pregnancy test done $\leq$ 7 days prior to pre-registration is required

Age $\geq$ 18 years and ECOG Performance Status 0 or 1

Registration (Step 1) Eligibility Criteria (see Section 3.3)

Patient must continue to be eligible for curative intent surgical resection

FDG avid malignancy that is classified as an FDG PET non-responder, which are defined as having < 35% reduction in the FDG uptake of the primary tumor when compared to baseline.

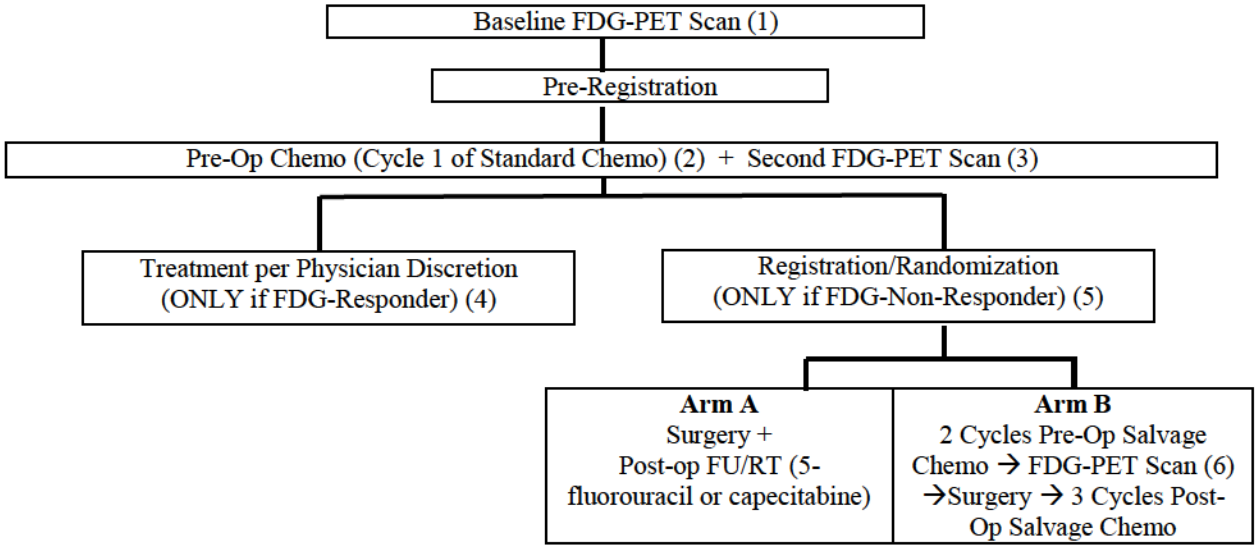
Chronic concomitant treatment with strong inhibitors of CYP3A4 and strong CYP3A4 inducers is not allowed. Such drugs must be discontinued 14 days prior to the start of study treatment. See Sections 8.1.9 and 8.1.10 for more information.

Patient must have received one cycle of the following regimens during the pre-registration time period Epirubicin (optional), Oxaliplatin (or Cisplatin), Capecitabine (or Fluorouracil)

Toxicity recovery including the following: Grade $\leq$ 2 neuropathy; Grade $\leq$ 2 diarrhea; Grade $\leq$ 2 mucositis

Pre-registration chemotherapy given within 42 days of initiation of randomized treatment

Schema



1 Baseline FDG-PET scan is to be performed within 28 days of Cycle 1 pre-op chemo

2 Pre-op chemo (Cycle 1 of standard chemo) = Epirubicin (optional) + Oxaliplatin (or Cisplatin) + Capecitabine (or Fluorouracil)

3 Second scan is to be performed between days 15-19 of Cycle 1 of pre-op chemo.

4 A FDG-Responder is classified as someone who had $\geq$ 35% decrease in SUV_{max} on central review of the second FDG-PET scan; they will be classified as screen failures and will not continue to the registration step.

5 A FDG-Non-Responder is classified as someone who had < 35% decrease in SUV_{max} on central review of the second FDG-PET scan.

6 Third scan is to be performed within 14 days of planned resection (Arm B Only)

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan. Sites must be ICL credentialed prior to patient enrollment (See Section 15.0 for details).

Table of Contents

1.0 BACKGROUND

Patients with locally advanced gastric cancer achieve a survival advantage with the addition of adjuvant therapy to surgical resection. As evidenced by several large phase III random assignment studies, standard treatment algorithms now include the use of peri-operative chemotherapy[1], post-operative chemo-radiation[2, 3], or post-operative chemotherapy[4-6] as adjuvant treatment options. However, no matter the treatment paradigm, the benefit of therapy in addition to surgery is modest. Across all treatment strategies, patients with locally advanced gastric cancer are afforded a 10-15% absolute improvement in survival over surgery alone when additional treatment is prescribed. The limited benefit of adjuvant therapy is likely due to the persistence of microscopic disease that was not eradicated by the additional therapy. Based on numerous studies, it is also established that a good FDG-PET response, which can be identified early following initiation of therapy, is associated with improved patient survival. However, it remains unresolved whether or not FDG-PET can be used as a barometer for the response in micrometastatic disease. Specifically, does a good FDG-PET response simply reflect a tumor with better underlying biology that was destined not to recur, or does a good FDG-PET response indicate a higher likelihood that micrometastases were killed. If the latter is true, then patients with a poor FDG-PET response to chemotherapy (i.e. associated with a higher chance of recurrence) may then be salvaged with alternative treatment. This proposal tests this question directly.

In patients who are classified as FDG-PET non-responders, we will examine the utility of salvage therapy versus standard of care. If we demonstrate an improvement in FDG-PET response and survival in FDG-PET non-responding patients who receive salvage therapy, it would support two important concepts that would advance the field: (1) that FDG-PET may be used as a surrogate for response in micrometastatic disease, and (2) early intervention with salvage chemotherapy is meaningful. Alternatively, if salvage therapy does not improve patient outcomes in FDG-PET non-responders, it would suggest that early FDG-PET response may be only a prognostic marker, identifying tumors with better biology that are destined to do well, or that our salvage treatment options are presently inadequate.

1.1 Rationale for selected approach and trial design.

A standard treatment paradigm for patients with locally advanced gastric cancer is to administer pre-operative chemotherapy followed by complete surgical resection, followed by additional post-operative chemotherapy[1]. Serial FDG-PET/CT scanning can identify response to pre-operative chemotherapy by evaluation of the change from baseline in the standardized uptake value (SUV) of the administered FDG (^{18}F-2-fluoro-2-deoxyglucose). This response may be identified early in the pre-operative treatment plan, before completion of the first cycle [7-11]. FDG-PET non-responders, which comprise approximately 50% of patients who initiate pre-operative therapy, have significantly worse outcomes. Early assessment of response may afford the opportunity to modify therapy in those patients who are not responding in an effort to improve patient outcomes. In essence, this approach uses functional FDG-PET imaging as a radiographic biomarker to personalize therapy – i.e. allows for a decision on appropriate therapy to be made early (within 2-3 weeks) following initiation of therapy. Attempts to capitalize on the early identification of response to preoperative therapy have included stopping ineffective therapy and going directly to surgery[9], and adding radiation therapy to the same chemotherapy in FDG-PET non-responding patients[12, 13]. Although both approaches failed to improve patient outcomes in the FDG-PET non-responding group, it is notable that both approaches also involved changes to local-regional therapy – i.e. neither approach applied a change to systemic therapy. Our proposal examines specifically the use of salvage systemic chemotherapy in FDG-PET non-responding patients to determine if the early application of alternative therapy can improve the outcome of patients with locally advanced gastric cancer not responding to standard pre-operative therapy.

1.2 Trial importance

The demonstration of the benefit of additional treatment following surgical resection in gastric cancer was initially reported in 2001 by the INT-0116 investigators who reported their results of the US phase III study of post-operative chemoradiation versus surgery alone[2]. Since this landmark study, there have been several phase III studies across the globe that have demonstrated a similar benefit of additional treatment to surgery alone in patients with locally advanced gastric cancer. There is widespread acknowledgement that the benefit of current treatment paradigms is marginal (approximately 10-15% improvement in survival) and there is an ongoing intensive research effort to improve patient outcomes in this setting.

The recent US Intergroup study (CALGB 80101) attempted to improve efficacy by intensification of post-operative chemotherapy with the addition of epirubicin and cisplatin in addition to post-operative fluorouracil sensitized radiation. This negative study suggests that intensification of chemotherapy in unselected patients is not useful[14]. An alternative approach is to add radiation to patients who are not responding to pre-operative chemotherapy for patients with locally advanced disease[12]. However, the addition of local-regional radiotherapy in non-responding patients was also not beneficial when compared with a historical control.

An untested approach is to examine the potential role of alternative, or salvage, systemic chemotherapy, in patients who are not responding to initial pre-operative therapy. This approach leverages the fact that gastric cancer is a chemotherapy sensitive disease, with many active chemotherapy agents[15]. Indeed, salvage chemotherapy has already demonstrated improved survival in the advanced, metastatic disease setting, and is now a standard treatment option [16, 17]. Specifically, we propose to examine the efficacy of salvage chemotherapy in FDG-PET non-responders in the pre-operative setting. Several studies now have demonstrated that FDG-PET/CT can be used to identify non-responding patients early in their treatment course. This protocol tests the paradigm that early switching to alternative systemic treatment early in the treatment will improve patient outcomes. A positive result, i.e. that early identification of non-response is clinically relevant and actionable, will change current therapeutic paradigms and would have a potential profound effect on the management of patients with local-regional malignancies, not only gastric cancer, but across many solid tumor malignancies where pre-operative therapy is indicated.

1.3 Use of PET-SUV to Predict Response

Several studies have examined whether the change in SUV of the primary tumor with chemotherapy is useful in determining the response to the intervening therapy. Notably, the studies evaluated different treatment regimens, with similar results, suggesting that FDG-PET metabolic response may be a universal property of cancer therapeutics. Most studies used pathological response as the gold standard for evaluation of chemotherapy efficacy. This is commonly measured using the Mandard system[18] or a simple modification of this system, where pathological response is classified according to the percentage of viable tumor cells remaining, with non-responders having >10% tumor cells remaining, partial response 0–10%, and complete responders 0% viable tumor cells.

A first prospective study in 2001 by Weber et al of 40 patients with adenocarcinoma of the GE junction and gastric cardia demonstrated a median reduction in SUV of responders of more than three times that of non-responders and was significantly correlated with pathological response ($P < 0.001$). Response was also significantly associated with survival. Those with no response had a 2-year survival of 37% versus 60% in PET responders. A prospective trial by Ott et al used a predetermined level of reduction in SUV to determine the cut-off point for metabolic responder versus non-responder. This had been previously determined to be a reduction of 35% from baseline[19], which had been demonstrated to have a sensitivity and specificity of 93%

and 95%, respectively, for the detection of a pathological response[8, 19]. Sixty five patients with locally advanced GE junction tumors undergoing preoperative chemotherapy were enrolled. Baseline tumor FDG uptake was 8.1 ± 3.4 SUV for assessable patients. SUV uptake significantly decreased to 5.4 ± 2.0 (~33%) in the follow-up scan. Eighteen patients were classified as metabolic responders and 38 as metabolic nonresponders. The pathological response was highly significantly correlated with the metabolic response ($P < 0.001$); 44% of patients with a metabolic response had a pathological response, compared to 5% of metabolic non-responders. Median overall survival for non-responders was 18 months, significantly shorter than overall survival for the group as a whole at 32 months. Median survival for metabolic responders had not yet been reached at the time of publication. A similar study was performed at Memorial Sloan Kettering Cancer Center as a validation study[11]. In this study, patients with locally advanced but resectable gastric/GE junction adenocarcinoma received preoperative chemotherapy with irinotecan and cisplatin for two cycles. An FDG-PET CT scan was performed at baseline and again at day 15 and day 35. This study confirmed the results initially reported by Weber et al, demonstrating that a significant drop in SUV from baseline was associated with the pathologic response to therapy as well as with patient survival[11].

The primary utility of a change in FDG-PET SUV from baseline as a marker for response to chemotherapy and subsequently survival is that this information is available early in the treatment plan, and thus could potentially be used in order to guide future management. This approach was taken by Lordick et al in the MUNICON trial [9]. This study recruited 119 patients with locally advanced tumors of the GE junction undergoing preoperative chemotherapy. Patients who did not meet a predefined metabolic response level on FDG-PET of a 35% reduction from baseline SUVmax 2 weeks after commencing treatment did not continue with chemotherapy but proceeded directly to surgery. Metabolic responders completed the course of preoperative chemotherapy and then proceeded to surgery; 49% of patients were metabolic responders and 51% were metabolic non–responders. Of the metabolic responders, 58% achieved a major histological response, with 0% in the non-responders. R0 surgical resection was possible in 96% of metabolic responders and in 74% of metabolic non-responders. On pathologic assessment, metabolic responders demonstrated earlier stage tumors than metabolic non-responders. Metabolic non-responders had a median event-free survival of 14.1 months compared to 29.7 months in metabolic responders. It was noted that metabolic responders who did not have a pathological response had survival comparable to those who were metabolic non-responders, implying that a metabolic response was necessary but not sufficient for improved survival [9].

In a cross trial comparison between the original study by Ott et al, where chemotherapy was continued despite a metabolic non-response, and MUNICON where non-responders proceeded directly to surgery, amongst those patients that went on to complete surgical resection, survival between non-responders in both groups was similar. This suggests that, amongst metabolic non-responding patients, patient survival was unaffected (either adversely or positively) by continuing with ineffective chemotherapy or by stopping ineffective chemotherapy and proceeding early to surgery. These results have led to a clinical trial in which failure to respond to initial induction chemotherapy with a reduction in SUV on PET is followed by introduction of a salvage regimen of non-cross resistant chemotherapy in an effort to improve outcome (NCT00737438 on clinicaltrials.gov; Memorial Sloan Kettering study, IRB 08-081). PET responders (≥35% decline in SUV) continued standard ECX for 2 more cycles prior to surgery, whereas, PET non-responders switched to 2 cycles of salvage irinotecan/docetaxel based therapy[20]. Though this study closed prematurely, in the first 20 patients enrolled, 11/20 were classified as FDG-PET responders. Ten out of 11 (91%) underwent R0 resection: 1/10 pathologic CR, 3/10 pathologic PR. Nine out of 20 patients were PET non-responders, and switched to salvage therapy. Seven out of 9 non-responders had R0 resection, and none achieved

a pathological response. The DFS for PET responders was 27.8 months (95% CI 10.3-27.8) and DFS in salvage group has not been reached. These data support the proposed study of an early cross over to improve patient outcomes with salvage therapy.

1.4 Targeted Therapy

Recently, several targeted therapies have been examined in gastric cancer, with few positive results. Since the success of trastuzumab in the ToGA trial for metastatic gastric cancer there is interest in multi-targeted inhibition of pathways. In the ToGA study, trastuzumab, a humanized anti-HER2 monoclonal antibody was evaluated in addition to fluropyridimidine and platinum combination chemotherapy. The median OS was improved significantly in the trastuzumab arm compared with the chemotherapy-alone arm (13.5 months vs. 11.1 months, p = 0.0048; hazard ratio [HR], 0.74; 95% confidence interval, 0.60 to 0.91) and benefit was most evident in patients with HER2 overexpressing tumors (OS 16 months vs. 11.8 months[21]. Lapatinib is a dual inhibitor of the tyrosine kinase domains of HER1 and HER2. Two international randomized studies have completed accrual testing lapatinib in addition to systemic chemotherapy. In the TYTAN trial, lapatinib in addition to paclitaxel was compared to paclitaxel alone in patients progressing on platinum-based first line therapy. Median overall survival was 11.0 months for the combination compared with 8.9 months with paclitaxel alone but did not reach statistical significance (hazard ratio [HR]: 0.84; p = 0.2088). In a preplanned subgroup analysis median OS among patients in the HER2 IHC 3+ subgroup was 14.0 months vs 7.6 months in favor of the addition of lapatinib (HR: 0.59; p = 0.0176)[22]. The LOGiC trial compares first line therapy with capecitabine and oxaliplatin with or without lapatinib. Accrual was complete as of March 2013 and results are awaited. In the localized setting, the addition of trastuzumab to pre-operative chemoradiation is being examined in esophageal cancer (RTOG 1010). The proposal to evaluate trastuzumab in patients with locally advanced gastric cancer through the US Cooperative groups was met with limited enthusiasm because of concerns for patient accrual.

Inhibition of the EGFR pathway has been examined in two recent phase III studies, the EXPAND and the REAL-3 trials which explored the addition of two monoclonal antibodies against EGFR- cetuximab and panitumumab respectively- in combination with platinum/fluoropyrimidine chemotherapy [23, 24]. Both trials failed to show OS benefit [9.4 vs 10.7 months, p= 0.9547 in the EXPAND trial] and actually suggested inferior survival with the addition of anti-EGFR therapy [OS, 8.8 months vs. 11.3 months, p = 0.013, REAL-3]. Further development of EGFR inhibition in gastric cancer is unlikely at this point.

Antiangiogenic therapy has been examined in advanced gastric cancer as well. The AVAGAST study failed to show any improvement in OS with the addition of bevacizumab to standard platinum/fluoropyrimidine therapy in first-line unselected metastatic gastric cancer patients[25]. In subset analyses it was observed that patients with high baseline plasma VEGF-A levels showed a trend toward improved OS (HR 0.72; 95% CI, 0.57 to 0.93) vs. patients with low VEGF-A levels (HR, 1.01; 95% CI, 0.77 to 1.31; interaction P = 0.07)[26]. Ramucirumab (IMC-1121B) is a fully human IgG1 monoclonal antibody targeting VEGF-receptor 2. The REGARD study, a placebo-controlled, double-blind, phase III international trial, was conducted in the second line setting in patients with metastatic gastric or GEJ adenocarcinoma. Median OS was 5.2 months for ramucirumab and 3.8 months for placebo [HR 0.776 (95% CI, 0.603-0.998; p = 0.0473)][27]. The role of antiangiogenic therapy remains investigational in the preoperative setting. There is an ongoing phase III study evaluating standard chemotherapy with or without bevacizumab in the preoperative setting run in England by the MRC (MAGIC-B, NCT00450203).

1.5 Salvage Chemotherapy In Gastric Cancer

Gastric cancer is a chemotherapy-sensitive disease, with multiple standard first-line therapies associated with response rates of ~35-50%, and second-line response rates of ~15-35%[15]. There have been 2 recent studies that demonstrate a clear advantage of salvage chemotherapy (2nd line) following progression on first line therapy for metastatic disease. Taxanes are active in gastric cancer, and there is considerable data of taxane-based combination therapies in the salvage setting.

Summarizing data from phase II 2nd line studies following progression on cisplatin/fluorouracil based first line therapy reveals a response rate range of 11-35%, median time to tumor progression range of 2.7-4.4 months, and median 2nd line overall survival of 6.0-9.1 months with taxane based therapy. The choice of docetaxel/irinotecan was chosen as the salvage regimen based on the fact that the drugs are not cross-reactive with the first line therapy, and there is adequate salvage data in this setting. The specific non cross-resistant regimen we are proposing, weekly irinotecan and docetaxel, was examined in the salvage setting in metastatic gastric cancer[28]. The investigators observed a salvage response rate of 33%, with most common toxicity being febrile neutropenia (8%), nausea and vomiting, and diarrhea (both < 5%).

1.6 Post-operative Chemoradiation

The potential benefit of the addition of post-operative chemoradiation following preoperative chemotherapy and adequate surgery is currently being tested in a phase III Dutch study (CRITICS, NCT00407186), with expected results in 2016. The use of salvage chemo/RT in PET non-responders has been examined previously. The MUNICON-II study examined the role of salvage chemoradiation in PET non-responders in patients with distal esophageal and GEJ tumors, and found that the addition of chemoradiation following poor PET response to chemotherapy was not associated with improvement in pathologic response rates and did not improve survival when compared to historical controls[12]. However, despite these data, in which patients are demonstrated to have lack of response to standard preoperative chemotherapy, post-operative chemoradiation is commonly administered, extrapolating the results of INT-0116. We will therefore include post-operative chemoradiation as a standard option for patients in the salvage group who are randomly assigned to direct surgical resection.

1.7 Rationale for using 35% decrease in SUV as the cutoff in Gastric Cancer

Two studies evaluating FDG PET scans in the preoperative setting in gastric cancer were performed at MSKCC (MSK IRB 03-032[11] and IRB 08-081[29], both manuscripts in preparation), together treating 62 patients with gastric cancer. In addition, Ott and colleagues[30] reported their experience in 44 patients with gastric cancer, providing a total experience of 106 patients with localized gastric cancer having been evaluated with an early PET scan to predict treatment response. Ott and colleagues used the 35% cutoff as currently proposed and found a significant correlation with patient survival. The MSK 03-032 study similarly found a significant correlation with PET response and survival, despite using a different preoperative chemotherapy regimen of irinotecan and cisplatin. Specifically, the 03-032 study examined the decrease in SUVmax serially at the end of cycle 1 (day 15) and at the end of cycle 2 (day 35) of preoperative chemotherapy. We found that the median decrease in SUVmax was 35% at day 15, which is identical to the median decrease identified by Weber and colleagues initially taken at day 14 with cisplatin and fluorouracil.[19] This cutoff of 35% has been used subsequently as the threshold value to distinguish response in gastroesophageal cancer using many different preoperative chemotherapy regimens, where the PET scan for response assessment is performed early in the treatment plan. This suggests that a decrease in FDG PET uptake may be a surrogate for cytotoxic therapy response, independent of the actual treatment

regimen used. In the MSK 03-032 study, we also found that the median SUVmax decrease by day 35 was 42%, and also significantly correlated with survival.[11] This finding has also been previously reported, suggesting that SUV uptake continues to decrease as patients who respond to treatment continue on therapy.[7, 31] Our current proposal examines a PET scan after cycle 1 (day 16-19), and uses a 35% cutoff, which is consistent with previous studies, and which has the most validated data across both gastric and esophageal malignancies. Notably, this is also the cutoff used in protocol 08-081, which has provided preliminary consistent positive results already.[29]

Together, we believe these data support utilizing the 35% threshold as a biomarker for response in advanced gastric cancer.

1.8 Rationale for Current Study Design

As mentioned above, there is one published study examining the role of salvage chemoradiation in patients with a poor PET response to chemotherapy (MUNICON-II)[12]. These data might suggest that patients with a poor metabolic response to initial chemotherapy have refractory underlying tumor biology because in this study, salvage chemoradiotherapy did not improve survival. However, patients who received salvage chemoradiation on this study received either cisplatin or fluorouracil as chemotherapy radiosensitizers – the same chemotherapy agents that they received prior to the PET scan. Our hypothesis is that systemic chemotherapy that has not been previously given to the patient at full systemic doses may better eradicate microscopic metastatic disease than additional local-regional therapy. We propose to examine the role of alternative, salvage systemic chemotherapy in PET non-responding patients. This is supported by two lines of evidence – first, that gastric cancer is a chemotherapy–sensitive disease with many agents having modest activity, and second that salvage strategies have proven beneficial in the metastatic setting with documented improvement in overall survival in randomized studies, and is now standard of care. This second point suggests that patients who have progression on initial therapy still have the opportunity to achieve a survival benefit with salvage treatment. Our study design addresses the value of early switching to salvage chemotherapy prospectively, examining the hypothesis that full doses of systemic non-overlapping chemotherapy improve patient survival, thereby directly addressing the underlying question of whether or not an early assessment of response (by an early PET scan) is actionable.

Further, we have preliminary evidence that 'second line' chemotherapy can indeed salvage non-responding patients in the neoadjuvant setting as well. Specifically, we initiated a single institution study to examine the role of salvage chemotherapy in the peri-operative setting, and found that in PET non-responding patients, salvage chemotherapy appeared to improve survival to that of responding patients[29]. Specifically, with a median follow up of 38.2 months, 2-year disease free survival was 55% (95% CI 30-85%) in PET responders and 56% (95% CI 20-80%) in PET non-responders who received salvage irinotecan/docetaxel[29]. Also notably, we used the identical construct of EOX chemotherapy, with a PET scan at the end of cycle 1, and then docetaxel/irinotecan to salvage PET non-responding patients. These data to support the concept of salvage chemotherapy in gastric cancer in the peri-operative setting.

1.9 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including

performance status, either as stratification or prognostic covariates.[32, 33] It will take approximately one minute to complete this measure.

2.0 OBJECTIVES

2.1 Primary objective

To assess and compare the overall survival (OS) of patients with locally advanced gastric cancer classified as FDG-PET non-responders after one cycle of pre-operative chemotherapy randomly assigned to receive either salvage chemotherapy before and after surgery or immediate surgery followed by fluorouracil sensitized radiotherapy.

2.2 Secondary objectives

2.2.1 To assess and compare progression-free survival (PFS) between the treatment arms (Arms A and B).

2.2.2 To assess and compare R0 resection rate between the treatment arms (Arms A and B).

2.2.3 To assess and compare pathologic complete response (pCR) rate between the treatment arms (Arms A and B).

2.2.4 To assess the adverse events (AE) profile and safety of each treatment arm (Arms A and B), including post-operative mortality rate, 30-day post-operative targeted adverse events (i.e., dehiscence, significant infection, and re-operation rate).

2.2.5 To examine the changes of FDG-PET SUV induced by pre-operative chemotherapy at different time points (from baseline to completion of one cycle of treatment before randomization, and 2 cycles of salvage treatment) in patients randomized to salvage treatment arm (Arm B).

2.2.6 To collect measurement of fatigue and overall perception of QOL at registration of the study. (Alliance registration QOL assessment study)

2.3 Other objective(s)

Results of the primary analysis will be examined for consistency, while taking into account the stratification factors and/or covariates of baseline QOL and fatigue.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-Registration (Step 0) Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease**

___ Histologically confirmed Adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II, III)

___ Pre-treatment clinical stage of T3-4NanyM0 or TanyNpositiveM0 as determined by laparoscopy, CT scan (or PET/CT that includes diagnostic CT), or endoscopic ultrasound (histologic confirmation of lymph involvement is not required). **Therefore, patients can have measurable or non-measurable disease.**

Patients with T1-2N0M0 tumors or patients with metastatic disease are NOT eligible.

___ **3.2.2 Patients must be eligible for curative intent surgical resection.**

___ **3.2.3 FDG Avid malignancy**

Patients must have an FDG avid tumor(s).

FDG avid tumors are defined as a primary tumor with an increased uptake in the region of the tumor that has an SUV of > 5.0 or a tumor:liver SUV ratio of > 1.5.

___ **3.2.4 No prior history of:**

___ Congestive heart failure (NYHA class I to IV)

___ Known DPD deficiency

___ **3.2.5 No current grade 2, 3, or 4 of neuropathy.**

___ **3.2.6 No known hypersensitivity to any of the following agents: oxaliplatin, cisplatin, capecitabine, 5-flurouracil, docetaxel, or irinotecan.**

___ **3.2.7 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative serum pregnancy test pregnancy test done ≤ 7 days prior to pre-registration is required.

___ **3.2.8 Age ≥ 18 years**

___ **3.2.9 ECOG Performance Status 0 or 1**

___ **3.2.10 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine*	≤ 1.5 x upper limit of normal (ULN)
Total Bilirubin**	≤ 1.5 x upper limit of normal (ULN)
AST and ALT	≤ 2.5 x upper limit of normal (ULN)
Alkaline Phosphatase	≤ 2.5 x upper limit of normal (ULN)

* Either lab result or calculated clearance

** Except in patients with Gilbert's disease

3.3 Registration (Step 1) Eligibility Criteria to Treatment Arms A or B

___ **3.3.1 Patient must continue to be eligible for curative intent surgical resection**

___ **3.3.2 Disease Progression**: FDG avid malignancy that is classified as an FDG PET non-responder.

PET non-responders are defined as having < 35% reduction in the FDG uptake of the primary tumor when compared to baseline.

___ **3.3.3 Concomitant Medications**

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial. Patients on strong CYP3A4 inhibitors must discontinue the drug 14 days prior to the start of study treatment. See Section 8.1.9 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment. See Section 8.1.10 for more information.

___ **3.3.4 Patient must have received only one cycle of the following regimens (with or without epirubicin) during the pre-registration time period and no other therapy for gastric or gastroesophageal junction cancer:**

- Oxaliplatin, and Capecitabine
- Oxaliplatin, and Fluorouracil
- Cisplatin, and Capecitabine
- Cisplatin, and Fluorouracil

___ **3.3.5 Toxicity recovery should include the following:**

- Grade ≤ 2 neuropathy
- Grade ≤ 2 diarrhea
- Grade ≤ 2 mucositis

___ **3.3.6 Pre-registration chemotherapy given within 42 days of treatment (treatment meaning surgery if Arm A, chemotherapy if Arm B)**

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at [redacted]. For questions, please contact the CTEP Investigator Registration Help Desk by email at [redacted]

4.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at [redacted]. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at [redacted]

4.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.3.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A021302 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NCTN – ALLIANCE link to expand, then select trial protocol #A021302
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

4.3.2 Requirements for A021302 Site Registration

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Imaging Core Lab (ICL) at IROC Ohio confirmation
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

4.3.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal

EMAIL [redacted] (for regulatory document submission only)

FAX: [redacted]

MAIL: [redacted]

4.3.4 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3.5 Credentialing

Sites must also be certified by the Imaging Core Lab at IROC Ohio for the Imaging Component (see Sections 6.3 and 15.1.2) and IROC Houston (RPC) for IMRT Radiotherapy (see Section 15.1.3)

See Section 15.0 for further IROC requirements.

4.4 Patient Pre-Registration Requirements

Informed consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Pre-registration Requirement: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

Eligibility of patients as outlined in Section 3.2 of the protocol should be confirmed prior to pre-registration.

4.5 Patient Registration/Randomization Requirements

The second FDG-PET scan will be centrally reviewed by the Imaging Core Lab (ICL) at IROC Ohio to determine metabolic activity of the tumor during cycle 1 of standard pre-op chemotherapy. See Section 6.3 for scan submission and review procedures.

If the metabolic activity of the tumor has decreased by ≥35%, as measured by maximum standardized uptake value (SUVmax), the patient is considered a FDG responder and therefore a screen failure. Further treatment would be at the treating physician's discretion.

If the metabolic activity decreases less than 35% from the initial scan, the patient is deemed a FDG-Non Responder. The patient would continue to be registration and randomization to one of the treatment arms of the study (Arms A or B).

Eligibility of patients for one of the treatment arms (Arms A and B) as outlined in Section 3.3 of the protocol should be confirmed prior to registration.

4.6 Patient Pre-Registration and Registration/Randomization Procedures using OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < [redacted] >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. A user manual is available for OPEN users on the CTSU site.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- Institution confirms credentialing requirements as they are enrolling into the study.
- Institution has been surgeon credentialed.

All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted]

4.7 Stratification Factors and Treatment Assignments

4.7.1 Tumor Location: Stomach vs. Gastroesophageal junction (Siewert type II, III)

4.7.2 Pre-Op Chemo Regimen: Cisplatin vs Oxaliplatin

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

The tests and procedures outlined in the study calendar have been reviewed by a Medicare coverage analyst.

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before pre-registration and registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before pre-registration and/or registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.
- To be completed ≤ 42 DAYS before pre-registration and/or registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

	Prior to Pre-Registr-ation*	Prior to Registr-ation	Arm A: Day 1 of Weeks 1 and 4 of ChemoRT	Arm B: Day 1 of Each Cycle (Pre and Post Surgery)**	Prior to Surgery	Post treatment follow up***	At PD, withdra wal, or removal ***
Tests & Observations							
History and physical, weight, PS†	X		X	X	X	X	X
Height	X						
Pulse, Blood Pressure	X		X	C	X	X	
Echo or MUGA (Recommended not required)	X						
Adverse Event Assessment#	X	X	X	X	D		
Registration Fatigue/ Uniscale Assessment		X(1)					
Laboratory Studies							
Complete Blood Count, Differential, Platelets	X		X	C	X	X	
Serum Creatinine,	X		X	X	X	X	
AST, ALT, Alk. Phos., Bili	X		X	X	X	X	
Serum HCG	X(2)						
Staging							
FDG-PET Scan (A)	X (3)	R			D		
CT chest/abd/pelvis (B)	X (3)					X	
Correlative studies: For patients who consent to participate							
Tissue and Blood samples	*See Section 6.0 for Specimen Submission Requirements for Consenting Patients*						

* Labs completed prior to pre-registration may be used for day 1 of cycle 1 tests if obtained ≤ 16 days prior to treatment.

** Treatment on Arm A (surgery) must begin within 42 days completion of the pre-registration chemotherapy. Treatment on Arm B (chemotherapy) must begin within 28 days of day 1 of pre-

registration chemotherapy. All tests, observations, and labs for Arms A and B have a 5 day window.

*** Physical examination, adverse event assessment and labs are required 21 to 35 days after the end of treatment. All patients are required to complete a physical exam, labs, and scans 6 months (+/- 4 weeks) following surgery. Thereafter, physical exam and labs are every 12 weeks (+/- 4 weeks) and scans are every 24 weeks (+/- 4 weeks) until disease progression or for 3 years after registration, whichever comes first. Thereafter, survival information is required every 6 months until 5 years following registration. Patients who do not receive adjuvant therapy (in both arms A and B for a reason other than ineligibility) are required to complete a physical exam and labs 3 months (+/- 4 weeks) following surgery. See also Section 12.0.

† Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration. See Section 9.3 for expedited reporting of SAEs.

1 To be completed after registration and ≤ 7 days prior to treatment, see Section 1.9 and Appendix I.

2 For women of childbearing potential (see Section 3.3). Must be done ≤ 7 days prior to pre-registration.

3 Baseline scans can include either: 1) a CT chest/abd/pelvis and FDG-PET scan or 2) an FDG-PET/CT scan with diagnostic quality CT. The CT in either case must be of diagnostic quality, performed with both IV and oral contrast, and acquired with 5 mm or less slice thickness. If option 2 is used, a separate CT need not be performed. Supporting documentation is to be submitted, per Section 6.1.1. Baseline FDG-PET scan should be performed within 28 days of starting platinum/FU based cycle 1 chemotherapy, and the diagnostic CT should be performed within 42 days of starting platinum/FU based cycle 1 pre-registration chemotherapy.

A FDG-PET Scan imaging is from base of skull to mid-thigh. PET scan is to be performed prior to and during cycle 1 of pre-registration chemotherapy (day 15-19) in all patients. In Arm B, PET scan is to be performed after 2 cycles of salvage chemotherapy, within 14 days of planned surgical resection.

B CT scan is to be performed prior to pre-registration chemotherapy. After completion of protocol therapy, see footnote *** for scan frequency

C Also to be performed on Day 8 of Cycles 1 and 2 of Pre-Op Salvage Chemotherapy

D Required for patients on Arm B only

R Research Funded. Scan should be performed on or between days 15 through 19. Fluorouracil or capecitabine should be held for 48 hours prior to PET scan.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail a [redacted].

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis, surgery, and progression/recurrence. Supporting documentation will include radiology, pathology, and surgical reports. These must be submitted at the following time points:

- Baseline Clinic Note
- Endoscopy and Pathology report of Diagnosis at Baseline
- Operative and Pathology report at Surgical Resection
- PET and CT scan reports (as well as endoscopic reports, if available), during pre-registration and while on study treatment
- PET, CT scan, (as well as endoscopic reports, if available), and/or pathology reports at progression/recurrence

6.2 Specimen collection and submission for banking

For patients that consent to banking of their specimens: All participating institutions must ask patients for their consent to participate in the banking of their specimens for future correlative studies, although patient participation is optional. Potential uses for these samples are outlined in Section 14.1. For patients who consent to participate, tissue and blood will be collected at the following time points for these studies:

	Within 30 days of registration	At surgery	Shipping conditions	Submit to:
Pre-Treatment Diagnostic Tissue Block [2]	X[1]		Cool pack/ship over night	ABOSU
FFPE tissue block – Tumor Tissue[2]		X[1]	Cool pack/ship over night	ABOSU
FFPE tissue block – Adjacent Normal Tissue[3]		X[1]	Cool pack/ship over night	ABOSU
Whole Blood[1] (EDTA/lavender top)	1 x 10 mL		Cool pack/ship over night	ABOSU

1 Blocks/cores and whole blood to be banked at Alliance Biorepository at Ohio State University. Potential uses are described in Section 14.1.

2 If tissue blocks are unavailable, we will request up to 20 unstained slides (5 micron thick) of tumor tissue and 2 H&E slides representative of disease.

3 If tissue blocks are unavailable, we will request up to 20 unstained slides (5 micron thick) of normal tissue and 2 H&E slides representative of normal tissue.

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted].

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A021302), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged.

All specimens should be sent to the following address:

Alliance Biorepository at Ohio State

6.2.2 Collection of paraffin blocks of archived normal and tumor tissue for banking

For patients who consent to participate, tumor blocks will be banked for potential analyses described in Section 14.1.

Paraffin block of pre-treatment diagnostic tissue should be submitted, as well as paraffin blocks of normal and tumor tissue obtained from surgical resection. These specimens should be sent to the Alliance Biorepository at Ohio State University (ABOSU) at ambient temperature with cold packs in appropriately padded and secure containers to avoid extreme heat and physical damage. Please specify the source of the tumor block (primary or metastatic site).

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, up to 20 unstained slides of normal and tumor tissue should be sent to ABOSU at ambient temperature with cold packs and proper padding with 2 H&E slide representative of the disease.

Label the sample with the following identification:

1) Procurement date
2) Alliance patient number
3) Alliance study number (i.e., A021302)
4) Sample type
5) Institutional surgical pathology number

The goal of the Alliance is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the biorepository will be vacuum packed to prevent oxidation and will be stored at 4° C to minimize degradation of cellular antigens. For these reasons it is preferred that the biorepository bank the block until the study investigator requests thin sections. Please contact the biorepository if additional assurances with your hospital pathology department are required.

6.2.3 Whole Blood submission for banking

For patients who consent to participate, whole blood samples will be banked for potential studies described in Section 14.1. This sample should be collected prior to surgery.

Collect 10 mL of peripheral venous blood in an EDTA (lavender) tube. The tube should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the ABOSU.

Label the sample with the following identification:

1) Procurement date
2) Alliance patient number
3) Alliance study number (i.e., A021302)
4) Whole Blood

The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

6.3 FDG-PET Imaging Requirements, Credentialing and Submission Instructions – *Required for ALL patients*

6.3.1 PET/CT Imaging Credentialing Procedure

Prior to registering patients, all participating sites should review the imaging protocol and required forms with the CRA as well as individuals from the imaging facility who will be acquiring the PET/CT images. Data and form submission guidelines will be reviewed and contact information will be verified via correspondence with the ICL at IROC Ohio.

6.3.2 Requirements for Participation

1) The participating center must have, or have access to, a facility with an integrated positron-emission tomography and computed tomography (PET/CT) scanner.

2) The participating center must have the ability to submit PET and CT studies electronically to the ICL in digital DICOM format (other formats: BITMAP, JPG, hardcopy or scanned files are not acceptable).

3) Participating sites must be credentialed by the ICL so that the performance characteristics and infrastructure requirements are met, as follows:
   - If a site has been credentialed by the ICL for participating in CALGB 50303, CALGB 50604, CALGB 50801, CALGB 50904, and/or CALGB 80803 PET/CT imaging studies, a protocol refresher only will be needed for participating in Alliance A021302.
   - If a site has not been credentialed by the ICL, however the site participated or is participating in any other legacy Alliance PET/CT imaging trials, a protocol refresher (and a Virtual Site Visit, if necessary) is required for participating in Alliance A021302.
   - If a site has neither been credentialed by the ICL nor participated in any legacy Alliance PET/CT or CT imaging trials, the Alliance ICL (IROC Ohio) will adhere to the ACRIN criteria for PET/CT imaging approval procedures. Consistency in the acquisition protocol both from a time and an acquisition mode is required. In addition, data management must be done in a standardized process.

In order for an institution to be approved to participate in this study, they will be required to review the data acquisition and quality management process during the virtual site visit coordinated by the ICL at IROC Ohio, which will be scheduled after submission of the following:

a. Two test patients (FOR ALL PET/CT instruments utilized). Images of two unidentified patients shall consist of three volume or multislice files as follows: a) Whole body CT from PET/CT scanner; b) Whole body (torso) emission with attenuation correction (A/C); and c) Whole body (torso) emission without A/C.

b. Uniform phantom data with SUV measurement of the phantom (FOR ALL PET/CT instruments utilized). Water-fillable uniform phantom: The phantom must be filled with water, and a known amount of F-18 (either as fluoride or as FDG) should be injected into the phantom. The activity injected should be determined by measurement of the syringe before and after the injection in a properly calibrated dose calibrator. The injected activity should be chosen to result in an activity concentration similar to that encountered in clinical FDG imaging (i.e., 1 – 1.5 mCi of F-18 should be added to the 6,283 mL phantom: 2 mCi for the 9.293 mL phantom). After thoroughly mixing the phantom, the phantom must be scanned with the same protocol used for the patient imaging. The images also must be reconstructed with the same algorithm and filters sued for patient imaging. A circular or elliptical region of interest (ROI) covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET/CT Instrument Technical Specifications Form. The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1.

c. Alternatively, Ge-68/Ga-68 calibration phantom: This phantom can readily be scanned with the same protocol used for patient imaging. The assay date and activity from the calibration certificate of this phantom must be reported on the PET/CT Instrument Technical Specifications Form. The images must be reconstructed with the same algorithm and filters used for patient imaging. A circular or elliptical ROI covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET Instrument Technical Specifications Form. The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1

d. PET/CT Instrument Technical Specifications Form (FOR ALL PET/CT instruments utilized).

e. Imaging Site Personnel Form

If an institution's PET/CT scanner has already undergone legacy ACRIN credentialing, documentation of this certification may be provided to the ICL at IROC Ohio in lieu of the requirements above. The ICL at IROC Ohio regularly performs team telephone calls as well as virtual site visits, and serves as consultant to help the local sites resolve questions with regard to adherence to the acquisition and reconstruction protocol.

See Section 7.4 for FDG-PET scan requirements.

6.3.3 Central Review of PET Imaging

If there is a discrepancy between the central review and local site, an adjudicator organized through the Alliance Imaging Core Lab will blindly determine with which interpretation (local or central) they agree. The adjudicator's decision will then become the final analysis decision from the Imaging Committee through the Alliance Imaging Core Laboratory and will become the interpretation which must be used by the local site's PI if the patient is to remain on the protocol (please refer to Sections 7.4.1 and 7.4.2 for details on PET/CT interpretation). If there are discrepancies between the local reads and the final adjudicated central review interpretation, these will be discussed with the individual sites and a consensus decision will be made as to the participation of the patient in this trial. It is the PI's responsibility to determine whether to base clinical decisions on the local read or the central read if there is a discrepancy; however, if the patient is to remain on protocol, interpretation from the centralized review must be used.

6.3.4 PET Scan Submission Instructions

The following PET/CT images will be collected digitally for archival:

- Baseline (prior to study treatment)
- During cycle 1of the pre-operative chemotherapy (target day 15-19)
- After 2 Cycles preoperative salvage chemotherapy

The complete PET/CT scan in digital **DICOM format** as well as the FDG-PET Scan Information Forms will be submitted to the ICL at IROC Ohio within **3 business days** of preregistration scan at baseline or within **3 business days** of scanning during cycle 1 and within **3 business days** of scan after 2 cycles of pre-operative salvage. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the ICL at IROC Ohio. The ICL at IROC Ohio will notify site and the Alliance A021302 imaging committee within **2 business days** of the data receipt as well as within **3 business days** of the quality check report upon data receipt.

The site will de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g, 112136) and protocol number (e.g., A021302), respectively. The following complete data sets must be sent:

1. Transmission CT data
2. Emission data with CT attenuation correction
3. Emission data without CT attenuation correction

Data can be submitted to the ICL at IROC Ohio electronically via Triad data transfer, Web-based data transfer and FTP data transfer, or alternatively through Mail/Shipment.

TRIAD Data Transfer:

TRIAD data transfer is the dedicated data transfer approach served by IROC Cooperative under the National Clinical Trail Network (NCTN). The utilization of TRIAD depends on its availability for specific trials. Please contact the Alliance ICL at IROC Ohio via e-mail at [redacted] for details of the standard TRIAD access information.

Web-based data transfer:

Any PCs with internet access can be used to upload images to the Imaging Core Lab via this approach. The standard Web access information will be provided separately through the specific trial e-mail [redacted], per the request by participating sites before their first data submission.

FTP Transfer:

Any FTP software can be used to upload images to the secure FTP Server of the ICL at IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.

Local scan interpretation reports and the FDG-PET Scan Information Form can be sent to the ICL at IROC Ohio via [redacted]

Shipment/Mail Transfer:

If the electronic data transfer approaches cannot be achieved at sites, the de-identified digital images in DICOM format can be burned to CDs, labeled with Alliance021302 patient ID (e.g., 112136), date of study and study period (e.g., baseline, during cycle 1 of preoperative chemotherapy), and mailed to the ICL at IROC Ohio at:

IROC Ohio
[redacted]

Send an e-mail notification to inform the Imaging Core Lab at IROC Ohio at [redacted] once the data transfer is completed. Address any questions or problems about the data transfer to the ICL at IROC Ohio by calling the Corelab IT group at [redacted] for help.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of pre-registration.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Pre-registered patients will receive standard pre-operative chemotherapy consisting of epirubicin (optional), platinum, and fluoropyrimidine[1, 34]. Patients will undergo a FDG-PET/CT during cycle 1 of pre-operative therapy (target day 15-19). Patients will hold capecitabine (or fluorouracil) for 48 hours prior to the FDG-PET/CT scan. See Section 7.1.1 or Appendix IV for additional details. The FDG-PET/CT scan will define a FDG-PET responder versus a FDG-PET non-responder. Patients with a good metabolic response are defined as having ≥ 35% reduction in FDG uptake on the PET scan compared to baseline, whereas patients with < 35% reduction in FDG uptake when compared to baseline will be considered non-responders.

FDG-PET responders are considered screen failures and will not move on from pre-registration to registration.

Patients defined as FDG-PET non-responders will be registered and randomized to go directly to surgery (Arm A) or to salvage chemotherapy (Arm B). Patients MUST begin treatment on Arm A (treatment meaning surgery) within 42 days from completing platinum based cycle of chemotherapy given during pre-registration. Patients assigned to Arm B should begin treatment on Arm B (treatment meaning 1st cycle docetaxel irinotecan) within 28 days from day 1 of platinum based cycle of chemotherapy during pre-registration.

Arm A patients (assigned to surgery first) will also receive post-operative FU/RT, which should begin within 49 days of surgery. Post-operative FU/RT may consist of either 5-fluorouracil or capecitabine. Patients who are unable to initiate post-operative FU/RT within 56 days of surgery will not be required to have it.

Arm B patients are treated with 2 cycles docetaxel + irinotecan. Following completion of docetaxel + irinotecan, a PET scan should be performed within 14 days of planned resection. The purpose of this PET scan is to ensure patient does not have metastatic disease and is still a surgical candidate. Then patients should undergo surgery, which should occur within 42 days of completing docetaxel + irinotecan. After surgery, patients should receive 3 further cycles of docetaxel + irinotecan, which should begin within 60 days of surgery.

7.1 Chemotherapy (or Adjuvant, or Neo-adjuvant therapy, if applicable)

7.1.1 Pre-registration Chemotherapy

Agent	Dose	Route	IV Duration	Days
Epirubicin (optional) (1)	50 mg/m^2	IV	Per Institutional Standard	Day 1
Oxaliplatin (2) OR Cisplatin (3,4)	130 mg/m^2 60 mg/m^2	IV IV	Per Institutional Standard Per Institutional Standard	Day 1
Capecitabine * OR Fluorouracil*	625 mg/m^2 bid 200 mg/m^2/day	Oral IVCI	N/A	Days 1-21 Days 1-21

(1) Epirubicin is optional – patients may proceed with therapy without epirubicin. Patients receiving epirubicin may receive reduced doses of epirubicin of 40mg/m^2 at treating physician's discretion

(2) Patients may receive reduced dose of oxaliplatin at 115mg/m2 at treating physician's discretion

(3) Patients may receive reduced dose of cisplatin at 50mg/m2 at treating physician's discretion

(4) Choice of oxaliplatin or cisplatin is at treating physician's discretion

* Medication should be held for 48 hours prior to on treatment FDG-PET scan performed on target day 15-19. Medication can resume after the FDG-PET scan through, but not beyond, day 21 (total # of days of capecitabine/fluorouracil received is 19 days).

7.1.2 Arm B Chemotherapy

Agent	Dose	Route	IV Duration	Days	Cycle Frequency
Docetaxel	30 mg/m^2	IV	Per Institutional Standard	Days 1 and 8	every 3 weeks
Irinotecan	50 mg/m^2	IV	Per Institutional Standard	Days 1 and 8	every 3 weeks

7.2 Surgery (Arms A and B)

At the time of surgical resection, as outlined by the protocol, the surgeons will follow standard surgical procedures for the resection of a gastric cancer specimen as outlined by the NCCN guidelines for gastric cancer. This includes adequate resection of the involved area of the stomach to achieve negative microscopic margins utilizing a distal gastrectomy, subtotal gastrectomy or total gastrectomy, as needed. T4 resection may require en bloc resection of involved structures. Wedge resections of the stomach are not considered appropriate resections for gastric adenocarcinoma and will be excluded.

Gastric resection should include the regional lymphatics including perigastric lymph nodes and those along the named vessels of the celiac axis with a goal of examining at least 15 or greater lymph nodes. Due to natural variations in lymph node counts from individual to individual, patients with lymph node counts less than 10 may undergo an amended final analysis. All patients should submit follow-up data.

Reconstruction via a Bilroth I, Bilroth II or Roux-en-Y reconstruction is recommended.

7.2.1 Surgical Quality Assurance

General Guidelines

The surgical quality will be assessed by the Surgical Study Chair. Surgical data from this study will be reviewed at regular meetings of the Surgical Quality Assurance Committee (SQAC) of the Alliance. This committee meets quarterly to review ongoing Alliance protocols with surgical components.

Any deviations in surgical quality identified by the SQAC will be addressed by the surgical Co-Chair of this trial, Dr. Vivian Strong.

All adverse events in the post-operative period will be documented to determine risk of complications related to neoadjuvant therapy followed by surgery.

7.2.2 Definitions of Deviations in Protocol Performance

Major Deviations

The following will be considered major protocol deviations:

- Wedge resection for a gastric cancer
- Failure to perform a perigastric lymph node dissection

Minor Deviations

The following will be considered minor protocol deviations:

- Less than 10 lymph nodes harvested during operation
- Microscopically positive margin for cancer

- Failure to perform a frozen section of the proximal margin at the time of surgery
- Incomplete documentation of anastomotic complication

Summary Quality Assurance Evaluation and Scoring

If a point score below 20 is determined, the Surgical Co-Chair will review the site and determine if remediation, retraining or exclusion from the protocol is required. Such action will be determined within 30 days of finishing the QA score assessment.

7.3 Post-Operative Chemoradiation (For patients randomized to Arm A)

Post-operative chemoradiation is to begin within 49 days of surgery.

7.3.1 Chemotherapy

Agent	Dose	Route	Days	Cycle Length
Fluorouracil	200 mg/m^2/day	IV	Continuous	5 weeks
		OR		
Capecitabine	800 mg/m^2 bid	Oral	Daily During Radiation	5 weeks

Chemotherapy is administered concurrently with radiation. Fluorouracil is administered as an IV continuous infusion for 7 days every week during RT. Capecitabine is administered only Monday through Friday during radiation. An optional patient capecitabine medication diary is provided in Appendix II for patient convenience. It does not need to be submitted to the Alliance Statistics and Data Center.

7.3.2 Radiotherapy

Radiation therapy will be started on the first day of combined chemoradiation. The total dose of RT will be 45 Gy in 1.8 Gy fractions. A volumetric treatment planning CT study will be required for this study. Each patient will be positioned and immobilized as per institutional standards in the treatment position on a flat table. Treatment plans will be submitted for review within 3 days of the start of radiation therapy.

Please see Section 15.1.3 for credentialing requirements.

7.3.2.1 Technical Factors

Linear accelerators with a minimum energy of 6 MV will be used. A multiple field 3-D conformal technique or IMRT will be used. All fields will be treated each day. The patient will be treated in the supine position. Radiation will be delivered 5 days/week, once per day.

Digital submission of treatment plans is required for this portion of the study. See Section 7.3.2.13.

7.3.2.2 Target Volume Definitions

ICRU-50 and 62 prescription methods and nomenclature shall be utilized for this study. This will apply for conformal and non-conformal techniques. These volumes shall be based on the following information: preoperative imaging including barium swallow (if available) and CT/MRI findings, surgical findings including size and location of the primary lesion and pathologically involved lymph nodes, and location of surgical margins. Normal tissue tolerance limits are defined in Section 7.3.2.9.

Gross Tumor Volume (GTV): As these patients are being treated in the adjuvant setting there is no GTV. However, the area of the entire mass defined by preoperative imaging and pathological findings at the time of resection of the primary lesion should be defined. Areas of involved adenopathy should be carefully depicted and their geographic relationship to the primary lesion be accurately defined on planning images.

Clinical Target Volume (CTV): The CTV in general is defined in this study according to the description and tables below. These volumes are defined according to location of the primary tumor, as well as T and N stage

Planning Target Volume (PTV): For the purpose of this study, a margin for motion and set-up variability is to be added to the clinical target volume. Depending on immobilization methods and patient cooperation, this may vary but must be at least 1 cm. Exact margins will be left up to the treating radiation oncologist and do not need to be uniform in all directions. If the treating radiation oncologist needs to decrease the PTV for normal tissue concerns defined in Section 7.3.2.9, please obtain permission from the RT Study Coordinator.

7.3.2.3 General Guidelines of Impact of T and N Stage on Inclusion of Remaining Stomach, Tumor Bed, Nodal Sites within Irradiation Fields

In general, for patients with node positive disease, there should be wide coverage of tumor bed, residual stomach, resection margins, and nodal drainage regions. Fields need to be modified to assure that tolerance of kidneys, spinal cord, liver, heart and lungs are respected. For node negative disease, if there is a good surgical nodal resection (evaluation of 15+ nodes), and there are wide surgical margins on the primary tumor (at least 5 cm), treatment of the nodal beds is not necessary. Treatment of the residual stomach should depend on a balance between the likely normal tissue morbidity and the perceived risk of relapse in the residual stomach.

The tables below define the sites that should be treated for various locations and T and N stages of the primary lesion (AJCC 7th Edition). If a tumor involves more than one site, then the coverage should correspond to the at risk areas for both of the sites.

7.3.2.4 General Guidelines for Gastroesophageal Junction Tumors

For tumors of the gastroesophageal (GE) junction, the fields should be as below. In addition, the fields need to be extended into the chest to cover adequately any tumor bed located in the chest with margin. The extent of thoracic coverage will be dependent on the known involvement, but should generally extend approximately 5 cm proximal to the area of known esophageal involvement. Care should be taken to treat the peri-esophageal tissues at the level of the tumor fully.

Site of Primary and T, N Stage	Inclusion into Irradiation Fields#:			Tolerance Organs or Structures to be Considered
	Stomach	Remaining Volumes	Tumor Bed Nodal Volumes	
Gastro-esophageal Junction	If can exclude 2/3 one kidney (usually right)	T stage dependent	N stage dependent	Heart, lung, spinal cord, kidneys, liver
T3N0	Variable dependent on surg-path findings*	Medial left hemi-diaphragm; adjacent body of pancreas	None or peri-gastric, peri-esophageal; Optional^: mediastinal, celiac	
T4N0	Preferable, but dependent on surg-path findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence, +/- peri-gastric, peri-esophageal, mediastinal, celiac	
T1-2 N+	Preferable	Not indicated for T1; for T2 Medial left hemi-diaphragm; adjacent body of pancreas	Peri-esophageal, mediastinal, proximal peri-gastric, celiac	
T3-4 N+	Preferable	As for T3, T4 N0	As for T1-2N+ and T4N0	

* For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increased normal tissue morbidity.

Use pre-op imaging, surgical clips and post op imaging.

^ Optional node may be excluded for T3N0 lesions, if 15+ nodes have been pathologically examined.

7.3.2.5 General Guidelines for Cardia/Proximal Third of the Stomach Tumors

Site of Primary and T, N Stage	Inclusion into Irradiation Fields#:			Tolerance Organs or Structures to be Considered
	Stomach	Remaining Volumes	Tumor Bed Nodal Volumes	
Cardia/proximal third of stomach	Preferred, but spare 2/3 of one kidney (usually right)	T stage dependent	N stage dependent	Kidneys, spinal cord, liver, heart, left lung
T3N0	Variable dependent on surg-path findings*	Medial left hemi-diaphragm, adjacent body of pancreas (+/- tail)	None or peri-gastric; Optional ^: peri-esophageal, mediastinal, celiac	
T4N0	Preferable, but dependent on surg-path findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence, +/- peri-gastric, celiac, peri-esophageal, mediastinal**	
T1-2N+	Preferable	Not indicated for T1; for T2 Medial left hemi-diaphragm, adjacent body of pancreas (+/- tail)	Peri-gastric, celiac, splenic, supra-panc, +/- peri-esophageal, pancreato-duodenal, porta-hepatis, mediastinal, **	
T3-4 N+	Preferable	As for T3,T4N0	As for T1-2N+ and T4N0	

* For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional, if this would result in substantial increased normal tissue morbidity.

\# Use pre-op imaging, surgical clips and post op imaging.

** Pancreatico-duodenal and porta-hepatis nodes are at minimal risk if nodal positivity is minimal (i.e., if only 1-2 nodes are positive and 15+ nodes have been examined, these sites do not need to be irradiated). Peri-esophageal and mediastinal nodes are at risk, and should be included, if there is esophageal extension

^ Optional node may be excluded for T3N0 lesions if 15+ nodes have been pathologically examined.

7.3.2.6 General Guidelines for Body/Middle Third of Stomach Tumors

Site of Primary and T, N Stage	Inclusion into Irradiation Fields#:			Tolerance Organs or Structures to be Considered
	Stomach	Remaining Volumes	Tumor Bed Nodal Volumes	
Body/middle third of stomach	es – but spare 2/3 of 1 kidney (usually right)	T stage dependent	N stage dependent- spare 2/3 of right kidney	Kidneys, spinal cord, liver
T3N0	Yes	Body of pancreas (+/- tail)	None or peri-gastric; Optional^: celiac, splenic, supra-pancreatic, pancreato-duodenal, porta-hepatis	
T4N0	Yes	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence +/- peri-gastric, celiac, supra-pancreatic, splenic, pancreato-duodenal, porta-hepatis	
T1-2 N+	Yes	Not indicated for T1; for T2 Body of pancreas (+/- tail)	Peri-gastric, celiac, supra-pancreatic, splenic, pancreato-duodenal, porta-hepatis; optional-splenic hilum	
T3-4N+	Yes	As for T3,T4N0	As for T1-2N+ and T4N0	

*Use pre-op imaging, surgical clips and post op imaging

^ Optional node may be excluded for T3N0 lesions if 15+ nodes have been examined pathologically

7.3.2.7 General Guidelines for Antrum/Pylorus/Distal Third of the Stomach Tumors

Site of Primary and T, N Stage	Inclusion into Irradiation Fields#:			Tolerance Organs or Structures to be Considered
	Stomach	Remaining Volumes	Tumor Bed Nodal Volumes	
Antrum/Pylorus/ distal third stomach	Yes – but spare 2/3 of 1 kidney (usually left)	T stage dependent	N stage dependent	Kidneys, liver, spinal cord
T3N0	Variable dependent on surg-path findings*	Head of pancreas, (+/- body), 1st and 2nd part duodenum	None or peri-gastric; Optional^: pancreato-duodenal, porta-hepatis, celiac, supra-pancreatic	
T4N0	Preferable, but dependent on surg-path findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site(s) of adherence +/- peri-gastric, pancreato-duodenal, porta-hepatis, celiac, supra-pancreatic	
T1-2N+	Preferable	Not indicated for T1; for T2 Head of pancreas, (+/- body), 1st and 2nd part duodenum	Peri-gastric, pancreato-duodenal, porta-hepatis, celiac, supra-pancreatic; Optional^ – splenic hilum^	
T3-4N+	Preferable	As for T3,T4N0	As for T1-2N+ and T4N0	

* For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increased normal tissue morbidity.

\# Use pre-op imaging, surgical clips and post op imaging

^ Optional node may be excluded if 15+ nodes examined pathologically and 0-2 nodes positive

7.3.2.8 Target Dose Constraints

Prescribed dose: Dose will be prescribed to an isodose line that encompasses the PTV and that satisfies the dose uniformity requirements below.

Dose Definition: Dose is specified in Gy to muscle

Tissue Heterogeneity: Calculation shall take into account the effects of tissue heterogeneities. Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. An extended list of approved and unapproved algorithms, as well as contact information for further questions, may be found at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf.

Fractionation: The total dose will be 45 Gy given in 25 fractions. Dose per fraction will be 1.8 Gy. The patient will be treated with one fraction per day with all fields treated per day.

Dose Uniformity: The dose to 99% of the PTV must be at least 93% of the prescribed dose, and no more than 2cc within the PTV may receive a dose greater than 120% of the prescribed dose.

Rests: There are no planned rests on this study. Please contact the study coordinator for treatment interruptions greater than three days.

7.3.2.9 Normal tissue Dose Constraints

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

Normal Tissue Constraints:

1. Lungs
   a. $V_{20Gy} \leq 20\%$
   b. and $V_{30Gy} \leq 15\%$
   c. and $V_{40Gy} \leq 10\%$
   d. $V_{10Gy} \leq 40\%$
2. Cord
   a. Max $\leq$ 45 Gy
3. Bowel
   a. Max bowel dose < Max PTV dose
   b. $D_{05} \leq 45$ Gy
4. Heart
   a. $V_{25Gy} \leq 75\%$ (GE junction tumors)
   b. Mean < 30 Gy (non-GE junction tumors)
5. Left Kidney, Right Kidney (evaluate each one separately and combined):
   a. $V_{20Gy} \leq 32\%$ (combined)
6. Liver
   a. $V_{30Gy} \leq 30\%$

b. Mean < 32 Gy

7. Residual Stomach
   a. Mean < 30 Gy (if not within PTV)
   b. Max dose < 54Gy

7.3.2.10 Treatment Planning

Simulation: Patients will be positioned supine with arms above the head immobilized as per institutional standards for immobilization. A CT simulation will be performed using oral and IV contrast, when possible, using ≤3 mm slice thickness. In patients for whom treatment will be delivered using respiratory gating or tracking, the planning CT scan should be performed with the patient in a breath-hold in end-expiration.

Motion Management: Respiratory and abdominal motion can be significant. We recommend an assessment of motion at the time of simulation and utilization of delivery and immobilization techniques according to institutional practice. A surrogate such as the diaphragm may be used to assess the degree of motion for gastric body in patients who have had less than a total gastrectomy. To determine the extent of respiratory motion for gastroesophageal junction tumors, a respiratory correlated CT scan may be obtained at the time of simulation. This scan will be performed throughout the breathing cycle (i.e., 4-dimensional CT) so that separate CT data sets associated with each phase of respiration can later be reconstructed. Treatment delivery can be done using the motion management technique available at the institution and can include treatment during free-breathing as long as the motion determined from the 4DCT has been included in the PTV. The Motion Management Reporting Form shall be submitted to document the method used (see Section 7.3.2.13).

Beam Arrangements: Beams shall be chosen for optimal coverage of the PTV while satisfying the dose constraints for normal tissues in Section 7.3.2.9.

7.3.2.11 Field Verification

As a minimum requirement, institutions are required to obtain verification images at the start of treatment and each week thereafter. Prior to the first treatment images that verify the position of the isocenter placement must be obtained. For 3D-CRT this imaging can include individual portal views. Weekly imaging can consist of portal views for 3D-CRT and isocenter verification images. For IMRT orthogonal images verifying isocenter position are required. More frequent (daily) imaging is encouraged particularly for patients treated with motion management techniques, but is not required.

7.3.2.12 Definitions of Deviations in Protocol Performance

Prescription Dose

- **Per Protocol:** ≥ 99% of the PTV receives ≥ 93% of the prescribed dose, and a contiguous volume of no more than 2cc inside the PTV receives a dose greater than 120% of the prescribed dose.
- **Variation Acceptable:** Between 95% and 99% of the PTV receives 93% of the prescribed dose, or a volume of 2cc within the PTV receives a dose between 120% and 125% of the prescribed dose.

- **Deviation Unacceptable:** The dose to 1 cc of tissue outside the PTV exceeds 120% of the prescribed dose, or less than 95% of the PTV receives 93% of the prescribed dose, or the dose to a volume of 2cc within the PTV exceeds 125% of the prescribed dose.

Volume

- **Variation Acceptable:** Margins less than specified, or margins up to 2 cm greater than specified.
- **Deviation Unacceptable:** Fields transect tumor or specified target volume(s), or fields are more than 2 cm greater than specified.

Critical Organ

- **Variation Acceptable:** The lung V20 exceeds 20% or the V10 exceeds 40% (see dose limits in Section 7.3.2.9).
- **Deviation Unacceptable:** The V45 for the spinal cord exceeds 0.1 cc; the heart mean dose exceeds 30 Gy for non-GE Junction tumor or V25 exceeds 75% for GE junction tumors; the mean liver dose exceeds 32Gy, the lung V20 exceeds 30% or the V10 exceeds 50% (see dose limits in Section 7.3.2.9).

Treatment Interruption

- **Variation Acceptable:** Treatment interruptions between five and nine normally scheduled treatment days.
- **Deviation Unacceptable:** Treatment interruptions totaling more than nine normal scheduled treatment days.

7.3.2.13 Quality Assurance Documentation

Digital Submission:

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the IROC Rhode Island (QARC) Web site at [redacted]. Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Within 3 days of the start of radiotherapy, the following data shall be submitted for review:

External beam Treatment Planning System

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. Submission of DRR's is not required for IMRT.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in Section 7.3.2.9. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.

- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- Copies of the initial PET/CT scan and diagnostic CT scan, if the PET/CT was not done with contrast, used in defining the target volume. (Scans submitted to the Imaging Core lab will be forwarded to IROC RI. Additional copies of these scans do not need to be sent.)
- Copy of the endoscopy report
- Prescription Sheet for Entire Treatment
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review.

Forms, Records, and Documents

- RT-1 Dosimetry Summary Form
- Motion Management Reporting Form

*Within **one week** of the completion of radiotherapy, the following data shall be submitted:*

- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points
- Documentation listed above showing any modifications from original submission.

Supportive Data and Forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail [redacted] or mailed to:

[redacted]

Questions regarding the completion of the RT-1 Dosimetry Summary Form and RT-2 data forms, dose calculations or documentation should be directed to:

[redacted]

Questions regarding the radiotherapy section of this protocol should be directed to:

7.4 FDG-PET/CT Imaging Procedures, Interpretation, Analysis, and Quality Assurance

FDG PET/CT scans will be acquired pre-therapy (within 42 days prior to initiation of cycle 1), during cycle 1 of pre-registration chemotherapy (days 15-19) and just prior to surgery (post cycle 2 for non-responders assigned to salvage chemotherapy, Arm B). Note that the SUVmax of the primary tumor is the primary PET parameter. Additional findings (i.e. other areas of uptake) will be recorded as well, but the key parameter is the SUVmax of the primary tumor. The same reconstruction parameters should be done for the baseline FDG-PET/CT studies, pre-op chemotherapy PET/CT studies, and the Arm-B salvage chemotherapy PET/CT.

Prior to injection, all patients will have fasted for at least 4 hours prior to injection of ^{18}FDG to diminish physiologic glucose uptake and to reduce serum insulin levels to near basal level, thereby diminishing ^{18}FDG uptake by organs such as the heart. Blood sugar (measured by glucometer) cannot exceed 200 mg/dL at the time of ^{18}FDG PET/CT study. If blood sugars exceed 150 mg/dL, a note should be made of that on the remarks addenda. An attempt should be initially made to control the blood glucose level by encouraging the patient to drink water and remeasuring after a short period. If the blood glucose cannot reach reasonable control on the day of the PET/CT scan, it will require the rescheduling of the PET/CT study. If the glucose level cannot be controlled (i.e., the blood glucose still exceeds 200 mg/dL), the patient will not be included. Patients are to be kept well hydrated and IV furosemide (10 mg) may be administered to increase urinary elimination of the tracer, and minimize image artifacts caused by urinary stasis, potentially confounding the interpretation of local ^{18}FDG uptake in the pelvis.

Whole body emission acquisition of both the pretherapy PET/CT and the post-therapy PET/CT MUST start 60 minutes following 7-20 mCi ^{18}FDG injection (+/- 10 minutes) with a target of 60 minutes. No studies will be accepted if the imaging start time for the PET/CT is less than 50 minutes. For start times greater than 70 minutes but less than or equal to 75 minutes, studies will be accepted with note of the deviation and subsequent scans for that subject will target the new injection to start time within 10 minutes prior but not to be 75 minutes or greater. The exact same period of uptake time must be used for the post one cycle of pre-op chemotherapy PET/CT emission acquisition (no more than a +/- 10 minute difference from the baseline). It is critical that post-therapy emission scans be performed in an identical way to the baseline scan with the same scanner, same scan direction (skull to thighs or thighs to skull) and same arm positioning (arms up or arms down). The field of view is to minimally encompass the region between the base of the skull and the mid-thighs. Coincidence imaging using hybrid SPECT/PET systems is unacceptable. If there is a change in the PET or PET/CT system at any site during the duration of the PET/CT imaging portion of the study, there must be evidence that the SUV's calculated using both systems (i.e., the previous and new one) for

phantoms imaged with both systems are very similar (i.e., < 10% difference). This verification will be made via coordination between the site and the Imaging Core Lab.

7.4.1 Baseline PET/CT Scan Interpretation

Semiquantitative analysis will be used to determine the change in FDG uptake using the SUVmax approach for PET/CT scans obtained at baseline and 15-19 days into therapy. SUV analysis will be performed using the maximum voxel SUV (SUVmax) to assess response to therapy. A 35% or greater decrease in SUV will constitute response to therapy. Regions of interest (ROIs) will be manually placed around the entire extent of any abnormality and around the most intense portion of this abnormality to determine the average and maximum tissue activity within the ROI, respectively (SUVmax), and decay corrected to time of injection.

7.4.2 Interpretation of Concomitant and Post Induction Chemotherapy PET/CT Scans

Semiquantitative analysis will also be used to determine the change in ^{18}FDG uptake from pretherapy baseline PET/CT using the SUVmax approach (i.e., change in SUVmax, see below) during or following induction chemotherapy. This will be correlated with clinical and histopathological response to therapy as well as disease-free and overall survival. For assessment of new lesions that may appear during or following induction chemotherapy, visual interpretation, as described above, will be used to determine if the new lesion is positive or negative for tumor in conjunction with available clinical and radiological findings. A new site seen by PET/CT will only be considered disease progression if corroborated by biopsy or other established imaging methods. Patients with disease progression, considered M1 disease, documented by PET/CT imaging and confirmed by biopsy or imaging should be removed from protocol therapy. An increase in the SUVmax (see below) of > 20% at any time during or post induction chemotherapy will only be considered as possible "indication" of disease progression, unless correlated by disease progression documented by biopsy or other imaging modalities such as barium esophagram or CT, in which case disease progression will be established.

8.0 Dose and Treatment Modifications

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

8.1.4 Antiemetics should be used at the discretion of the attending physician.

Suggested regimens during the pre-registration chemotherapy are steroids, 5HT3 antagonists, and/or aprepitant, and during the post-registration chemotherapy are steroids and 5HT3 antagonists.

8.1.5 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). Escalation (i.e. to lomotil and/or tincture of opium) should be at the discretion of the attending physician.

The following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

8.1.6 Hypersensitivity Reaction: Manage as per institutional standard.

8.1.7 Edema: Steroid premedication for docetaxel infusion is at the discretion of the treating physician. If edema occurs, manage with diuretics at treating physician discretion.

8.1.8 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2010 Update of Recommendations on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. J Clin Oncol 28(33): 4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) is discouraged.
    a. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
    b. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.9 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial during post-registration chemotherapy on Arm B. The follow drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with docetaxel:

- Indinavir
- Clarithromycin
- Ketoconazole.

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

An information handout and wallet-size card providing information for patients and their caregivers regarding potential drug interactions have been made available in Appendix III.

8.1.10 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial during post-registration chemotherapy on Arm B. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with docetaxel.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

An information handout and wallet-size card providing information for patients and their caregivers regarding potential drug interactions have been made available in Appendix III.

8.2 Dose Modifications

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Neither docetaxel nor irinotecan will be re-escalated once reduced.
- If both irinotecan and docetaxel are held for 3 weeks or more during pre-operative chemotherapy, chemotherapy will be discontinued and the patient will be referred for resection.
- If both irinotecan and docetaxel are held for 3 weeks or more during post-operative chemotherapy, chemotherapy will be discontinued
- If dose reductions beyond level -2 are required, then the agent will be discontinued.
- Depending on the specific toxicity, a single chemotherapy drug (i.e. either irinotecan or docetaxel) may be modified without alteration of the other drug.

CTEP-AERS reporting may be required for some adverse events (See Section 9.0)

8.2.1 Dose Levels of Arm B (Docetaxel and Irinotecan)

Dose Level	Drug Name	Dose (mg/m^2)
0*	Docetaxel	30
-1	Docetaxel	25
-2	Docetaxel	20

*Dose level 0 refers to the starting dose.

Dose Level	Drug Name	Dose (mg/m^2)
0*	Irinotecan	50
-1	Irinotecan	40
-2	Irinotecan	30

*Dose level 0 refers to the starting dose.

8.2.2 Dose Modifications for Arm B:

8.2.2.1 Hematologic Toxicities

For **grade 3 neutrophil count decreased on day 1 or 8**, delay docetaxel and irinotecan until grade ≤ 2, then resume docetaxel at 1 dose level decreased, and irinotecan at same dose

For **grade 4 neutrophil count decreased or grade 3 or 4 febrile neutropenia**, delay docetaxel and irinotecan until grade ≤ 2, then resume docetaxel and irinotecan with one dose level decreased

For **grade 2 platelet count decreased**, delay docetaxel and irinotecan until grade ≤ 1, then resume docetaxel at one dose level decreased, and irinotecan at same dose

For **grade 3 or 4 platelet count decreased**, delay docetaxel and irinotecan until grade ≤ 1, then resume docetaxel and irinotecan with one dose level decreased

8.2.2.2 Neurotoxicity

For **grade 2 neuropathy**, continue docetaxel at one dose level decreased, and irinotecan at the same dose

For **grade 3 or 4 neuropathy**, discontinue docetaxel

8.2.2.3 Gastrointestinal Toxicity

For **grade 3 nausea or vomiting**, delay docetaxel and irinotecan until grade ≤ 2, then restart irinotecan at 1 dose level decreased, and docetaxel at the same dose

For **grade 4 vomiting**, delay docetaxel until grade ≤ 2, then restart docetaxel and irinotecan with one dose decreased

For **grade 2 diarrhea**, delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel and irinotecan at same dose

For **grade 3 diarrhea**, delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel at same dose and irinotecan at 1 dose level reduced

For **grade 4 diarrhea**, delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel and irinotecan at one dose decreased

For **grade 3 anorexia**, delay docetaxel and irinotecan until grade ≤ 2, then restart docetaxel and irinotecan at 1 dose level reduced and irinotecan at same dose

For **grade 4 anorexia**, delay docetaxel and irinotecan until grade ≤ 2, then restart docetaxel and irinotecan at 1 dose level reduced

For **grade 2 stomatitis**, treat with docetaxel at 1 dose level reduced and irinotecan at same dose level

For **grade 3 or 4 stomatitis**, delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel and irinotecan at 1 dose level reduced

8.2.2.4 Hepatobiliary Toxicity

For **grade 2 or 3 AST or ALT elevated,** delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel and irinotecan at one dose level decreased

For **grade 4 AST or ALT elevated**, discontinue docetaxel and irinotecan

For **grade 2 bilirubin elevated**, delay docetaxel and irinotecan until grade ≤ 1, then restart docetaxel and irinotecan at 1 dose level decreased

For **grade 3 or 4 bilirubin elevated**, discontinue docetaxel and irinotecan

8.2.2.5 Renal Insufficiency:

For grade 3 or 4 creatinine increased and NOT attributed to study treatment, delay irinotecan until grade ≤ 1 then restart irinotecan at same dose

8.2.2.6 Opthalmalogic Toxicities:

For **grade 3 watering eyes,** delay docetaxel until grade ≤ 1, then restart docetaxel at 1 dose level decreased

For **any grade cystoid macular edema,** discontinue docetaxel

8.2.2.7 General disorders

For **grade 3 or 4 edema**, omit docetaxel until grade < 2, then resume docetaxel at one dose level decreased

For **grade 3 or 4 fatigue,** delay docetaxel and irinotecan until grade ≤ 2, then resume docetaxel at 1 dose level decreased and irinotecan at same dose level

For **grade 4 hypersensitivity reaction,** discontinue offending study agent.

8.2.2.8 Non-hematologic Toxicities

For all other **grade 3 or 4 non-hematologic toxicities** likely related to docetaxel and/or irinotecan, omit docetaxel and/or irinotecan until resolved to < grade 1, then resume docetaxel and/or irinotecan at one dose decreased

8.2.2.9 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

8.2.3 Dose Levels during chemoradiation in Arm A:

Dose Level	Drug Name	Dose (mg/m^2/day)
0*	5FU	200
-1	5FU	150
-2	5FU	100

*Dose level 0 refers to the starting dose.

Dose Level	Drug Name	Dose (mg/m^2) bid M-F during RT
0*	capecitabine	800
-1	capecitabine	600
-2	capecitabine	400

*Dose level 0 refers to the starting dose.

8.2.4 Dose Modifications during chemoradiation in Arm A:

8.2.4.1 5FU Dose Modifications:

5FU should be delayed at any point that radiotherapy is delayed, regardless of whether there is 5FU related toxicity present

Hematologic Toxicity:

For **grade 2 platelet count decreased**, delay 5FU until grade ≤ 1 then resume at same dose

For **grade 3 or 4 platelet count decreased**, delay 5FU until grade ≤ 1 then resume at 1 dose level decreased

Gastrointestinal Toxicity:

For **grade 3 or 4 diarrhea**, delay 5FU until grade ≤ 1 then resume at 1 dose level reduced.

For **grade 3 or 4 mucositis**, delay 5FU until grade ≤ 1 then resume at 1 dose level reduced.

Hepatic Insufficiency:

For **grade 3 or 4 bilirubin increased** and NOT related to study treatment, delay 5FU until grade ≤ 2, then resume at same dose level

Skin Toxicity:

For **grade 2 or 3 palmar-plantar erythrodysesthesia syndrome**, delay 5FU until grade ≤ 1, then resume at 1 dose level reduced.

8.2.4.2 Capecitabine Dose Modifications:

Hematologic Toxicity:

For **grade 2 platelet count decreased**, delay capecitabine until grade ≤ 1 then resume at same dose

For **grade 3 or 4 platelet count decreased**, delay capecitabine until grade ≤ 1 then resume at 1 dose level decreased

Gastrointestinal Toxicity:

For **grade 3 or 4 diarrhea**, delay capecitabine until grade ≤ 1 then resume at 1 dose level reduced.

For **grade 3 or 4 mucositis**, delay capecitabine until grade ≤ 1 then resume at 1 dose level reduced.

Renal Insufficiency

For **grade 2, 3, or 4 creatinine increased and** NOT attributed to study treatment, delay capecitabine until grade ≤ 1, then restart capecitabine at same dose level.

Skin Toxicity:

For **grade 2 or 3 palmar-plantar erythrodysesthesia syndrome**, delay capecitabine until grade ≤ 1, then resume at 1 dose level reduced.

8.2.4.3 Non-hematologic Toxicities

For all other **grade 3 or 4 non-hematologic toxicities** likely related to 5FU or capecitabine, omit 5FU or capecitabine until resolved to < grade 1, then resume 5FU or capecitabine at one dose level decreased

8.2.4.4 Radiotherapy Dose Modifications

The dose of radiation will be 45GY in 25 fractions as standard for post-operative therapy for gastric cancer. Dose modifications are not anticipated, but may arise based on treatment related toxicity.

Radiotherapy should be held for any of the following treatment related toxicities:

- Grade 3 or 4 platelet count decreased
- Grade 3 or 4 neutropenia, or for febrile neutropenia
- Grade 2, 3 or 4 renal insufficiency
- Grade 3 nausea, or grade 3 or 4 vomiting.
- Grade 3 or 4 dehydration

Radiotherapy may resume once any of the above toxicities improve, generally returning to < grade 1. Additional breaks in therapy can be performed at the discretion of the treating radiation oncologist. If patients are held for more than 2 consecutive weeks, or if radiotherapy is interrupted for a cumulative duration of 4 weeks or more during the course of radiotherapy, further radiotherapy will be discontinued.

8.2.6 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events: Solicited and Adverse Events: Other forms are used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Anorexia	Metabolism and nutrition disorders
Weight Loss	Investigations
Fatigue	General disorders
Diarrhea	Gastrointestinal disorders
Peripheral motor neuropathy	Nervous systems disorders
Peripheral sensory neuropathy	Nervous systems disorders
Febrile neutropenia	Blood and lymphatic system disorders
Anemia	Blood and lymphatic system disorders

9.2 CTCAE Routine Study Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) accessed via https://eapps-ctep.nci.nih.gov/ctepaers/.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 CIP Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a CIP Non-IND/IDE trial ≤ 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions to CTEP-AERS reporting:

- All adverse events reported via AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 diarrhea and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 diarrhea does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 mucositis and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 mucositis does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 neuropathy and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.

- Grade 3 neuropathy does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hand foot syndrome and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 hand foot syndrome does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-4 hypersensitivity reaction and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 hypersensitivity reaction does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 edema and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 edema does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 dehydration and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 dehydration does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 fatigue and hospitalization resulting from such does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 fatigue does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) with hospitalization resulting from such do not require AERs reporting, but should be reported via routine AE reporting
- Grade 3 or 4 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) does not require AERs reporting, but should be reported via routine AE reporting
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female during therapy or within 28 days after completion of treatment on A021302 must be reported via CTEP-AERS. In CTCAE version 4.0, use the event term, "pregnancy, puerperium, and perinatal condition-other, pregnancy (grade 3)".

- CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). Fetal death should be reported as pregnancy, puerperium and perinatal conditions- other pregnancy loss (grade 4).
- The CTEP-AERS report should be amended for any neonatal deaths occurring within 28 days of birth considered at least possibly related to treatment. Use the event term "general disorders and administration site conditions-other, neo-natal loss" (grade 4).

- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

10.0 DRUG INFORMATION

10.1 General Considerations:

- The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.
- It is not necessary to change the doses of all study agents due to changes in weight unless the calculated dose changes by ≥10%.

10.2 Epirubicin (Ellence®)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 2 mg/ml (25 ml and 100 ml)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions.

Solution: Store intact vials refrigerated at 2°C to 8°C (36°F to 46°F); do not freeze. Product may "gel" at refrigerated temperatures; will return to slightly viscous solution after 2-4 hours at room temperature (15°C to 30°C). Discard unused solution from single dose vials within 24 hours of entry.

Administration

Refer to the treatment section for specific administration instructions. Infuse over 15-20 minutes or slow I.V. push; if lower doses due to dose reduction are administered, may reduce infusion time proportionally. Do not infuse over <3 minutes. Infuse into a free-flowing I.V. solution. Avoid the use of veins over joints or in extremities with compromised venous or lymphatic drainage.

Vesicant; avoid extravasation.

Prophylactic antiemetics should be administered per institutional standard.

Drug Interactions

Concomitant use of Epirubicin with other cardioactive compounds that could cause heart failure (e.g. calcium channel blockers) requires close monitoring of cardiac function throughout treatment.

It is likely that the use of epirubicin with radiotherapy may sensitize tissues to the cytotoxic actions of irradiaton. Administration of epirubicin after previous radiation therapy may induce an inflammatory recall reaction at the site of irradiation.

Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicn metabolism.

Cimetidine increased the AUC of epirubicin by 50%. Cimetidine treatment should be stopped during treatment with epirubicin.

Pharmacokinetics

Distribution: Vss: 21-27 L/kg

Protein binding: ~77% to albumin

Metabolism: Extensively via hepatic and extrahepatic (including RBCs) routes

Half-life elimination: Triphasic; Mean terminal: 33 hours

Excretion: Feces (34% to 35%); urine (20% to 27%)

Adverse Events

Common known potential toxicities, >10%:

Central nervous system: Lethargy

Dermatologic: Alopecia

Endocrine & metabolic: Amenorrhea, hot flashes

Gastrointestinal: Nausea/vomiting, mucositis, diarrhea

Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia

Local: Injection site reactions

Ocular: Conjunctivitis

Miscellaneous: Infection

Less common known potential toxicities, 1% to 10%:

Cardiovascular: LVEF decreased, HF

Central nervous system: Fever

Dermatologic: Rash, skin changes

Gastrointestinal: Anorexia

Hematologic: Neutropenic fever

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Abdominal pain, acute lymphoid leukemia (ALL), acute myelogenous leukemia (AML), anaphylaxis, arrhythmia, arterial embolism, ascites, atrioventricular block, bradycardia, bundle-branch block, cardiomyopathy, chills, dehydration, dyspnea, ECG abnormalities, erythema, esophagitis, flushing, GI burning sensation, GI erosions/ulcerations, GI pain, GI bleeding, hepatomegaly, hyperpigmentation (oral mucosa, nails, skin), hypersensitivity, hyperuricemia, myelodysplastic syndrome, myocarditis, neutropenic typhlitis, phlebitis, photosensitivity, pneumonia, premature menopause, premature ventricular contractions, pulmonary edema, pulmonary embolism, radiation recall, sepsis, shock, sinus tachycardia, stomatitis, ST-T wave changes (nonspecific), tachyarrhythmias, thromboembolism, thrombophlebitis, toxic megacolon, transaminases increased, urine discoloration (red), urticaria, ventricular tachycardia

Nursing Guidelines

Assess patient carefully for any previous history of heart disease. Cardiotoxicity is a known risk and may manifest by early or late events. Early cardiotoxicity consists of sinus tachycardia, ST-T wave changes, AV block, ventricular tachycardia. Delayed cardiotoxicity (cardiomyopathy) is manifested by LV CHF. The risk of CHF increases with cumulative doses. Cardiotoxicities may be life threatening. Monitor cardiac function assessments regularly.

Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alert to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales.

Epirubicin is mutagenic. Discuss birth control issues with patient. Advise patient against pregnancy during and for 6 months after treatment.

Advise female patients that epirubicin may induce irreversible amenorrhea in pre-menopausal women.

Epirubicin is a vesicant. Venous sclerosis may result from injection into a small vein or repeated injections into the same vein. Check IV patency before and frequently during administration. If extravasation occurs, refer to your extravasation policy. Extravasation may cause severe tissue necrosis, pain, and lesions. Central venous access may be necessary for patients with poor peripheral access. Discuss options with treating physician.

Epirubicin causes rapid cellular destruction. Assess for signs of tumor lysis syndrome, i.e., hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Clinical signs would be arrhythmias, neuromuscular irritability, weakness, nausea/vomiting/diarrhea, paresthesias, decreased heart rate, and flaccid paralysis. Instruct patient to report muscle cramps or twitching to health care team immediately.

Assess baseline renal function for comparison, then watch electrolytes and physical signs for compromised renal function, i.e., nausea/vomiting/diarrhea, lethargy, flank pain, edema, hematuria, azotemia, oliguria, and anuria. Encourage hydration and diuresis. Monitor I&O and weight. Observe for distended neck veins, edema, SOB, and pulmonary rales.

Epirubicin causes nausea and vomiting in about 90% of patients, especially when given with other emetogenic agents. Administer antiemetics prophylactically and monitor for their effectiveness.

Drug may cause stomatitis. Emphasize the need for good oral hygiene.

"Radiation recall" is a possibility. Assess patient for previous or current sites of radiation therapy. Monitor skin in those areas carefully.

Myelosuppression is common. Monitor CBC closely and advise patient to report any signs or symptoms of infection, unusually bruising, and/or bleeding to the health care team immediately.

Advise patient of alopecia.

Advise patient that urine may turn pink for 1-2 days after drug administration.

Patients with impaired liver function must have dose reduction. Monitor liver function tests closely.

10.3 Oxaliplatin (Eloxatin®, OXAL)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as: Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, 40 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and; do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D_5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Do not prepare using a chloride-containing solution (e.g., NaCl). Dilution with D_5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light.

Administration

Refer to the treatment section for specific administration instructions. Administer as I.V. infusion over 2-6 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

Drug Interactions

Increased Effect/Toxicity: Nephrotoxic agents may increase Oxaliplatin toxicity. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).
Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin

Pharmacokinetics

Distribution: V_d: 440 L
Protein binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)
Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives phase: 16.8 hours
Excretion: Primarily urine (~54%); feces (~2%)

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported with Monotherapy.
Common known potential toxicities, > 10%:

Central nervous system: Fatigue, fever, pain, headache, insomnia
Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis
Hematologic: Anemia, thrombocytopenia, leukopenia
Hepatic: Liver enzymes increased
Neuromuscular & skeletal: Back pain, peripheral neuropathy (may be dose limiting). The most commonly observed oxaliplatin toxicity is acute and cumulative neurotoxicity, observed in patients treated at doses above 100 mg/m^2/cycle. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and perioral region as well as unusual laryngopharyngeal dysesthesias characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm). OXAL neurotoxicity appears to be exacerbated by exposure to cold. Patients on this study will be counseled to avoid cold drinks and exposure to cold water or air. Should a patient develop laryngopharyngeal dysesthesia, their oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent should be given and the patient observed in the clinic until the episode has resolved. Because this syndrome may be associated with the rapidity of OXAL infusion, subsequent doses of OXAL should be administered as a 6-hour infusion (instead of the normal 2-hour infusion).
Acute and cumulative neurotoxicities are dose limiting for OXAL. The acute neurotoxicity is characterized by paresthesias and dysesthesias that may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days.
Cumulative doses of OXAL above 680 mg/m^2 may produce functional impairment

characterized by difficulty performing activities requiring fine sensory-motor coordination; impairment is caused by sensory rather than motor changes. The likelihood of experiencing neurotoxicity is directly related to the total cumulative dose of OXAL administered. The relative risk of developing neurotoxicity was 10%, 50%, and 75% in patients who received total cumulative OXAL doses of 780 mg/m^2, 1,170 mg/m^2, and 1,560 mg/m^2, respectively. Both acute and cumulative neurotoxicities due to OXAL have lessened in 82% of patients within 4 to 6 months, and have completely disappeared by 6 to 8 months in 41% of patients. In addition, the likelihood that neurologic symptoms will regress has been shown to correlate inversely with cumulative dose.
Respiratory: Dyspnea, cough

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism
Central nervous system: Dizziness
Dermatologic: Rash, alopecia, hand-foot syndrome
Endocrine & metabolic: Dehydration, hypokalemia
Gastrointestinal: Dyspepsia, taste perversion, flatulence, mucositis, gastroesophageal reflux, dysphagia
Genitourinary: Dysuria
Hematologic: Neutropenia
Local: Injection site reaction
Neuromuscular & skeletal: Rigors, arthralgia
Ocular: Abnormal lacrimation
Renal: Serum creatinine increased
Respiratory: URI, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia
Miscellaneous: Allergic reactions, hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope, hiccup

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Gastrointestinal: Life threatening enteric sepsis secondary to neutropenia and diarrhea.
Hepatic: Veno-occlusive disease of the liver is a rare serious adverse event that has occurred in association with administration of oxaliplatin and fluorouracil.
Otic: Clinical ototoxicity occurs in less than 1% of patients following oxaliplatin administration, and sever ototoxicity has not been reported

Nursing Guidelines

GI toxicity similar to cisplatin occurs with doses above 30 mg/m^2. It can be almost constant and frequently severe, but not always dose-limiting. Monitor for nausea and vomiting and treat accordingly.

Dose-limiting side effect can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m^2). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team. Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

OXAL is incompatible with NS. Flush lines with D5W prior to and following OXAL infusion.

Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion. If ≥Grade 2 laryngopharyngeal dysesthesia occurs during the administration of OXAL, do the following:

- Stop OXAL infusion
- • Administer benzodiazepine and give patient reassurance
- • Test oxygen saturation via a pulse oximeter
- • At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.
- • Rapid resolution is typical within minutes to a few hours. Can recur with retreatment.

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions		
Clinical Symptoms	**Laryngopharyngeal Dysesthesias**	**Platinum Hypersensitivity**
dyspnea	present	present
bronchospasm	absent	present
laryngospasm	absent	present
anxiety	present	present
O_2 saturation	normal	decreased
difficulty swallowing	present (loss of sensation)	absent
pruritus	absent	present
urticaria/rash	absent	present
cold-induced symptoms	yes	no
BP	normal or increased	normal or decreased
Treatment	anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion	oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Alopecia is rare with OXAL alone, but is seen with 5-FU-OXAL combination. Advise patient.

Mild-moderate diarrhea has been seen -- usually of short duration. Treat accordingly.

Respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered OXAL. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold OXAL until interstitial lung disease is ruled out for cases of Grade ≥3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the MD immediately as these could be a sign of VOD or other serious condition.

Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

Patients may experience sleep disturbances, specifically insomnia. Encourage good sleep hygiene, and instruct patient to report any problems with sleep to the MD, to assess for the potential use of sleeping aids.

Cold-induced transient visual abnormalities can be experienced by patients while receiving OXAL, although the relationship to OXAL has not been completely determined. Instruct patient to report any problems with vision to the MD.

Extrapyramidal side effects and/or involuntary limb movement has been seen with OXAL administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the MD.

10.4 Cisplatin (Platinol®, CDDP)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as:
Solution [preservative free]: 1 mg/mL (50 mL, 100 mL, 200 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Do not refrigerate solution, a precipitate may form. Further dilution stability is dependent on the chloride ion concentration and should be mixed in solutions of sodium chloride concentrations at least 0.3% NaCl. Further dilutions in 0.9% NaCl, D_5/0.45% NaCl, or D_5/0.9% NaCl to a concentration of 0.05-2 mg/mL are stable for 72 hours at 4ºC to 25ºC. The infusion solution should have a final sodium chloride concentration equal to or greater than 0.2% NaCl.

Administration

Refer to the treatment section for specific administration instructions. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Pretreatment hydration with 1-2 L of fluid is recommended prior to cisplatin administration; adequate hydration and urinary output (> 100 mL/hour) should be maintained for 24 hours after administration. Hydration may be accomplished by adding the appropriate dose of cisplatin to 750 mL 0.5 D5/0.45% NaCl with 25 grams of Mannitol (approximating 1000 mL final volume) and infused over 2 hours. The IV rate of administration has varied from a 15- to 120-minute infusion, 1 mg/minute infusion, 6- to 8-hour infusion, 24-hour infusion, or per protocol; maximum rate of infusion of 1 mg/minute in patients with CHF.

Drug Interactions

Increased Effect/Toxicity: Delayed bleomycin elimination with decreased Glomerular filtration rate. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Sodium thiosulfate and amifostine theoretically inactivate drug systemically; have been used clinically to reduce systemic toxicity with administration of cisplatin.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Pharmacokinetics

Distribution: Rapidly into tissue; high concentrations in kidneys, liver, ovaries, uterus, and lungs
Protein binding: >90%
Metabolism: Nonenzymatic; inactivated (in both cell and bloodstream) by sulfhydryl groups; covalently binds to glutathione and thiosulfate
Half-life elimination: Initial: 20-30 minutes; Beta: 60 minutes; Terminal: ~ 24 hours; Secondary half-life: 44-73 hours
Excretion: Urine (>90%); feces (10%)

Adverse Events

Consult the package insert for the most current and complete information.
Common known potential toxicities, > 10%:
Central nervous system: Neurotoxicity: Peripheral neuropathy is dose- and duration-dependent
Dermatologic: Mild alopecia
Gastrointestinal: Nausea and vomiting
Hematologic: Myelosuppression (mild with moderate doses, mild to moderate with high-dose therapy)
Hepatic: Liver enzymes increased
Renal: Nephrotoxicity (acute renal failure and chronic renal insufficiency)
Otic: Ototoxicity, manifested as high frequency hearing loss; ototoxicity is especially pronounced in children
Less common known potential toxicities, 1% - 10%:
Local: Tissue irritation
Rare known potential toxicities, <1% (Limited to important or life-threatening):
Anaphylactic reaction, arrhythmias, blurred vision, Bradycardia, cerebral blindness, hemolytic anemia, liver enzymes increased, mild alopecia, mouth sores, optic neuritis, and papilledema

Nursing Guidelines

May react with aluminum IV set, forming a black precipitate and losing its potency.

Assess laboratory values prior to drug administration, especially CBC, platelets, creatinine.

Patient should be hydrated before administration. Stress post infusion hydration maintenance to reduce risk of nephrotoxicity.

Administer aggressive antiemetic therapy pre- and post-treatment.

Monitor for signs of neurotoxicity and ototoxicity. Instruct patient to report any numbness, burning, or tingling in hands and feet to health care team. Also instruct patient to report any changes in hearing or ringing in the ears to health care team.

Monitor magnesium and potassium levels, and for signs and symptoms of hypomagnesemia and hypokalemia, supplements may be needed.

Instruct patient about alopecia.

Use cautiously with loop diuretics as these may increase the risk of ototoxicity.

Monitor for signs and symptoms of allergic reactions. Treat according to your institution's protocol.

Monitor renal function tests.

10.5 Capecitabine (Xeloda)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available in 150 mg and 500 mg tablets for oral administration.

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions.
Store at room temperature of 25ºC, with excursions between 15ºC and 30ºC permitted.

Administration

Refer to the treatment section for specific administration instructions. Usually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal (Because current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. In all clinical trials, patients are instructed to take with water within 30 minutes after a meal).

Drug Interactions

Increased Effect/Toxicity: Phenytoin and warfarin levels or effects may be increased. **[U.S. Boxed Warning] Capecitabine may increase the anticoagulant effects of warfarin; monitor closely.**

Nutrition Interactions: Food reduced the rate and extent of absorption of capecitabine.

Pharmacokinetics

Absorption: Rapid and extensive
Protein Binding: <60%; ~35% to albumin
Metabolism:
Hepatic: Inactive metabolites
Tissue, Active metabolite, Fluorouracil
Distribution: V_d: 46 mL/kg
Half-life elimination: 0.5-1 hour
Time to peak: 1.5 hours; Fluorouracil, 2 hours
Excretion: Urine (96%), Feces (<3%)

Adverse Events

Consult the package insert for the most current and complete information. Frequency listed derived from Monotherapy trials.
Common known potential toxicities, > 10%:
Cardiovascular: Edema
Central nervous system: Fatigue, fever, pain

Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome), dermatitis.
Gastrointestinal: Diarrhea may be dose limiting, nausea, vomiting, abdominal pain, stomatitis, appetite decreased, anorexia, constipation.
Hematologic: Lymphopenia, anemia, neutropenia, thrombocytopenia.
Hepatic: Bilirubin increased.
Neuromuscular & skeletal: Paresthesia.
Ocular: Eye irritation.
Respiratory: Dyspnea.

Less common known potential toxicities, 5% - 10%:

Cardiovascular: Venous thrombosis, chest pain.
Central Nervous System: Headache, lethargy, dizziness, insomnia, mood alteration, depression.
Dermatologic: Nail disorder, rash, skin discoloration, alopecia, Erythema.
Endocrine& metabolic: Dehydration.
Gastrointestinal: Motility disorder, oral discomfort, dyspepsia, upper GI inflammatory disorders, hemorrhage, ileus, taste perversion.
Neuromuscular & skeletal: Back pain, weakness, neuropathy, myalgia, arthralgia, limb pain
Ocular: Abnormal vision, conjunctivitis.
Respiratory: Cough.
Miscellaneous: Viral infection.

Rare known potential toxicities, <5% (Limited to important or life-threatening):

Angina, ascites, asthma, atrial fibrillation, Bradycardia, bronchitis, bronchopneumonia, bronchospasm, cachexia, cardiac arrest, cardiac failure, cardiomyopathy, cerebral vascular accident, cholestasis, coagulation disorder, colitis, deep vein thrombosis, diaphoresis, duodenitis, dysphagia, dysrhythmia, ECG changes, encephalopathy, epistaxis, fungal infection, gastric ulcer, gastroenteritis, hematemesis, hemoptysis, hepatic failure, hepatic fibrosis, hepatitis, Hypokalemia, hypomagnesemia, hyper-/hypotension, hypersensitivity, hypertriglyceridemia, idiopathic thrombocytopenia purpura, ileus, infection, intestinal obstruction, keratoconjunctivitis, lacrimal duct stenosis, leukopenia, loss of consciousness, lymphedema, MI, multifocal leukoencephalopathy, myocardial ischemia, myocarditis, necrotizing enterocolitis (typhlitis), oral candidiasis, pericardial effusion, thrombocytopenic purpura, pancytopenia, photosensitivity reaction, pneumonia, pruritus, pulmonary embolism, radiation recall syndrome, renal impairment, respiratory distress, sedation, sepsis, skin ulceration, tachycardia, thrombophlebitis, toxic megacolon, tremor, ventricular extrasystoles.

Nursing Guidelines

Instruct patients to take the tablets within 30 minutes of a meal (breakfast and dinner). Tablets should be swallowed with 6 8 oz. of water.

Instruct patient to avoid taking a missed dose, to never double up on a dose, and to notify the health care team if a dose has been missed.

Diarrhea can be severe and dose-limiting. Instruct patient to contact the health care team immediately if they experience >4 BMs/day and/or nocturnal diarrhea above baseline. Monitor carefully for dehydration and need for fluid and electrolyte replacement. Standard antidiarrheal treatment, e.g., loperamide is recommended.

Nausea and vomiting can be severe and dose-limiting. Instruct patient to report nausea and vomiting to the health care team if they experience >2 episodes of emesis in a 24-hour period. Initiate symptomatic treatment.

Hand and Foot Syndrome is common and dose-limiting (redness, swelling, pain, numbness, tingling, blistering, and moist desquamation). Instruct patient to notify health care team immediately if symptoms appear. Chemotherapy may have to be discontinued until symptoms subside with future dose reduction initiated. The syndrome may recur with a rechallenge.

- Advise patient to apply cool compress for comfort.
- Advise patient to avoid harsh soaps and to use alcohol-free emollients.
- Administer analgesics as prescribed.
- Administer systemic steroids and pyridoxine as prescribed.

Treat stomatitis symptomatically -- may try dabbing vitamin E oil on lesions. Do not swallow oil. Advise frequent and careful oral hygiene.

Assess for warfarin use. Patients taking coumadin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

Carefully assess patient's understanding and need of instruction in adequate birth control measures. Discuss importance of avoiding pregnancy. Periodically re-assess.

Renal impairment: Check creatinine values weekly and calculate creatinine clearance weekly for signs of renal impairment (if this is part of test schedule!!). Follow dose modifications.

The use of Sorivudine or its analogue, Birivudine, is contraindicated for this study due to a possible, even fatal, drug reaction. Assess patient's drug use. Impress on patients the importance of avoiding these drugs while on study.

Cardiotoxicity (including MI, angina, dysrhythmias, and cardiac arrest) has been seen with capecitabine. Observe patients closely for signs of cardiac dysfunction. Instruct patient to report any chest pain or palpitations to the health care team immediately or seek emergency medical attention.

Monitor patient closely who are taking concomitant phenytoin therapy. There have been reports of increased levels of phenytoin in patients who are also taking capecitabine. These patients may require more frequent monitoring of their phenytoin levels and dose adjustments as necessary.

Cimetidine may alter the clearance of capecitabine and cause toxic levels. Cimetidine should be avoided while taking capecitabine.

10.6 Fluorouracil (Adrucil®, 5FU)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions.

Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL

of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. .

Administration

Refer to the treatment section for specific administration instuctions.

Fluorouracil may be given IV push, IV infusion. Refer to the treatment section for specific administration instructions. Avoid extravasation, may be an irritant.

Drug Interactions

Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

Pharmacokinetics

Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g., pleural effusions and ascitic fluid), marrow, intestinal mucosa, liver and other tissues
Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.
Half-life elimination: Biphasic: Initial: 8-20 minutes; two metabolites, FdUMP and FUMP, have prolonged half-lives depending on the type of tissue.
Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

Adverse Events

Consult the package insert for the most current and complete information.
Common known potential toxicities, > 10%:

Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.
Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.
Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)
Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.
Local: Irritant chemotherapy.

Less common known potential toxicities, 1% - 10%:

Dermatologic: Dry skin
Gastrointestinal: GI ulceration

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

Nursing Guidelines

Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

Administer antiemetics as indicated.

Diarrhea may be dose–limiting; encourage fluids and treat symptomatically.

Assess for stomatitis; oral care measures as indicated. May try vitamin E oil dabbed on sore, six times daily. Cryotherapy recommended with IV push administration.

Monitor for neurologic symptoms (headache, ataxia).

Inform patient of potential alopecia.

Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

10.7 Docetaxel (Taxotere®, TATER)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Note: Docetaxel is now available as a one-vial formulation in two concentrations: 10 mg/mL and 20 mg/mL. The older formulation included 2 vials which consisted of a concentrated docetaxel vial and a diluent vial, resulting in a reconstituted concentration of 10 mg/mL. Admixture errors could occur due to the concentration difference between the new formulations of 10 mg/mL and 20 mg/mL and the old formulation (10 mg/mL). Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Storage conditions: Store the packaged docetaxel between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

One-vial formulation: Note: One-vial formulation is available in two concentrations: 10 mg/mL and 20 mg/mL. Further reconstitution with diluent is not required. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Solutions prepared from the one-vial formulation and diluted for infusion should be used within 4 hours of preparation (infusion should be completed within 4 hours).

Two-vial formulation: Vials should be diluted with 13% (w/w) ethanol/water (provided with the drug) to a final concentration of 10 mg/mL. Do not shake. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Diluted solutions of the two-vial formulation are stable in the vial for 8 hours at room temperature or under refrigeration. Solutions prepared with the two-vial formulation and diluted for infusion in D_5W or NS are stable for up to 4 weeks (Thiesen, 1999) at room temperature of 15ºC to 25ºC (59ºF to 77ºF) in polyolefin containers; however, the manufacturer recommends use within 4 hours (infusion should be completed within 4 hours).

Administration

Refer to the treatment section for specific administration instructions. Administer IV infusion over 1-hour through nonsorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary. Do not administer to patients with a history of hypersensitivity to docetaxel or polysorbate 80. Docetaxel is an irritant with vesicant-like properties. **Note:** Premedication with dexamethasone 8 – 10 mg orally twice daily for 3-5 days, beginning the day before docetaxel administration is recommended to decrease the incidence and severity of fluid retention and prevent hypersensitivity reactions and pulmonary/peripheral edema. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy.

Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP3A4; **Inhibits** CYP3A4 (weak).
Increased Effect/Toxicity: CYP3A4 inhibitors may increase the levels/effects of docetaxel. Concomitant use of docetaxel with a potent CYP3A4 inhibitor should be avoided. Refer to the package insert or LexiComp[1] for example inhibitors. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Taxane derivatives may enhance the adverse/toxic effect of anthracyclines.
Decreased Effect: CYP3A4 inducers may decrease the levels/effects of docetaxel. Refer to the package insert or LexiComp[1] for example inducers.
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid St John's wort (may decrease docetaxel levels).

Pharmacokinetics

Docetaxel exhibits linear pharmacokinetics at the recommended dosage range.
Distribution: Extensive extravascular distribution and/or tissue binding; V_d: 80-90 L/m2, V_{dss}: 113 L (mean steady state)
Protein binding: ~94% to 97%
Metabolism: Hepatic; oxidation via CYP3A4 to metabolites
Half-life elimination: Terminal: ~11 hours
Excretion: Feces (~75%, <8% as unchanged drug); Urine (<5%)

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported for docetaxel Monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.
Common known potential toxicities, > 10%:

Cardiovascular: Fluid retention
Central nervous system: Neurosensory events including neuropathy, fever, neuromotor events.
Dermatologic: Alopecia, cutaneous events, nail disorder
Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia
Hepatic: Transaminases increased
Neuromuscular & skeletal: Weakness, myalgia
Respiratory: Pulmonary events
Miscellaneous: Infection, hypersensitivity

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Left ventricular ejection fraction decreased, hypotension
Dermatologic: Rash/erythema
Gastrointestinal: Taste perversion
Hepatic: Bilirubin increased, alkaline phosphatase increased
Local: Infusion-site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein
Neuromuscular and skeletal: Arthralgia
Ocular: Epiphora associated with canalicular stenosis

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Acute myeloid leukemia, acute respiratory distress syndrome, anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation, drug fever, duodenal ulcer, Dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, intestinal pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, Myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

Nursing Guidelines

Monitor CBC closely, as neutropenia, and thrombocytopenia are common and may be life threatening, and dose limiting. Instruct patient to report any signs or symptoms of infection, any unusual bruising, or bleeding.

Administer antiemetics as ordered. Evaluate for their effectiveness.

Monitor for signs/symptoms of hypersensitivity reactions that may include chills, rigors, dyspnea, bronchospasms, etc. Stop infusion immediately and administer proper emergency treatment.

Because of the risk of anaphylaxis and development of edema, instruct patient that is imperative to take steroid premedications as ordered.

Instruct patient on proper oral care, as mucositis may occur.

Advise patient about alopecia.

Monitor liver function tests.

Drug is a vesicant. Monitor infusion site frequently for signs of irritation or infiltration. Drug extravasation causes acute streaking, burning pain, and discoloration at the site. Skin may be reddened for several weeks and occasionally blister and/or peel. Reactions are usually reversible over time. Because of this central venous access may be necessary. Discuss with MD if patient has poor peripheral venous access. If docetaxel concentrate or diluted solution comes into contact with skin, wash with soapy water immediately. If it comes into contact with mucosa, wash with warm water immediately.

Instruct patient to report any signs of peripheral neuropathy to the health care team (pain, numbness, tingling).

Monitor for signs and symptoms of fluid retention, weight gain, ascites and CHF.

Instruct patient about possible facial flushing, rash, and skin and nail changes. Monitor for signs and symptoms of hand/foot syndrome. However premedication with steroids can minimize this side effect. Discuss with MD possible ways to manage itching and skin changes that may occur up to a week after docetaxel administration. Advise patients that nails may crack, peel, or fall off all together. This may be a chronic toxicity. Instruct patient to keep nails clean, short and to avoid wearing nail polish or artificial nails.

10.8 Irinotecan (Camptosar®, CPT11)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 20 mg/mL (2 mL, 5 mL, 15 mL) [contains sorbitol 45 mg/mL; do not use in patients with hereditary fructose intolerance].

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Doses should be diluted in 250-500 mL D_5W or 0.9% NaCl to a final concentration of 0.12-2.8 mg/mL. Due to the relatively acidic pH, Irinotecan appears to be more stable in D_5W than 0.9% NaCl. Solutions diluted in D5W are stable for 24 hours at room temperature or 48 hours under refrigeration at 2ºC to 8ºC. Solutions diluted in 0.9% NaCl may precipitate if refrigerated. Do not freeze.

Administration

Refer to the treatment section for specific administration instructions.

Administer by I.V. infusion, usually over 90 minutes.

Drug Interactions

Cytochrome P450 Effect: Substrate (major) of CYP2B6, 3A4
Increased Effect/Toxicity: CYP2B6 and CYP3A4 inhibitors may increase the levels/effects of irinotecan. Bevacizumab may increase the adverse effects of Irinotecan (e.g., diarrhea, neutropenia). Ketoconazole increases the levels/effects of Irinotecan and active metabolite; discontinue ketoconzaole 1 week prior to Irinotecan therapy; concurrent use is contraindicated.
Decreased Effect: CYP2B6 and CYP3A4 inducers may decrease the levels/effects of irinotecan.
Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John's wort decreases therapeutic effect of irinotecan; discontinue ≥ 2 weeks prior to irinotecan therapy; concurrent use is contraindicated.

Pharmacokinetics

Distribution: V_d: 33-150 L/m^2
Protein binding, plasma: Predominantly albumin; Parent drug: 30% to 68%, SN-38 (active metabolite): ~95%
Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; SN-38 undergoes conjugation by UDP- glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. Conversion of Irinotecan to SN-38 is decreased and glucoronidation of SN-38 is increased in patients who smoke cigarettes, resulting in lower levels of the metabolite and overall decreased systemic exposure. SN-

38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele). Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. The lactones of both Irinotecan and SN-38 undergo hydrolysis to inactive hydroxyl acid forms.
Half-life elimination: SN-38: Mean terminal: 10-20 hours
Time to peak: SN-38: Following 90-minute infusion: ~1 hour
Excretion: Within 24 hours: urine: Irinotecan (11% to 20%), metabolites (SN-38 <1%, SN-38 glucuronide, 3%)

Adverse Events

Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:
Cardiovascular: Vasodilation
Central nervous system: Cholinergic toxicity (includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever, pain, dizziness, insomnia, headache, chills
Dermatologic: Alopecia, rash
Endocrine & metabolic: Dehydration
Gastrointestinal: Late onset diarrhea, early onset diarrhea, nausea, abdominal pain, vomiting, cramps, anorexia, constipation, mucositis, weight loss, flatulence, stomatitis
Hematologic: Anemia, leukopenia, thrombocytopenia, neutropenia
Hepatic: Bilirubin increased, alkaline phosphatase increased
Neuromuscular & skeletal: Weakness, back pain
Respiratory: Dyspnea, cough, rhinitis
Miscellaneous: Diaphoresis, infection

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Edema, hypotension, thromboembolic events
Central nervous system: Somnolence, confusion
Gastrointestinal: Abdominal fullness, dyspepsia
Hematologic: Neutropenic fever, hemorrhage, neutropenic infection
Hepatic: AST increased, ascites and/or jaundice
Respiratory: Pneumonia

Rare known potential toxicities, <1% (Limited to important or life-threatening):
ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, Bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, deep thrombophlebitis, dysarthria, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial lung disease, intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, muscle cramps, myocardial ischemia, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus, pulmonary toxicity (dyspnea, fever, reticulnodular infiltrates on chest x-ray), renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhlitis, ulceration, ulcerative colitis, vertigo

Nursing Guidelines

If possible, check for any history of hypersensitivity reaction to any previous drug formulated with polysorbate 80.

Cholinergic symptoms of lacrimation, nasal congestion, diaphoresis, flushing, ABD cramping, and diarrhea can occur at the beginning, during, or immediately after the CPT-11 infusion. It is suggested that the patient remain in the treatment area for a minimum of one hour following the completion of the **very first** CPT-11 infusion. If diarrhea occurs within one hour of infusion follow institution's policy regarding administration of Atropine.

11.0 MEASUREMENT OF EFFECT

11.1 PET/CT Imaging Interpretation of Baseline and Post-Induction Chemotherapy PET Scans

11.1.1 Schedule of Evaluations

For the purposes of this study, patients randomized onto salvage chemotherapy plus surgery arm should be reevaluated by FDG PET/CT < 2 weeks prior to surgical resection for clinical tumor response. Supporting documentation of response should be submitted, per Section 6.1.1.

11.1.2 Baseline PET/CT Scan Interpretation

The baseline PET/CT scan (performed prior to pre-op chemotherapy, scan #1) will be interpreted by an experienced nuclear medicine physician at each participating site who will be responsible for image interpretation and clinical reporting for the local site. The images will be interpreted together with pertinent clinical findings and findings of other imaging modalities such as standard (i.e., contrast-enhanced) CT or MRI, or endoscopic ultrasound if performed. Interpreting the PET/CT scans in this fashion mimics the usual clinical situation, in which this information is incorporated into the interpretation, especially in the case of an equivocal scan finding that may be easily explained by the CT/MRI scan result (e.g., anatomic variation of the bowel or bladder) or clinical information (e.g., increased uptake at a site of recent surgery or biopsy). Sites will be responsible for submitting PET/CT imaging datasets (per Section 6.3) and an adjunctive data form. If the baseline PET/CT scan is deemed not to be evaluable, the ICL at IROC Ohio staff will use the opportunity to educate the personnel at the local site to ensure that future studies are performed according to protocol, and may request a repeat baseline PET/CT scan.

Visual assessment will be used to interpret the PET/CT findings as positive or negative at baseline. Abnormal (positive) ^{18}FDG tumor uptake using visual assessment will be defined as "any focal or diffuse FDG uptake above background that is incompatible with normal anatomy." Visual interpretation will be the primary criterion used for positivity/negativity of baseline findings, since this is currently the only validated approach for gastric cancer. However, to objectively assess the degree of ^{18}FDG uptake, a semi-quantitative approach using the SUV (standardized uptake value) will also be employed. The primary reasons for determining the SUV's on the baseline PET/CT studies are to:

1) Provide a baseline parameter for calculating the change in maximum SUV (SUVmax) of the primary gastric tumor and any established/confirmed tumor metastases following induction chemotherapy.

2) Determine whether the patient will be eligible to undergo subsequent PET/CT scans for monitoring of treatment response under this protocol by establishing that at least the primary gastric tumor is ^{18}FDG -avid by visual interpretation with an SUV max of at least 5.0 or a tumor:liver ratio of at least 1.5. Visually the gastric mass must have ^{18}FDG uptake significantly above background (qualitative).

11.1.3 Interpretation of Concomitant Cycle 1 of Pre-Op Chemotherapy PET/CT Scans

The concomitant cycle 1 of pre-op chemotherapy PET or PET/CT scans will be interpreted preferably by the same PET/CT reader at each participating site who will be responsible for image interpretation. Here again, the images will be interpreted together with pertinent clinical findings and any available findings from other imaging modalities such as standard CT or MRI, as well as other imaging modalities performed at the discretion of the treating physician. Both lesions present at baseline as well as the appearance of new lesions on follow-up PET/CT will be incorporated in the interpretation. Both visual assessment and semiquantitative assessment using the SUVmax approach will be used to interpret the follow-up PET/CT findings. Semiquantitative analysis will also be used to determine the change in FDG uptake using the SUVmax approach (i.e., change in SUVmax, see below) following cycle 1 chemotherapy for registration eligibility. For assessment of new lesions that may appear following cycle 1 pre-surgery chemotherapy, visual interpretation, as described above, will be used to determine if the new lesion is positive or negative for tumor in conjunction with available clinical and radiological findings. A new site seen by PET/CT will only be considered disease progression if corroborated by biopsy or other established imaging methods. Patients with disease progression that constitutes metastatic disease documented by PET/CT imaging and confirmed by biopsy or imaging should be removed from protocol therapy. An increase in the SUVmax (see below) of > 20% in the primary gastric tumor following cycle 1 chemotherapy will only be considered as possible "indication" of local disease progression, unless correlated by disease progression documented by biopsy or other imaging modalities such as barium esophagram or CT, in which case disease progression will be established.

Patients will be categorized as responders or non-responders based on SUVmax of the primary gastric tumor. A response will be defined as a SUVmax decrease of ≥ 35% when compared to baseline. Non-responders (those patients whose primary tumor SUVmax does not decrease by at least 35%) will be randomized to surgery or salvage chemotherapy followed by surgery. Patients randomized to the salvage chemotherapy plus surgery arm must be reevaluated by FDG PET/CT < 2 weeks prior to surgical resection for clinical tumor response.

11.2 Semiquantitative PET/CT Analysis Using the SUV Approach

Semiquantitative analysis using the SUVmax approach will be used to assess the change in ^{18}FDG uptake of established/confirmed baseline lesions between baseline and the subsequent time point in Arm A patients and two subsequent timepoints in Arm B patients. SUV is the ratio of activity in a tissue (in μCi/ml) divided by the decay-corrected activity injected into the patient (in μCi/g). The resultant number is almost unitless (actually g/ml) and is a crude measure of degree of uptake of ^{18}FDG into any tissue. The decision to utilize the SUVmax method is based on the fact that it is the most commonly used quantitative method in clinical ^{18}FDG imaging, because of its practicality and its ease of calculation. The required information is the weight of the patient, the administered dose of ^{18}FDG, the elapsed time from injection to midpoint of ^{18}FDG image, and the activity in a tissue of interest determined from the PET/CT image. Importantly, this method does not require blood sampling. This parameter has also been found to be highly reproducible (mean difference between two measurements performed within a 1-week interval was about 10%), further supporting its use in serial semiquantitative analysis in PET/CT [35]. SUVmax will be determined from the PET/CT images. It must be ensured that the images at all sites are reconstructed according to the algorithms described below, and with the same spatial resolutions. Regions of interest (ROIs) will be manually placed around the entire extent of any abnormality to include the most intense portion of this abnormality to determine the maximum tissue activity within the ROI (SUVmax) and decay corrected to time of injection.

The tomographs will be calibrated at least monthly by imaging known activity that is also measured in a dose calibrator. Injected activity will be measured in a dose calibrator, corrected for residual activity in the syringe after injection, and decay corrected to time of injection.

SUVmax will be calculated as ROI max µCi/ml divided by injected activity µCi/g body weight. The change in SUVmax between the baseline and target day 15-19 of cycle 1 pre-op chemotherapy PET/CT studies will be calculated for all established/confirmed lesions seen by baseline PET/CT with an SUVmax of ≥ 5.0 or a tumor:liver ratio of > 1.5. The change in SUVmax of these lesions following therapy will be expressed as % decrease (or increase) in SUVmax from baseline to the day 15-19 of cycle 1 of pre-op chemotherapy PET/CT scan. The change in SUVmax for the primary gastric tumor identified at baseline will be calculated as well as the mean change in SUVmax for all established/confirmed lesions. These changes will be correlated with clinical and histopathological response to therapy as well as disease-free and overall survival. For lesions that have completely resolved by PET/CT (i.e., uptake in the area of previous disease is indistinguishable from background uptake), the SUV of the lesion will be considered as 0 (no tumor, uptake is not higher than background) and % decrease from baseline calculated as 100%.

11.3 Quality Assurance of PET/CT data

Every effort will be made to ensure that the collected PET/CT studies performed at the various sites are acquired and processed according to the protocol guidelines (Sections 6.3 and 11.1). This will be coordinated by the Imaging Co-Chair, Nathan Hall, M.D., PhD.

11.4 Progression of Disease

For both study arms, progression of disease on PET/CT scan alone (new sites of metastatic disease) prior to surgery should be corroborated by biopsy of distant metastatic disease sites, as clinically indicated. If a confirmatory biopsy of metastatic disease is not performed, it is recommended that a second imaging study be performed using a different imaging modality.

11.5 Pathological tumor response after surgery

Definitive assessment of pathologic tumor response will be established on the basis of surgical outcome. All patients that are candidates for surgical resection at the completion of pre-operative chemotherapy will be classified with respect to their pathologic tumor response.

11.5.1 Pathologic Tumor Response Criteria

Pathologic Complete Response (PCR): No gross or microscopic tumor identified with the surgical specimen. All lymph nodes should be free of tumor to document a PCR. If no gross tumor is visible, section around the area of inflammation (nodularity) should be made every 2-3 cm and specimens examined.

Pathologic Persistent Disease (PPD): Residual viable tumor in the resected specimen. This will then be subclassified as macroscopic (evident at the time of surgery) or microscopic (evident only at the time of pathology review) residual disease

11.6 Completeness of Surgical Resection

All operative and pathology reports from patients in the study must be submitted. Reports must contain information about gross and microscopic contamination of surgical resection margins.

11.6.1 Curative Resection Definition

Resections are defined as "curative" (i.e., complete resection; R0 resection) when all gross disease has been removed, and microscopic examination reveals all surgical margins free of tumor (i.e., pathological stage T1-3, NX, MO resected). Resections will still be considered curative if pathologic examination reveals positive lymph nodes as long as the nodes were completely resected.

11.6.2 Palliative Resection Definition

"Palliative resection" (i.e., incomplete resection) will be considered to have taken place when gross disease has been left behind (R2 resection), or when microscopic examination reveals surgical margins which are not free of tumor (R1 resection). Positive margins are defined as tumor at or less than 1 mm from the lateral ("deep"), proximal, or distal margins.

11.6.3 No resection

The primary tumor could not be removed.

11.7 Recurrence of disease:

11.7.1 NED

No evidence of disease (NED).

11.7.2 Recurrence of disease (REC).

Recurrence of disease (REC) must be confirmed by imaging and/or biopsy, with supporting materials submitted. Distant metastatic disease on CT or PET/CT imaging or evidence of locally recurrent disease constitutes recurrence of disease (REC), and should be documented by endoscopy, CT or PET/CT imaging. Elevated CEA levels only or physical findings only does not meet criteria for recurrence of disease.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Disease Progression: Remove from protocol therapy any patient with disease progression before surgery (Arm B patients) or recurrence after surgery (either Arm A or B patients). Document details, including tumor measurements for pre-operative disease progressions of Arm B patients, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies. In the case of either the patient is off protocol treatment or continue protocol treatment, patients should be followed for survival per the study calendar.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete follow-up requirements as specified below.

Patients who do not receive adjuvant therapy (regardless of study arm) are also required to have physical exam and labs 3 months (+/- 4 weeks) following surgery.

Baseline, on-study, endpoint (e.g., relapse or progression), off treatment, and survival data submission required.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 Statistical Considerations

13.1 Primary Endpoint

The primary endpoint of this study is overall survival (OS). OS is defined as time from randomization to death due to all causes.

13.2 Secondary Endpoints

13.2.1 Progression-free survival: PFS is defined as time from randomization to the first documentation of disease progression or death due to all causes, whichever comes first. The distribution of PFS will be estimated using the method of Kaplan-Meier [36] in each arm for FDG-PET non-responders. PFS will be compared between two treatment groups (Arm A and B) in FDG-PET non-responders using the log-rank test on ITT population.

13.2.2 R0 resection rate is defined as the proportion of patients achieved R0 resection during surgery. The R0 resection rate will be estimated by the number of patients had R0 resection divided by total number of patients who meet the analysis population definition. Confidence intervals for the true confirmed tumor response will be calculated according to the approach of Duffy and Santner [37]. Chi-sqaure test (or Fisher's exact test if the data in contingency table is sparse) will be used to compare R0 resection rate between experiment and control arms in FDG-PET non-responder cohort (Arm A and B).

13.2.3 Pathologic complete response rate is defined as the proportion of patients had pathologic complete response. The pCR rate will be estimated by the number of patients had pCR divided by total number of patients who meet the analysis population definition. Confidence intervals for the true confirmed tumor response will be calculated according to the approach of Duffy and Santner [37]. Chi-sqaure test (or Fisher's exact test if the data in contingency table is sparse) will be used to compare pCR rate between experiment and control arms in FDG-PET non-responder cohort (Arm A and B).

13.2.4 Adverse events (AE): All AE and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. The overall adverse event rates will be compared between two treatment groups in FDG-PET non-responders (Arm A and B) using Chi-square test (or Fisher's exact test if the data in contingency table is sparse). Analyses on AE data will be

based on safety population. See Section 9.0 for definitions of routine solicited and non-reportable adverse events.

13.2.5 FDG-PET SUV measures: Within the FDG-PET non-responders receiving salvage chemotherapy (Arm B), FDG-PET SUV measures will be obtained at before pre-registration chemotherapy, then after pre-registration chemotherapy and after 2 cycles of pre-operative savage chemotherapy. The profile of FDG-PET SUV measures over time will be summarized graphically. Methods for analyzing repeated measurements (e.g., GEE models) will be used to assess whether there is any time trend in FDG-PET SUV measures, the potential impact of savage chemotherapy, and any baseline patient demographic/disease characteristic predicting the identified trend. The changes in FDG-PET SUV measures at two latter time points compared to baseline will be summaries, and be evaluated whether these changes are correlated with surgical outcomes by logistic regression and/or long-term survival outcomes by Cox model.

13.3 Sample size

There will be 81 FDG-PET non-responders randomized to each arm (i.e. surgery vs salvage chemotherapy + surgery) of this study (total of 162 FDG-PET non-responding patients).

13.4 Power justification

The primary aim of this randomized phase II clinical trial is to examine and compare the overall survival (OS) of patients with locally advanced gastric cancer classified as FDG-PET non-responders between the experimental (salvage chemotherapy and surgery) and control (surgery alone) arms. This trial implements a group sequential design with one interim analysis for futility, adopting Rho family (Rho=1.5) beta spending function for controlling the overall type II error rates. Other endpoints of interest that will be evaluated include PFS, R0 resection rate, pCR, and AE profile.

The median OS in the control arm is assumed to be 20 months based on the results from recent trials (Ott 2003, Ott 2008, MUNICON I, MUNICON II). We additionally assume an accrual rate of 3 FDG-PET non-responders patients per month, and a minimal follow-up of 24 months. A sample size of 81 patients in each group (total of 81×2=162) with expected 120 events provides 80% power to detect a Hazard Ratio (HR, experimental arm related to control arm) of 0.70 at the significance level of 0.15 with one-sided test for the comparisons between the control and experimental regimens. With this design, we would target a median overall survival in the experimental arm of 28.57 months.

Power and Significance Level: The operating characteristics of current design can be tabulated according to various true hazard ratios, including the probabilities that the experimental regimen is superior to the control regimen, i.e. power which warrants further studies on experimental regimen, and probabilities of stopping the trial early due to futility of the experimental regimen.

If the true hazard ratio is …	**1.00**	**0.925**	**0.850**	**0.775**	**0.700**
Then the probability of declaring that the experimental regimen warrants further studies is …	0.15	0.26	0.42	0.62	0.80
Probability of stopping at the interim analysis due to futility is …	0.46	0.34	0.24	0.14	0.07

13.5 Analysis Populations

The analysis populations for FDG-PET non-responders include the following:

- Intent-to-treat (ITT) population: The ITT population includes all eligible patients randomized to treatment, irrespective of whether or not they receive any study medication.
- Per-protocol (PP) population: The PP population includes all eligible and randomized patients who receive at least one dose of pre-op study medication, and who have efficacy data post-randomization.
- Disease-specific population 1 (DSP): The DSP includes all eligible and randomized patients who received at least one dose of pre-op study medication, and who undergo surgery.
- Safety population: The safety population includes all randomized patients who receive at least one dose of study medication.

The primary efficacy analysis will be based on the ITT population. Sensitivity analysis will be performed on PP population. All safety analyses will be based on safety population. Other secondary and translational analyses will be conducted on the ITT, and/or PP population, and/or DSP as appropriate for the endpoint.

13.6 Treatment Efficacy Decision Rules:

13.6.1 Interim Analysis:

An interim analysis will be performed to assess treatment futility. The study will be terminated if there is strong evidence that the null hypothesis (i.e., no difference in treatment effect between experimental and control regimen), cannot be rejected. After the first observed 60 events (approximately 42 months after the first patient randomized, under null hypothesis), the interim analysis will be performed. If the estimated hazard ratio (experimental arm related to control arm) is greater than 1.024, favoring the control arm, we will terminate accrual and conclude that the experimental regimen is not promising with respect to OS comparing to the control regimen in FDG-PET non-responders. Otherwise, we will continue to full accrual. The trial will not be halted while these patients are evaluated for interim analysis. However, if the accrual is especially rapid, we may temporarily suspend accrual to prevent missing important acute toxicity patterns.

13.6.2 Final Analysis

The primary efficacy analysis will be performed on OS after 120 events observed (approximately 70 months after the first patient randomized, under the null hypothesis), assuming the trial proceeds to full enrollment. At the conclusion of the trial, the study will conclude that the experimental arm (surgery and salvage chemotherapy) is superior to the control arm (surgery alone) – i.e. the experimental regimen warrants further study – if the p-value of a one-sided log-rank test comparing OS between arms is less than 0.15 (equivalently, HR < 0.828), according to intent-to-treat principle. Otherwise, we will conclude that there is no statistically significant evidence of superiority of the experimental regimen.

13.7 Analysis plan:

The distribution of OS in each arm will be estimated using the method of Kaplan-Meier [36]. The stratified hazard ratio and OS rates at different time points (12 and 18, and 24 months, for example), along with corresponding confidence intervals (CIs) will be reported.

13.8 Early stopping rules based on R1/2 resection rate:

We include early stopping rules based on R1/R2 resection rate. If R1/R2 resection rate in surgery+salvage chemo arm is higher than that in surgery alone arm then the study will stop accrual for safety concerns. This assessment will be performed at two time points: when the surgical data are available on 1) the first 30 patients per arm (total of 60) and 2) the first 60 patients per arm (total of 120). The following table includes the stopping rules and the probability of stopping accrual early under H0 or H1 assumptions.

- H0: R1/R2 resection rate in surgery + salvage chemo arm (30%) is same as that in surgery alone arm (30%)
- H1: R1/R2 resection rate in surgery + salvage chemo arm is higher (50%) than that in surgery alone arm (30%)

		Stop accrual if		**% of stopping under**	
Interim look	**Cumulative # of patients**	**the z statistic is:**	**the difference in R1/R2 resection rate is:**	**H0**	**H1**
1	30 per arm (total of 60)	> 1.807	> 0.224	3.5%	42.4%
2	60 per arm (total of 120)	> 1.367	> 0.120	10%	83.0%

The H0 R1/R2 resection rate of 30% was determined by the data reported in PET non-responders received surgery alone or continuing same neoadjuvant regimen from studies of 03-032[11], Ott et al[30], and Municon I[9]. The boundary was determined using Rho family (Rho=1.5) alpha spending function to control for type I error rate (EAST v6.2). With total of 120 patients (60 per arm) and the specified stopping rules, there is 83% power to detect a difference (experimental arm minus control arm) of 0.2 in R1/R2 resection rate at the significance level of 0.10 with one-sided test.

13.9 Adverse events stopping rule:

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to the study (both groups) to allow for a full review of data according to the following AE stopping rule:

- if at any time more than 10 of the first 20 patients enrolled in arm B (or > 50% of all patients after 20 patients are accrued) have experienced at least one Grade 3 or worse adverse events prior to surgical resection, regardless of attributions, with the exception of grade 3-4 electrolyte adverse events, alopecia, or lymphopenia.
- if the number of deaths in salvage arm is more than the number of deaths in the control arm as per the criteria below, then accrual will be suspended for full AE review and potential protocol amendment:
    - In the first 90 patients (45 per arm), if the number of deaths within 90 days after surgery in the salvage arm is > 3x than the control arm when there is at least

one control arm, or > 4 deaths on salvage arm when there is no death on control arm.

13.10 Study monitoring and reporting

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

The study statistician will review adverse event data every week and a monthly team meeting including the study chair, study statistician and site PIs will take place to discuss any unexpected toxicity events and trial conduct concerns or issues.

13.10.1 CTEP Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by File Transfer Protocol (FTP) burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

13.11 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of study treatment in subsets defined by race, gender, or ethnicity. Although there is insufficient power to detect small or moderate effects, we will, as always, report the results by gender and ethnicity in exploratory analyses.

Domestic Accrual Targets					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	14	0	2	18
White	17	111	2	11	141
More Than One Race	0	0	0	0	0
Total	20	127	2	13	**162**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:	**American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

Section 14.1 describes the potential use of the optional banked biospecimens.

14.1 Tissue Specimens for Banking

14.1.1 Background

Please note that, as per CTEP guidance, the specific biomarker studies to be performed will be re-evaluated at the completion of the study and collection of tissue. Our ability to interrogate tissue samples is evolving at a very rapid rate. Current technology (using the Nimblegen or Haloplex platforms, for example) will allow for a majority of the collected biospecimens to undergo whole exome sequencing from FFPE tissue. This is an enormous opportunity to address several questions regarding markers that predict sensitivity and resistance to platinum based therapy (i.e. the EOX responding patients), predict sensitivity and resistance to docetaxel and irinotecan (i.e. the salvage regimen), associate with the metabolic state of the cancer (i.e. correlation with FDG-PET SUV), and prognostic biomarkers for patient outcome (i.e. response vs. non-response and survival).

14.1.2 Hypothesis

We hypothesize that underlying genetic aberrations may predict treatment response and patient outcome. (Funding for this correlative aim will be sought separately)

14.1.3 Methods

Tissue processing: Neoplastic epithelium will be identified by microscopic examination of tissue sections, and the same areas will be targeted in the corresponding paraffin-embedded tissue blocks to minimize contamination by non-lesional tissues. Tissue cores (1-2 mm diameter) from the areas of interest will be taken for DNA analysis using standard operating procedures [38]. The diagnosis in each case will be confirmed by a reference pathologist. Tumor-rich areas (>80% tumor volume based on review of a hematoxylin and eosin–stained slide) will be targeted for evaluation, and genomic DNA will be extracted, using a QIAamp DNI Mini kit (Qiagen, Valencia, CA), in accordance with the manufacturer's instructions. Extraction will occur in a 96-well plate format using the CyBi-Well liquid handling system (CyBio AG, Jenna, Germany). For sequencing, whole genome amplification will be performed, followed by high-throughput (384 well plate) bidirectional dideoxynucleotide sequencing of PCR-amplified gene products using standard protocols.

Sequencing: Please note, this is subject to re-review at a later date, once the tissue is available, to take advantage of the current technology at the time. Using current technology, whole-exome sequencing (WES) will be performed using the HiSeq2500 sequencers available at the Weill Cornell Epigenomic Core (or Institute of Precision Medicine). 3-4ug DNA will be extracted from tumors and matched tissue using Promega DNA extraction kits. DNA content and quality will be analyzed using Qubit and Bioanalyzer. In cases where low amount of DNA is available (<1ug), we will use the TruSeq Nano DNA Sample Prep Kit. Sequencing will then be performed using paired-end (PE) 101x2 targeting coverage of 80X coverage for tumors (8 HiSeq2500 lanes) and 40X for matched normal samples (4 HiSeq2500 lanes).

10 cc whole blood sample will be collected prior to resection in patients enrolled in the study for the purpose of WES for normal DNA comparison. We will consider examining the whole blood for polymorphisms thought to be important in drug metabolism and correlate with toxicity and efficacy (as an exploratory sub-aim of this correlative aim).

14.1.4 Statistical Design

WES analysis will include the following steps for each sample: i) initial QC of fastq files for base quality and duplications, ii) alignment using bwa aligner to a modified reference human genome from the 1000 genome project, and retaining only the uniquely mapped PE reads, iii) collapse duplicate reads using Picard tool, iv) local realignment for indel detection and recalibration of base quality scores using GATK, v) additional QC evaluation such as percent alignment, percent of exome covered and mean coverage. The result of this pipeline is a single BAM file suitable for variant analysis. To maximize the specificity and sensitivity of SNV detection sample-specific and somatic point nucleotide and indel variants will be called using three methods: MuTect, VarScan, and SNVmix. The results from these tools will be merged using ad-hoc rank-based algorithm that will combine results to a single unified list of candidate SNPs and indels. Further QC will be performed using SNP panel identification assay (SPIA) to ensure that tumor and normal samples are from the same individual as well as analysis to estimate and confirm tumor cell content. Functional interpretation of the variants will be performed using Mutation Assessor tool that predicts the functional impact of amino-acid substitutions, as a result of somatic mutations, in proteins. Finally, copy number alteration detection and segmentation will be performed using several approaches such as CoNIFER and VarScan.

A formal statistical plan will be developed prior to WES analysis, based on the quality of the tissue collected, current sequencing technology, and responses observed on the clinical trial.

15.0 General Regulatory Considerations and Credentialing

15.1 Institutional credentialing

15.1.1 Imaging core lab institutional requirements

Prior to registering patients, all participating sites should review the imaging protocol and required forms with the CRA as well as individuals from the imaging facility who will be acquiring the PET/CT images. Data and form submission guidelines will be reviewed and contact information will be verified via correspondence with the ICL at IROC Ohio.

The participating center must have, or have access to, a facility with an integrated positron-emission tomography and computed tomography (PET/CT) scanner. The participating center must have the ability to submit PET and CT studies electronically to the ICL in digital DICOM format (other formats: BITMAP, JPG, hardcopy or scanned files are not acceptable). Participating sites must be credentialed per Section 6.3.2 by the ICL so that the performance characteristics and infrastructure requirements are met. Every effort will be made to ensure that the collected PET/CT studies performed at the various sites are acquired and processed according to the protocol guidelines. This will be coordinated by [redacted] Imaging Co-Chair. PET/CT datasets that fall outside the protocol requirements will need to be repeated in a compliant way or the subject will not be included in the trial.

15.1.2 IMRT Radiotherapy Credentialing Requirements

CT-based conformal planning is required on this study.

Those treating with IMRT and not previously credentialed for use of IMRT in clinical trials must successfully irradiate the head and neck IMRT phantom available from IROC Houston (RPC) and complete or update their Facility Questionnaire on the IROC Houston website (http://rpc.mdanderson.org/rpc/). In addition, if IMRT is used in conjunction with gating or tracking methods to compensate for respiratory motion, the institution must successfully irradiate IROC Houston's Thorax-Lung Phantom with accompanying reciprocating platform to simulate motion.

Credentialing material must be submitted and approved before case evaluations can be finalized.

16.0 REFERENCES

1. Cunningham, D., et al., *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.* New England Journal of Medicine, 2006. 355(1): p. 11-20.
2. MacDonald, J., et al., *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.* N Engl J Med, 2001. 345(10): p. 725-30.
3. Macdonald, J.S., et al., *Chemoradiation of resected gastric cancer: A 10-year follow-up of the phase III trial INT0116 (SWOG 9008).* J Clin Oncol, 2009. 27: p. abs 4515.
4. Bang, Y.J., et al., *Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial.* Lancet, 2012. 379(9813): p. 315-21.
5. Sakuramoto, S., et al., *Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine.* N Engl J Med, 2007. 357(18): p. 1810-20.
6. Group, G., et al., *Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis.* JAMA, 2010. 303(17): p. 1729-37.
7. Wieder, H.A., et al., *Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment.* J Clin Oncol, 2004. 22(5): p. 900-8.
8. Ott, K., et al., *Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction.* J Clin Oncol, 2006. 24(29): p. 4692-8.
9. Lordick, F., et al., *PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial.* Lancet Oncol, 2007. 8(9): p. 797-805.
10. Ott, K., et al., *Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study.* Clin Cancer Res, 2008. 14(7): p. 2012-8.
11. Shah, M.A., et al., *A phase II study of preoperative chemotherapy with irinotecan(CPT) and cisplatin(CIS) for gastric cancer(NCI 5917): FDG-PET/CT predicts patient outcome.* Amercan Society of Clinical Oncology, Annual Proceedings, Orlando, FL., 2007: p. Anstract #4502.
12. Buschenfelde, C.M.Z., et al., *(18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial.* J Nucl Med, 2011. 52(8): p. 1189-96.
13. Lordick, F., et al., *Salvage radiochemotherapy in locally advanced gastroesophageal junction tumors that are metabolically resistant to induction chemotherapy: The MUNICON-2 trial.* Gastrointestinal Cancers Sympsium, Orlando, FL, 2008: p. Abstract #104.
14. Fuchs, C.S., 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-FV/LV before and after CRT: Intergroup trial CALGB 80101* J Clin Oncol, 2011. 29: p. abs4003.
15. Power, D.G., D.P. Kelsen, and M.A. Shah, *Advanced gastric cancer - Slow but steady progress.* Cancer Treat Rev, 2010. 36(5): p. 384-92.
16. Kang, J.H., et al., *Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone.* J Clin Oncol, 2012. 30(13): p. 1513-8.
17. Thuss-Patience, P.C., et al., *Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO).* Eur J Cancer, 2011. 47(15): p. 2306-14.
18. Mandard, A.M., et al., *Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma: Clinicopathologic correlations.* Cancer, 1994. 73: p. 2680-86.
19. Weber, W., et al., *Prediction of response to preoperative chemotherapy in adenocarcinoma of the esophagogastric junction by metabolic imaging.* J of Clin Oncol, 2001. 19(12): p. 3058-65.

20. Won, E., et al., *Phase II study of preoperative chemotherapy plus bevacizumab with early salvage therapy based on FDG-PET response in patients with locally advanced gastric and GEJ adenocarcinoma.* J Clin Oncol, 2013. 30(supple 34): p. abs 94.
21. Bang, Y.J., 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, randomised controlled trial.* Lancet, 2010. 376(9742): p. 687-97.
22. Bang, Y.-J. and e. al., *A randomized, open label, phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone in second-line treatment of HER2 amplified advanced gastric cancer (AGC) in Aian population: Tytan study.* ASCO Meeting Abstracts, 2013. 31(4 supple): p. 11.
23. Waddell, T.S. and e. al., *A randomized multicenter trial of epirubicin, oxaliplatin, and capecitabine (EOC) plus panitumumab in advanced esophagogastric cancer (REAL3).* J Clin Oncol, 2012. 30: p. LBA4000.
24. Lordick, F. and e. al., *Cetuximab in combination with capecitabine and cisplatin as first line treatment in advanced gastric cancer: randomized controlled phase III EXPAND study. .* Ann Oncol, 2012. 23: p. LBA3.
25. Ohtsu, A., et al., *Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study.* J Clin Oncol, 2001. 29(30): p. 3968-76.
26. Shah, M.A., et al., *Survival analysis according to disease subtype in AVAGAST: First-line capecitabine and cisplatin plus bevacizumab (bev) or placebo in patients with advanced gastric cancer.* J Clin Oncol, 2012. 30(suppl 4): p. abs 5.
27. Fuchs, C. and e. al, *REGARD: A phase III, randomized, double-blinded trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy. .* ASCO Meeting Abstracts, 2013. 31(4 supple): p. LBA5.
28. Hawkes, E., et al., *Docetaxel and irinotecan as second-line therapy for advanced oesophageal cancer. .* European Journal of Cancer, 2011. 47: p. 1146-51.
29. Won, E., et al., *Phase II study of preoperative chemotherapy plus bevacizumab with early salvage therapy based on FDG-PET response in patients with locally advanced gastric and GEJ adenocarcinoma.* J Clin Oncol, 2013. suppl 4: p. Abs 94.
30. Ott, K., et al., *Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial.* J Clin Oncol, 2003. 21(24): p. 4604-10.
31. Wahl, R.L., et al., *From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors.* J Nucl Med, 2009. 50 Suppl 1: p. 122S-50S.
32. Tan, A.D., et al., *A patient-level meta-analytic investigation of the prognostic significance of baseline quality of life (QOL) for overall survival (OS) among 3,704 patients participating in 24 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials.* J Clin Oncol, 2008. 26(May 20 suppl): p. abs 9515.
33. Sloan, J.A., et al., *A patient-level pooled analysis of the prognostic significance of baseline fatigue for overall survival (OS) among 3,915 patients participating in 43 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. .* J Clin Oncol, 2009. 27: p. 507s.
34. Cunningham, D., et al., *Capecitabine and oxaliplatin for advanced esophagogastric cancer.* N Engl J Med, 2008. 358(1): p. 36-46.
35. Brucher, B.L., et al., *Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography.* Ann Surg, 2001. 233(3): p. 300-9.
36. Kaplan, E.L. and P. Meier, *Nonparametric estimation from incomplete observations.* J of the Amer Statistical Association, 1958. 53: p. 457-81.

37. Duffy, D.E. and T.J. Santner, *Confidence intervals for a binomial parameter based on multistage tests*. Rev. June 1986. ed. Technical report1986, Ithaca, N.Y.: Mathematical Sciences Institute, Cornell University. 18 p.
38. Setlur, S.R., et al., *Estrogen-dependent signaling in a molecularly distinct subclass of aggressive prostate cancer*. J Natl Cancer Inst, 2008. 100(11): p. 815-25.

APPENDIX I - REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II: OPTIONAL PATIENT CAPECITABINE MEDICATION DIARY

Optional Patient Capecitabine Medication Diary (Optional; does not need to be submitted to the Alliance)

Patient Capecitabine Medication Diary
A021302

Study ID#: _____

Patients Initials: _____

Starting Dose: _____

INSTRUCTIONS TO PATIENT:

1. Complete form for the entire period during which you receive radiation therapy and capecitabine. The duration of treatment is usually 5 weeks but may be a bit longer if treatment is interrupted for any reasons.
2. Please follow the dosing instructions carefully.
3. Please record the date and approximate times you take the capecitabine tablets. Your physician or nurse will write down your dose and explain to you how many tablets are in your dose.
4. Start taking capecitabine on day 1 and take Monday through Friday while you are receiving radiation treatment.
5. You should take the capecitabine dose prescribed for you by mouth twice a day on Days 1-5, 8-12, 15-19, 22-26, and 29-33. Take a dose every morning and a dose every evening, about 12 hours apart. Take the dose with 8 ounces of water each time. It is best to take the dose within 30 minutes after eating food.
6. If you vomit after taking a dose, or if you forget to take a dose, please note it on this diary, and do not take capecitabine again until your next scheduled dose.
7. The use of a daily moisturizer to hands, feet and face are recommended. Please use sunscreen if you are going outdoors.
8. Please contact your health care team with any questions or for help understanding exactly how to take your medicine.
9. Bring this Medication diary with you when you meet with your doctor each week.
10. Your doctor might instruct you to temporarily stop the capecitabine due to side effects. Follow their instructions for stopping the medicine, and resume the medication when your doctor tells you that you have recovered from side effects and can restart the medicine
11. If your radiation is temporarily stopped due to side effects, do NOT take the capecitabine. Only take the capecitabine on days that you receive radiation.

PLEASE CONTINUE TO PAGE 2

Day	Date	Approximate times tablets taken a m.	p m.
1			
2			
3			
4			
5			
6	**Do not take capecitabine tablets today**	--	--
7	**Do not take capecitabine tablets today**	--	--
8			
9			
10			
11			
12			
13	**Do not take capecitabine tablets today**	--	--
14	**Do not take capecitabine tablets today**	--	--
15			
16			
17			
18			
19			
20	**Do not take capecitabine tablets today**	--	--
21	**Do not take capecitabine tablets today**	--	--
22			
23			
24			
25			
26			
27	**Do not take capecitabine tablets today**	--	--
28	**Do not take capecitabine tablets today**	--	--
29			
30			
31			
32			
33			
34	**Do not take capecitabine tablets today**		
35	**Do not take capecitabine tablets today**		

_____ _____

Patient signature **Date**

Physician's office will complete this section:

1. Date patient started radiation therapy: _____
2. Date patient completed radiation therapy: _____
3. Date patient started capecitabine: _____
4. Date patient finished capecitabine: _____

Physician/Nurse/Data Manager's signature _____Date_____

APPENDIX III: INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

*The patient _____ is enrolled on a clinical trial using **docetaxel**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Docetaxel interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Docetaxel interacts with a certain specific enzyme in your liver.

- The enzyme in question is **CYP3A4**. Docetaxel is broken down by this enzyme. The dose of docetaxel which you are taking assumes that these enzymes are working normally.
- Certain drugs may reduce the activity of **CYP3A4**, which can increase the amount of active drug in your system. This increases your chances of experiencing harmful side effects. Other drugs might increase the activity of **CYP3A4**, reducing the level of active drug in your system and making it less effective.
- Docetaxel must be used very carefully with such drugs; it is therefore vitally important that you provide your study doctor with a complete list of your medications. Before you begin the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "**strong inhibitors or inducers of CYP3A4**."
- Once the study begins, you and your healthcare providers must be very careful about adding or removing any drugs in this category. Your prescribers should look at the web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx, consult a medical reference, or contact your study doctor to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- *[The following are **examples** of text for common over-the-counter medications or supplements that may interact with the study agent.]* Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you

are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking docetaxel.
- *[Add other specific medications here, if necessary.]*

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

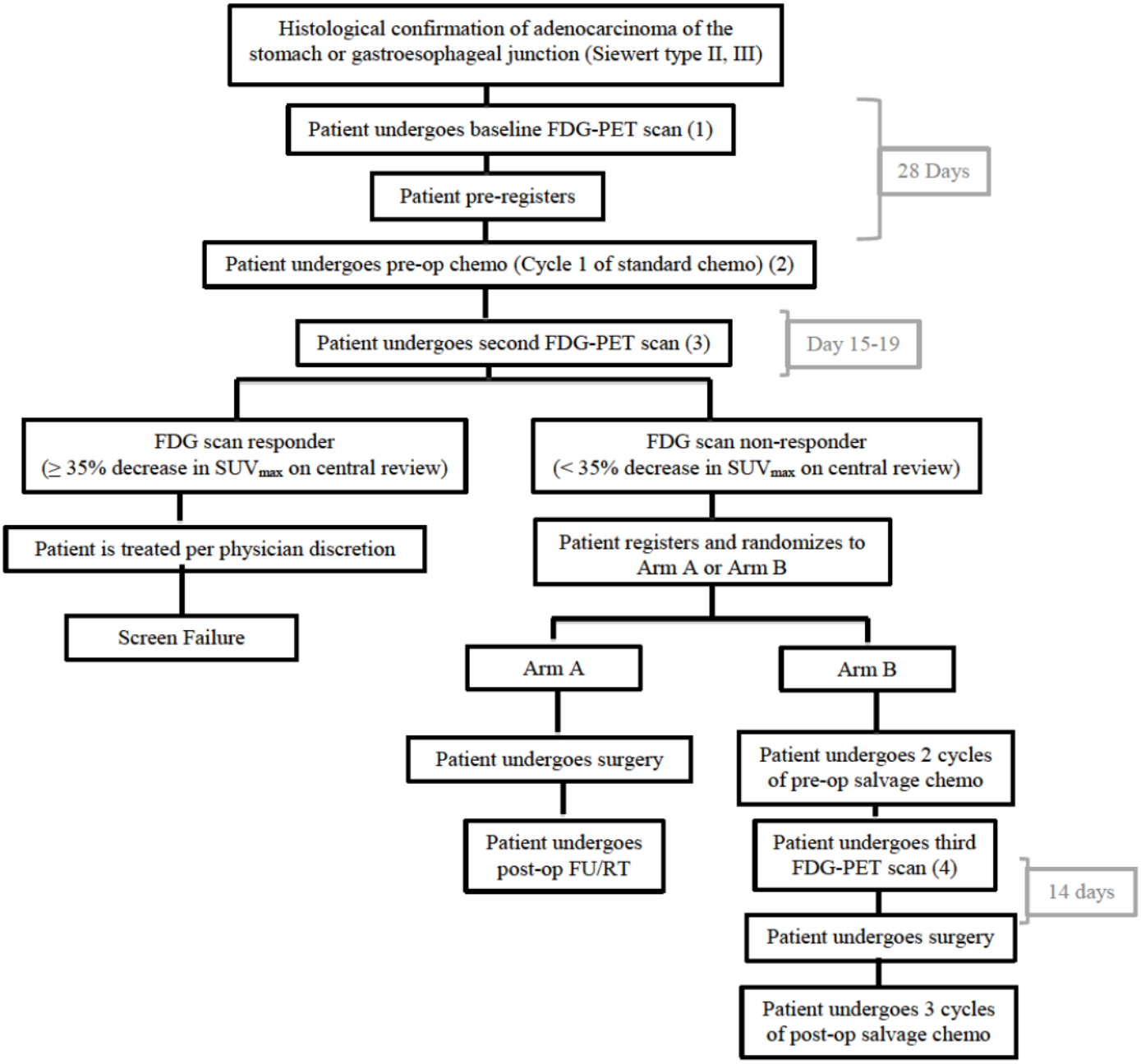
and he or she can be contacted at

_____.

[Note to investigators: This convenient wallet-sized information card is to be completed and then provided for the patient to clip out and retain at all times.]

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent docetaxel. This clinical trial is sponsored by the NCI. Docetaxel interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	Docetaxel interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/ for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX IV: EXTENDED STUDY SCHEMA



1) The baseline FDG-PET scan must occur within 28 days of the patient starting Cycle 1 of pre-op standard chemotherapy.
2) Cycle 1 of Standard Pre-Op Chemotherapy = Epirubicin (optional) + Oxaliplatin (or Cisplatin) + Capecitabine (or Fluorouracil)
3) The second FDG-PET scan must occur between day 15 and day 19 of Cycle 1 of pre-op standard chemo. Chemotherapy must be held for the 48 hours prior to the PET scan, and then immediately restarted to complete the cycle. Do not extend beyond 21 days total (total # of days of treatment is 19 days, with 2 day hold period).
4) The third FDG-PET scan must occur within 14 days of planned resection (Arm B Only).