

**A Pilot Study in Gastric Cancer of Assignment
to Postoperative Chemoradiation or
Chemotherapy based upon Surgical Lymph
Node Assessment after Preoperative
Chemotherapy, with Gene Assay as Correlate
of Biologic Response (GABLE)**

Protocol H-40682
Version 2.4, 01/29/2020

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COMPREHENSIVE
CANCER CENTER

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Coordinating Center: Dan. L. Duncan Comprehensive Cancer Center
Baylor College of Medicine Medical Center - McNair Campus
7200 Cambridge Street. BCM 905
Houston, TX 77030

Principal Investigator: Tannaz Armaghany M.D.
Baylor College of Medicine
Medicine: Hematology/Oncology
Baylor College of Medicine Medical Center - McNair Campus
7200 Cambridge Street. BCM 905
Houston, TX 77030

(713) 798-3750
Tannaz.Armaghany@bcm.edu

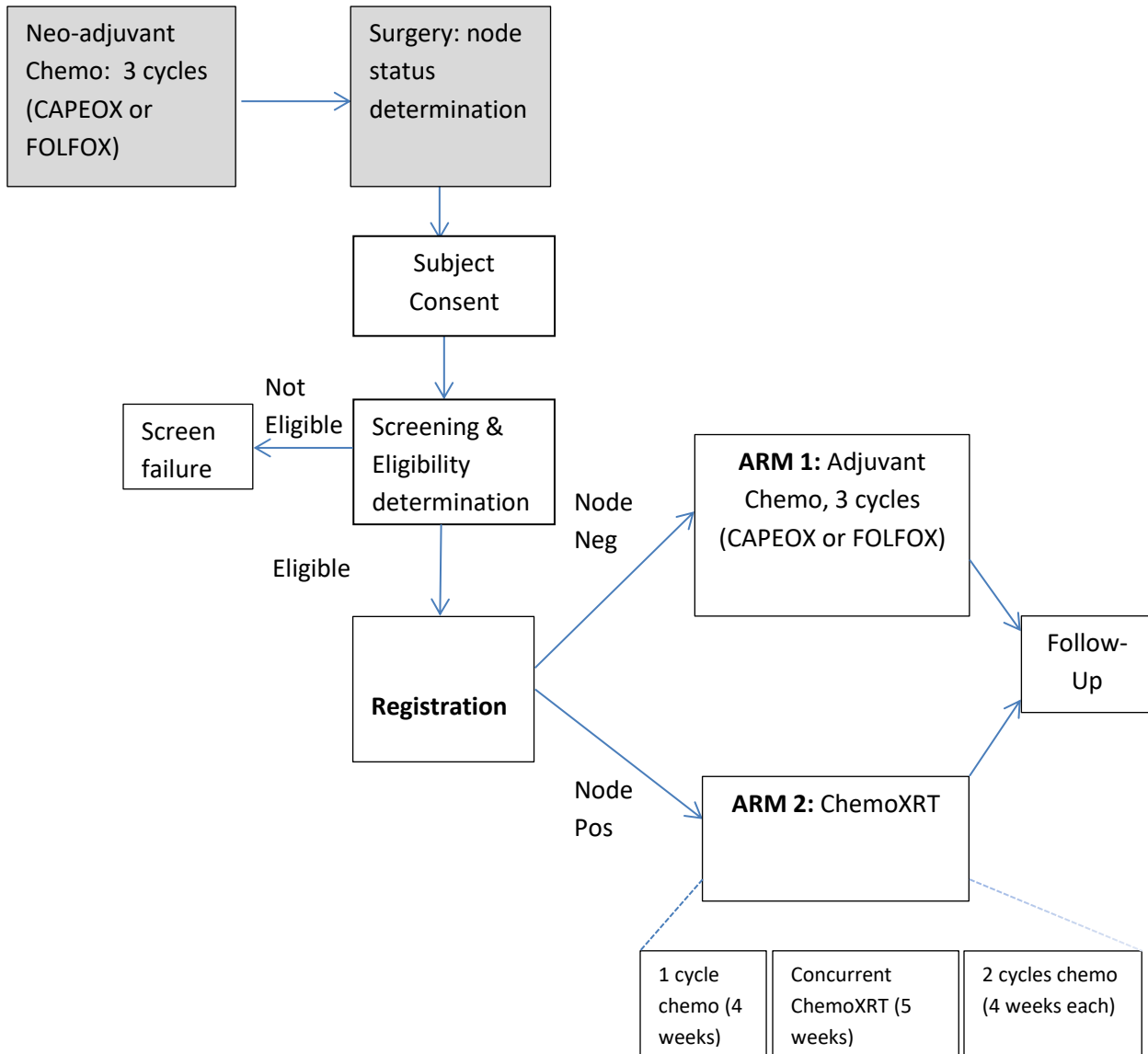
Co-Investigators: Benjamin L Musher, M.D.
Yvonne Sada, M.D.
Courtney Miller-Chism, M.D.
Henry Mok, M.D., Ph.D.
Eugene Choi, M.D
Alfredo Echeverria, MD

Statistician: Eunji Jo

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1.0 SCHEMA



1.1 Correlative studies: Specimens required for eligibility:

- 1.1.1 Tumor sample collected from diagnostic biopsy (pre-neoadjuvant chemo)
- 1.1.2 Tumor sample collected from surgery (post-neoadjuvant chemo)

2.0 SYNOPSIS

2.1 Primary Objective:

To determine the feasibility of patients enrolling and receiving either postoperative chemoradiation or chemotherapy alone, based upon nodal status at surgery, following preoperative chemotherapy.

2.2 Secondary Objectives:

To evaluate the rate of cancer recurrence in patients assigned to treatment based upon node status

To explore the potential correlation between changes in expression of a pre-specified panel of genes identified as relevant to gastrointestinal cancers in response to preoperative chemotherapy, using presence of nodal involvement at time of surgery as an indicator of response.

2.3 Primary Endpoint:

The proportion of patients who would meet the criteria would be estimated to demonstrated successful enrollment and treatment of therapies including postoperative chemotherapy or chemoradiation as indicated by the nodal features, which would justify development of a study powered to demonstrate survival benefit to patients using this approach. Expect that no more than 30% of patients will be unable to complete all protocol therapy.

2.4 Secondary Endpoints:

The recurrence rate while on trial will be reported for the two arms of the trial, and compared to historical controls

Observation of changes in gene expression as a response to chemotherapy, categorized based upon correlation to nodal status. Expect that no more than 10% of tumors will be unable to have tumor assessed on both pre- and post- chemotherapy tumor specimens.

2.5 Study Design:

Open-label, stratified, two arm design. All patients receive same initial standard preoperative chemotherapy and surgical resection. Patients will then be assigned to either standard postoperative chemotherapy if node negative at surgery or standard postoperative chemoradiation if node positive at surgery.

2.6 Number of Patients:

Forty patients.

3.0 BACKGROUND AND RATIONALE

3.1 Current Adjuvant Standards for Gastric Cancer

Gastric adenocarcinoma, also known as stomach cancer, is a global health problem. While surgical resection remains the only curative option for patients who develop this disease, because of its aggressive nature and high recurrence rates, all but the lowest stages of gastric cancer require additional, adjuvant therapy in addition to surgery. Currently, two competing standards exist for the adjuvant management of gastric cancer: peri-operative chemotherapy (based upon the MAGIC study), and postoperative combination chemoradiation therapy (based upon the MacDonald Intergroup study).^{1,2} These two standards were arrived at based upon two separate trials that did not directly compare the two approaches, and thus either approach is considered acceptable. Several modifications to the chemotherapy used in the peri-operative approach have been studied and are now accepted as standard as well.^{3,4,5} Selection oftentimes derives from physician preference and tumor characteristics such as symptoms or nodal stage, and a clear guideline for when to select one adjuvant approach over the other is lacking.

Currently, analysis of patient outcomes from the large, randomized phase III CRITICS trial is ongoing, and will attempt to answer if one approach is clearly favored.⁶ Patients enrolled in the CRITICS trial all received preoperative chemotherapy and standardized surgical resection. Patients were then randomized to receive either chemotherapy or chemoradiation therapies postoperatively. Enrollment is closed for the CRITICS trial; preliminary data suggest that neither arm of postoperative treatment is superior.⁷ These early data support what practitioners have long suspected, which is that no one adjuvant standard is universally superior, but that tumors from different patients and with different characteristics will respond better to different adjuvant approaches.

Unfortunately, knowing which tumors will respond better to which therapy remains unpredictable. Certain clinical features can help clinicians to make a recommendation for their adjuvant approach. For example, patients who have tumors that are symptomatic, such as with bleeding or gastric obstruction, are less likely to tolerate several months of surgical delay while chemotherapy is administered preoperatively, and thus will typically be offered upfront surgery, followed by adjuvant chemoradiation. For most patients, however, the administration of systemic therapy prior to surgery as a part of a perioperative approach is recommended. This approach is favored because of the local control and reduction in tumor that can result prior to surgery, which is thought to lead to better outcomes in the long term.

However, not all patients will experience a response to preoperative chemotherapy. In those patients whose tumors are found at surgery to remain advanced, with nodal involvement, despite preoperative chemotherapy, long-term outcomes have been shown to be poorer than those whose tumors responded well, with the absence of nodal involvement upon dissection.⁸ These data are based upon the retrospective analysis of those patients who were enrolled in the original MAGIC study. Approximately 75% of tumors were found to be in the category of having nodes involved with cancer at resection despite preoperative chemotherapy. Thus, for this majority of patients with gastric cancer who have an inadequate response to preoperative chemotherapy (i.e., who remain node-positive at surgery), an alternative approach to their postoperative adjuvant treatment rather than mere completion of postoperative chemotherapy is apparently necessary.

One reasonable alternative for the management of patients who remain node positive at surgery

could be to incorporate radiation into their postoperative adjuvant treatment. There is some evidence for this approach, coming from the South Korean ARTIST trial.^{9,10} In the ARTIST trial, patients who underwent gastrectomy for stomach cancer randomly received either post-operative chemotherapy or chemoradiation therapy. Although no overall survival benefit was seen overall in the ARTIST study, in subset analysis, node positive patients had a significant improvement in disease-free survival with adjuvant chemoradiotherapy versus adjuvant chemotherapy alone.

3.2 Rationale for Piloting Chemotherapy versus Chemoradiation

Historically, administration of postoperative adjuvant therapy of any type is challenging following gastrectomy. In both the MAGIC and in the MacDonald Intergroup trials, less than 50% of patients were able to complete the postoperative adjuvant therapy recommended.^{1,2} Given improvements in patient selection, surgical techniques, methods for accelerating recovery after surgery, and improved management of chemotherapy toxicity, it is reasonable to expect that many more patients are able to complete these recommended postoperative therapies in current practice. However, this has not been validated. The feasibilities of the individual components of the proposed approach in this protocol are established standards. However, the use of chemoradiation following both pre-operative chemotherapy and surgery as a standard recommendation, based upon an objective surgical finding, is novel. Typically, patients who receive post-operative chemoradiation have received no preoperative therapy. Thus, the administration of chemoradiation to a patient after surgery who received chemotherapy prior to surgery is experimental. Additionally, the treating physicians oftentimes elect to eliminate the radiation if they arbitrarily feel that the patient may not benefit from it. Assuming the rates of node positive disease mirror those observed in the MAGIC protocol's retrospective review⁸, then the majority of patients will receive the recommendation for chemoradiation. When recommended, the administration of postoperative radiation to chemotherapy following preoperative chemotherapy and surgery for this majority of patients with node positive disease may or may not be feasible, depending upon the patients' abilities to tolerate such therapy. If feasible, the ability to study the larger questions of outcomes will be possible; this needs to be known before such a larger study is entertained. Finding that such therapy is not feasible for routine recommendation and administration despite an objective surgical result suggesting it is indicated would necessitate development of a trial of an alternative intervention for the management of these patients who have an anticipated poorer outcome. Therefore, piloting the use of postoperative chemoradiation therapy to determine if this is a feasible recommendation for further exploration of benefit is warranted.

Given the improvements in the ability to administer these therapies, it is reasonable to expect that no more than 30% of patients would be unable to complete all recommended therapy. While the use of chemoradiation for the treatment of patients with node positive disease serves as an intervention arm, inclusion of the roughly 25% of patients who will likely have node negative disease and receive standard post-operative chemotherapy alone is important to confirm similar rates of successful completion of therapy.

3.3 Background on Proposed Correlative Studies

The disparity in tumor responses to preoperative chemotherapy supports biologic heterogeneity of these tumors. Understanding these biologic differences would be invaluable to the future therapeutic direction of their management. These differences are likely complex, existing as baseline genetic characteristics at diagnosis but also as dynamic changes in these characteristics in response to chemotherapy. Identifying these characteristics could allow clinicians to determine which patients' tumors are unlikely to respond to therapy upfront or how to modify ongoing therapy in response to tumor response and evolution as therapy is administered. Knowing that tumor nodal response to preoperative chemotherapy is a surrogate for outcomes in these patients can provide an important comparator for groups of gene expression and evolution.

Recent work into the characterization of gastric adenocarcinoma suggests that four distinct molecular subtypes exist.¹¹ These subtypes are characterized as Epstein-Barr virus positive, microsatellite unstable, genomically stable, and chromosome instable. Determination of the genetic features giving rise to each category is based upon analysis of virgin tumor samples, and thus does not consider variations that arise in response to treatment. Nevertheless, each subtype is characterized by the expression or mutation of specific genes or gene categories that can be profiled through routine analysis. Correlating these gene expressions to clinical nodal responses to chemotherapy could potentially offer insights into the biomarker driven determination of adjuvant treatment selection in gastric cancer. Additionally, monitoring these gene expression levels in response to therapy and making similar correlates could provide valuable information into the adaption of adjuvant therapy to the tumor's response to treatment in real time.

The genes associated with these four proposed subtypes of gastric cancer are by no means exhaustive, however, and the expression or alteration of other genes may yield further predictive and therapeutic information for the adjuvant treatment of these cancers. Casting a wider net is increasingly easy to accomplish, with the advent of genomic profiling of tumors. Particularly in the case of profiles that assess for expression of targetable genes, the ability to assess or monitor for their expression as they relate to chemotherapy response could have important implications for being able to incorporate the therapies into the adjuvant treatment process at critical junctures in the treatment sequence.

4.0 STUDY DESIGN

4.1 This study is a stratified, two-arm, open label, pilot design, for patients who have received the standard three cycles of preoperative chemotherapy and then standard surgical resection.

Patients found to be node-negative at time of surgery will be treated with standard three cycles of standard postoperative chemotherapy, **Arm 1**.

Patients found to be node-positive at time of surgery will receive radiation in addition to chemotherapy, **Arm 2**.

4.2 Treatment interventions

All patients will have received three cycles of preoperative chemotherapy (CAPEOX or FOLFOX, at the treating physician's discretion), followed by standard cancer surgery.

Patients will then be assigned to one of two treatment cohorts for postoperative therapy, based upon nodal involvement by cancer in the surgical specimen.

- 4.2.1 **Arm 1:** Patients who are found to be node negative at surgery will complete an additional three postoperative cycles of chemotherapy. Again, this chemotherapy will be CAPEOX or FOLFOX, at treating physician's discretion. This does not need to be the same regimen as was given pre-operatively, but could be changed to the other regimen, at the treating physician's discretion.
- 4.2.2 **Arm 2:** Patients who are found to be node positive at surgery will instead receive chemoradiation, using single agent fluoropyrimidine (5-fluorouracil or capecitabine) as the chemotherapeutic and receiving 45 Gy of radiation. This does not need to be the same fluoropyrimidine as was given pre-operatively with the oxaliplatin, but could be changed to the other fluoropyrimidine, at the treating physician's discretion.

4.3 Genetic profile correlative studies

- 4.3.1 All patients will have undergone two tumor tissue acquisitions during standard clinical practice. Specimens from these acquisitions must be available:
- Prior to initiation of preoperative chemotherapy, tumor tissue will be obtained from the diagnostic biopsy samples;
 - Tumor tissue will be obtained at the time of surgery.

Both of these samples will be a part of standard of care, thus no additional biopsies beyond this standard will be performed for the study.

A preselected panel of genetic markers will be assessed for expression within each sample, and compared for differences, pre- and post-chemotherapy. These differences will be correlated for any response in tumor, i.e., node positive versus node negative.

5.0 SUBJECT ELIGIBILITY: Patient Initials (L,FM): _____

5.1 Inclusion Criteria:

- 1) Must have pathologically-proven adenocarcinoma of the stomach or gastroesophageal (GE)-junction, stage M0, as established by both imaging and surgical pathologic staging.

Imaging: Clinical stage of M0 will be established by either CT (chest with contrast and abdomen/pelvis with and without contrast), or CT/PET (skull base to mid-thigh). This is standard post-surgery imaging.

Surgery: Surgical pathologic staging must be M0.

- 2) Must have completed 3 cycles of neo-adjuvant chemotherapy. Either CAPEOX or

FOLFOX is allowed. Dose modifications are allowed, but all 3 cycles must have been completed.

- 3) Must have undergone a surgical resection with definitive intent, either by open or laparoscopic resection of the primary gastric or GE junction cancer. Patients must have undergone a total gastrectomy, subtotal gastrectomy, or distal gastrectomy (depending on the location of primary gastric lesion) with at least a modified D2 lymphadenectomy.
- 4) Must be deemed as a good candidate for adjuvant chemotherapy or chemoradiation (to start within 3 months of surgery), in the opinion of the treating investigator. Plan must be to start adjuvant therapy within 90 days of surgery; adjuvant treatment cannot begin more than 90 days after surgery.
- 5) Must have diagnostic biopsy tissue (pre-neoadjuvant chemo) available for genetic testing.
- 6) Must have surgical tissue (post-neoadjuvant chemo) available for genetic testing.
- 7) Must be ≥ 18 years of age.
- 8) Must be able to provide informed consent.
- 9) Must have adequate kidney, liver, and bone marrow function, within 28 days prior to registration, as follows:
 - i. Hemoglobin ≥ 8.0 gm/dL
 - ii. Absolute neutrophil count (ANC) ≥ 1500 cells/mm³
 - iii. Platelet count $\geq 75,000$ /mm³
 - iv. Calculated creatinine clearance of > 60 mL/min/m², calculated as follows:
For males = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$
For females = $0.85 \times$ male value
 - v. Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
 - vi. AST (SGOT) and ALT (SGPT) ≤ 3.0 times the ULN
- 10) Must have life expectancy of greater than 3 months.
- 11) Must have an ECOG performance status 0-2.
- 12) Male or female patients of childbearing potential must be willing to use contraceptive precautions throughout the trial and 3 months following discontinuation of study treatment. Post-menopausal women must be amenorrheic for at least 12 months to

be considered of non-childbearing potential.

5.2 Exclusion Criteria

- 1) Other than the 3 cycles of neoadjuvant chemotherapy and surgery (mentioned above), must not have received other treatment for their gastric cancer.
- 2) Female patients who are pregnant, breast feeding, or of childbearing potential without a negative pregnancy test prior to baseline. Women of childbearing potential must have a negative serum pregnancy test as a part of eligibility, within 28 days of registration.
- 3) Patients unwilling or unable to comply with the protocol, or provide informed consent.
- 4) Patients with clinical evidence of metastatic disease.
- 5) Any medical condition that, in the opinion of the investigator, would exclude the patient from participating in this study and treatment plan.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Screening / Baseline Evaluation

- 6.1.1 Diagnostic (biopsy) and surgical confirmation of adenocarcinoma of gastric or GE junction origin; samples to be used for genetic profile.
- 6.1.2 A medical history and physical exam (H&P) to include the following information:
 - 6.1.2.1 A signs and symptoms assessment, including history of weight change
 - 6.1.2.2 Complete physical exam, including the following: vital signs, height, weight, and ECOG performance status.
 - 6.1.2.3 Baseline Toxicity Assessment
- 6.1.3 Laboratory studies must be obtained within 28 days (unless noted otherwise) prior to registration, to include the following:
 - 6.1.3.1 Complete blood count (CBC) with differential and platelets.
 - 6.1.3.2 Serum chemistries: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, and glucose.
 - 6.1.3.3 For women of child bearing potential, a serum β -HCG pregnancy test.

- 6.1.4 Tumor imaging with either CT (chest with contrast and abdomen/pelvis with and without contrast) or CT/PET (skull base to mid-thigh); must be within 42 days of treatment start.
- 6.1.5 Pathologic evaluation of tumor specimen will include standard lymph node evaluation. Nodal disease will be classified into one of two categories:
 - lymph node negative, where no nodes are involved with tumor, or lymph node positive, where one or more nodes are involved with tumor.

6.2 Arm 1: Adjuvant Chemotherapy: Evaluation of patients deemed lymph node negative at time of surgery and treated with postoperative chemotherapy:

- 6.2.1 Within 2 days before Day 1 treatment of each cycle (for either chemo regimen):

- 6.2.1.1 History and physical exam

- 6.2.1.2 Vital signs (blood pressure, respiratory rate, height, weight)

- 6.2.1.3 Complete blood count (CBC) with differential and platelets.

- 6.2.1.4 Serum chemistries: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, and glucose.

- 6.2.1.5 Adverse Event Assessment

6.3 Arm 2, Adjuvant Chemoradiation: Evaluations for patients deemed lymph node positive at time of surgery and treated with postoperative chemoradiation:

- 6.3.1 While on chemotherapy alone, within 2 days before Day 1 treatment of each cycle:

- 6.3.1.1 History and physical exam

- 6.3.1.2 Vital signs (blood pressure, respiratory rate, height, weight)

- 6.3.1.3 Complete blood count (CBC) with differential and platelets.

- 6.3.1.4 Serum chemistries: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, and glucose.

- 6.3.1.5 Adverse Event Assessment

6.3.2 While on concurrent chemoradiation (for 5 weeks), once per week:

6.3.2.1 History and physical exam

6.3.2.2 Vital signs (blood pressure, respiratory rate, height, weight)

6.3.2.3 Complete blood count (CBC) with differential and platelets.

6.3.2.4 Serum chemistries: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, and glucose.

6.3.2.5 Adverse Event Assessment

6.4 Post-Treatment Surveillance (Follow-Up)

6.4.1 After completion of adjuvant chemotherapy, subjects will undergo follow-up, every 3 months, +/- 14 days, for a total of 36 months from the date of surgery.

6.4.1.1 History and physical exam

6.4.1.2 Vital signs (blood pressure, respiratory rate, height, weight)

6.4.1.3 Complete blood count (CBC) with differential and platelets.

6.4.1.4 Serum chemistries: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, and glucose.

6.4.1.5 Survival Status

6.4.1.6 Recurrence of disease (date of recurrence)

6.4.1.7 Adverse Event Assessment (per Section 13.6.3)

6.4.2 Patients will undergo imaging for residual or recurring tumor with either CT (chest with contrast and abdomen/pelvis with and without contrast) or CT/PET (skull base to mid-thigh). The interval of this imaging can be every 3-6 months, at the discretion of the treating investigator.

7.0 TREATMENT PLAN

Preoperative chemotherapy: Patients will have received 3 cycles of neo-adjuvant chemotherapy (either CAPEOX or FOLFOX) at the treating physician's discretion. Dose modifications are allowed per standard clinic practice.

After the completion of the preoperative therapy, patients without evidence of obvious metastatic disease will undergo a surgical resection with definitive intent, either by open or laparoscopic resection of the primary gastric or GE junction cancer.

After completion of surgery, patients will be reviewed for eligibility. Eligible subjects will be registered to the study and assigned to Arm 1 or Arm 2.

Treatment should start within 3 months of surgery.

All adjuvant treatment regimens (both Arm 1 and Arm 2) are to be administered per standard clinic practices, including infusion duration times, dose modifications, treatment delays, and supportive care.

7.1 Arm 1: Postoperative chemotherapy, for those patients with node negative disease at time of surgery, will consist of three additional cycles of chemotherapy. Subjects can receive either CAPEOX or FOLFOX (regardless of the neo-adjuvant regimen), following the same dosing guidelines and management as below. Changing to the alternative fluoropyrimidine (capecitabine or 5-fluorouracil) from what was used pre-operatively is permissible at the discretion of the treating investigator.

7.1.1 CAPEOX will be dosed on a 21-day cycle:

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Oxaliplatin	130 mg/m ²	IV	Day 1	21-day cycle
Capecitabine	625 mg/m ²	PO (BID)	Days 1-5, 8-12, 15-19	21-day cycle

or

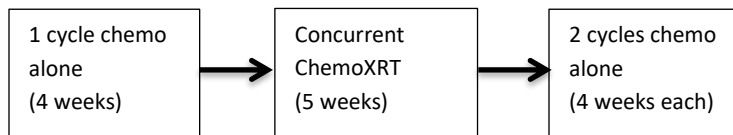
AGENT	DOSE	ROUTE	DAYS	INTERVAL
Oxaliplatin	130 mg/m ²	IV	Day 1	21-day cycle
Capecitabine	1000 mg/m ²	PO (BID)	Days 1-14	21-day cycle

7.1.2 FOLFOX will be dosed on a 14-day cycle. Agents are to be given in this order, according to standard clinic practice.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Oxaliplatin	85 mg/m ²	IV	Day 1	14-day cycle
Leucovorin	400 mg/m ²	IV	Day 1	14-day cycle
5-fluorouracil*	400 mg/m ²	IV bolus	Day 1	14-day cycle
5-fluorouracil*	2400 mg/m ²	Continuous IV infusion	Day 1-3	14-day cycle

* 5-fluorouracil will be dosed as 400 mg/m² through IV bolus, followed by 2400 mg/m² through continuous IV infusion, starting Day 1

7.2 Arm 2: Postoperative chemoradiation, for those patients with node positive disease at time of surgery, will consist of one cycle of chemotherapy, followed by concurrent chemoradiation (5 weeks), and followed by two additional cycles of chemotherapy.



7.2.1 Each cycle of chemotherapy-alone will consist of a single agent fluoropyrimidine, either capecitabine (per section 7.2.1.1) or 5-fluorouracil (per section 7.2.1.2), at the treating physician's discretion.

7.2.1.1 Capecitabine will consist of 750 mg/m², PO BID on days 1-14 of a 28 day cycle.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Capecitabine	750 mg/m ²	PO (BID)	Days 1-14	28-day cycle

7.2.1.2 5-fluorouracil will be given on days 1 and 15 of a 28 day cycle according to the following:

- Leucovorin will be dosed as 400 mg/m², IV infusion over 60 minutes
- 5-fluorouracil will be dosed as 400 mg/m², IV bolus followed by a 1200 mg/m², IV infusion over 46 hours

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Leucovorin	400 mg/m ²	IV	Day 1	28-day cycle
5-fluorouracil	400 mg/m ²	IV bolus	Day 1	28-day cycle
5-fluorouracil	1200 mg/m ²	Continuous IV infusion	Day 1-3	28-day cycle

7.2.1.3 Criteria for proceeding with treatment and managing side effects will be as in section 7.4 (below).

7.2.2 Chemoradiation will be administered over 5 weeks

7.2.2.1 The intent is to deliver 45 Gy in 1.8 Gy/fraction, 5 days a week for 5 weeks, to the entire gastric bed (including anastomosis) and draining lymph nodes.

7.2.2.2 Chemotherapy with radiation will consist of a single agent fluoropyrimidine, either capecitabine (per section 7.2.2.2.1) or 5-fluorouracil (per section 7.2.2.2.2), at the treating physician's discretion.

7.2.2.2.1 Capecitabine will consist of 750 mg/m², PO BID on days of radiation

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Capecitabine	750 mg/m ²	PO (BID)	Days of Radiation	5-weeks

7.2.2.2.2 5-fluorouracil will be dosed as 200 mg/m²/day, IV continuous infusion on days of radiation

AGENT	DOSE	ROUTE	DAYS	INTERVAL
5-fluorouracil	200 mg/m ²	IV (over 1 day)	Days of radiation	5-weeks

7.2.2.3 Criteria for proceeding with treatment and managing side effects will be as in 5.1.3.

7.3 Chemotherapy after chemoradiation: After finishing chemoradiation (section 7.2.2), subjects will receive two cycles of chemotherapy alone, as in 7.2.1. Changing to the alternative fluoropyrimidine (capecitabine or 5-fluorouracil) from what was used previously is permissible at the discretion of the treating investigator.

7.4 Chemotherapy side effect management

7.4.1 All patients will receive anti-emetic prophylaxis, IV, on day 1 of IV chemotherapy.

7.4.2 All patients will be prescribed oral anti-emetics as needed (per investigator discretion and standard clinical care).

7.4.3 Patients that develop diarrhea can be managed using as needed loperamide or other anti-diarrheals, at the discretion of the treating physician.

7.4.4 On Day 1 of each cycle (or, up to 2 days before Day 1), patients must meet the following criteria in order to proceed with treatment:

7.4.4.1 ANC ≥ 1,500/mm³

7.4.4.2 Platelets \geq 75,000/mm³

7.4.4.3 Hemoglobin \geq 8.0 gm/dL

7.4.4.4 Resolution of any non-hematologic toxicity to adequately controlled to the satisfaction of the treating investigator.

7.4.5 If a patient does not meet criteria in Section 7.4.4 on day 1 of a cycle, treatment should be held until resolution of such symptoms or signs to meet the criteria in Section 7.4.4.

7.4.6 Additional supportive care will be given based on the clinical judgment of the treating investigator, per standard clinical practice.

7.4.7 Chemotherapy dose modifications (reductions or delays) due to toxicity should be as per standard clinical practice, at the discretion of the treating investigator.

8.0 CRITERIA FOR STUDY CONTINUATION OR DISCONTINUATION

All patients who are enrolled on the study and begin any of their intended post-operative adjuvant therapy will be counted as evaluable for the study. This inclusion will be regardless of how much of the postoperative treatment they ultimately receive.

Criteria for discontinuation of post-operative treatment will be:

- a) Unacceptable toxicity
- b) Treatment delay due to toxicity > 2 weeks.
- c) Treatment delay for any other reason > 3 weeks.

Patients who discontinue treatment for these reasons will remain on protocol and will move on to surveillance/follow-up for disease recurrence

Disease recurrence, will be defined as radiographic tumor evidence detected by surveillance imaging. Confirmation of recurrence by biopsy will be at the discretion of the treating physician.

If a subject has disease recurrence during surveillance / follow-up, then further study follow-up can be discontinued; the subject will come off-study, and can be followed per standard clinical care at the investigator's discretion.

The patient may withdraw from the study at any time for any reason. Similarly, an investigator may remove a patient from the study for non-compliance with study protocol at any time. Patients removed from the study for these reasons will be replaced.

9.0 CORRELATIVE / SPECIAL STUDIES

Tumor samples obtained at diagnosis and from the surgical specimen will be referred for genetic profiles. These profiles are being developed in collaboration with the cancer genomics division in the department of molecular and human genetics at Baylor College of Medicine.

These profiles will assess alterations in gene expression consistent with the CGAR gastric cancer subtypes, correlating these to the nodal responses observed in the treated patients. Within these proposed subtypes of gastric cancer, it is reasonable to consider that different subtypes respond or evolve in different ways when treated with this standard chemotherapy. Being able to correlate these responses to the clinical outcomes at time of surgery (i.e.: the presence or absence of nodal disease) could be developed in future studies in a predictive manner. Thus, this will serve as an exploratory gene analysis, both for static gene expression at time of diagnosis as well as evolution of gene expression in response to chemotherapy, which could in turn be developed in future studies as a predictor of chemotherapy response. Tumor samples will remain in pathology archive and will be batch-sent for analysis.

Samples will not be banked after research. Any remaining samples will be discarded.

10.0 STATISTICAL CONSIDERATIONS

The primary objective is to determine the feasibility of patients enrolling and receiving either postoperative chemoradiation or chemotherapy alone, based upon nodal status. Based on our experience, we projected that the eligible patients would receive chemoradiation or chemotherapy alone in 3:1 ratio after surgery. We designed this pilot study on 30 patients who receive chemoradiation and on 10 patients who receive chemotherapy alone based upon nodal status at surgery, for a total of 40 patients. At 50% of complete rate, the confidence intervals will have widths of a most +/- 17% and +/- 26.5% (confidence intervals calculated using Wilson method). For control purposes, no more than 30% of patients with node negative disease should be unable to receive postoperative chemotherapy. In order for postoperative chemoradiation to be a feasible recommendation in patients who have lymph node positive disease at time of surgery after preoperative chemotherapy, a majority of patients must be able to receive this chemoradiation in its entirety.

The primary endpoint is the proportion of patients who complete the recommended therapies as indicated by their surgical nodal status. The primary endpoint will be evaluated when the last patient completes the postoperative chemotherapy or chemoradiation assigned. Descriptive and summary statistics will be computed for demographics and clinical data of all patients enrolled in the study. In each group, complete rates will be summarized with a point estimate and 95% confidence interval (Wilson method). If no more than 30% of patients are unable to complete all protocol therapy, then this will be considered a feasible treatment for these patients.

Time to recurrence and recurrence free survival are secondary outcomes. These will be summarized using survival analysis methods, such as Kaplan-Meier survival curves, median survival time and 97% confidence interval. For the correlative study, tumor samples obtained at diagnosis and from the surgical specimen to see the changes in gene expression, categorized based upon correlation to nodal status. A paired t-test and multiple comparisons will be performed. Analysis of tumor genetic profile should be almost universally assessable from tumor samples acquired. No special preparation is necessary for these samples. Expect that no more than 10% of patients will be unable to have tumor profiles assessed on both pre- and post- chemotherapy tumor specimens.

11.0 DATA AND SAFETY MONITORING AND QUALITY ASSURANCE

This study will be monitored regularly by the Data Review Committee (DRC) of the Dan L Duncan Comprehensive Cancer Center, at a frequency of at least once per year, in accordance with the

DLDCCC Data and Safety Monitoring Plan. The DRC will monitor the study for progress and enrollment, toxicities, adverse events, and soundness of data.

This study will be monitored by the DLDCCC Quality Assurance program for study conduct and quality of data.

12.0 DATA MANAGEMENT

The patient eligibility data, initial history and physical examination will be recorded on the protocol chart. A record of relevant outpatient visits and hospital admissions will be recorded in the patient's clinic chart.

All trial data will be recorded in OnCore.

For patients going off-study, a final assessment summary will be recorded by the investigator in the protocol chart indicating clearly the reasons for discontinuing protocol treatment.

13.0 ADVERSE EVENT REPORTING

13.1 Adverse Event: Any unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, whether or not it is considered related to the subject's participation in the research.

13.2 Descriptions and Grading: the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

13.3 Attribution / Relatedness: Each event should be evaluated for its relatedness to participation in the research:

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

13.4 Seriousness: A Serious Adverse Event (SAE) is any adverse event that:

- Results in death;
- Is life-threatening;
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

13.5 Expectedness: Definition of expected and unexpected adverse event.

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

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

13.6 Reporting:

13.6.1 Adverse events will be collected and reporting beginning on the first day of post-operative chemotherapy treatment, and continuing through completion of post-operative treatment.

13.6.2 All adverse events, grade 3 or above, regardless of relatedness, will be reported and recorded on the appropriate CRFs. Toxicities that were present at baseline (pre-treatment) should not be reported unless the toxicity worsens.

13.6.3 New AEs and SAEs that are ongoing at the end of postoperative chemotherapy will be followed for 2 weeks from the patient's receipt of the last dose of protocol therapy, unless they have resolved earlier. SAEs and drug related AEs ongoing at the end of treatment will be followed until resolution.

13.6.4 The AE description will include the nature of the experience, the date of onset, the resolution date, the severity of each sign or symptom reported using the NCI-CTCAE (v 4.0), the seriousness of the event, the relatedness to study treatment, the course of action taken (if any), and the outcome of the experience.

13.6.5 SAEs are to be reported to the institutional review board (IRB) according to the IRB's reporting requirements and required time frame.

13.6.6 Any event that is reportable to the BCM IRB must also be reported to the DLDCCC Data Review Committee (DRC) via the Patient Safety Officer at dldcc-pso@bcm.edu.

14.0 REFERENCES

1. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *N Engl J Med* 2006, **355**: 11-20.
2. MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001, **345**: 725-730.
3. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*. 2008, **358**: 36–46.
4. Ychou M, Boige V, Pignon J-PP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011, **29**: 1715–21.
5. Enzinger PE, Burtness BA, Niedzwiecki D, et al. CALBG 80403 (Alliance)/E1206: A randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. *J Clin Oncol* 2016, **34**: Epub ahead of print.
6. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer* 2011, **11**: 329.
7. Verheji M, Jansen EPM, Cats A, et al. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study. *J Clin Oncol* 2016, **34**: suppl; Abstr 4000.
8. Smyth EC, Fassan M, Cunningham D, et al. Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial. *J Clin Oncol* 2016, **34**: 2721-2727.
9. Lee J, Lim D, Kim S, et al. Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial. *J Clin Oncol* 2012; **30**: 268–73.
10. Park S, Sohn T, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol* 2015; **33**: 3130-3136.
11. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014, **513**: 202-209.

15.0 APPENDIX I: SCHEDULE AND FLOW OF EVALUATIONS

15.1 ARM 1: Node-Negative, Adjuvant Chemotherapy.

Study Procedures	Screening & Baseline (1)	Arm 1: Cycle 1 (6)	Arm 1: Cycle 2 (6)	Arm 1: Cycle 3 (6)	Post-Treatment Surveillance, every 3 months (7)
Informed Consent	X				
History & Physical Exam; Vitals (2); ECOG PS	X	X	X	X	X
CBC + differential + platelets	X	X	X	X	X
CMP: Serum Chemistries (3)	X	X	X	X	X
AE Assessment		X	X	X	X
Pregnancy Test	X				
Tumor for genetic profile (4)	X				
Imaging (5)	X				X
Chemo, Adjuvant		X	X	X	
Survival Status, Recurrence					X

1. Screening procedures must be obtained within 28 days registration, with the exception of radiographic studies and tumor samples for baseline profiles.
2. Vital signs includes blood pressure, respiratory rate, height, and weight.
3. Serum chemistries to include: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, glucose.
4. Tumor samples from diagnostic biopsy (before neo-adjuvant chemo) and surgery (after neo-adjuvant chemo) should be obtained (after subject consents to participate).
5. Can be either (1) CT of the chest with contrast and CT of the abdomen/pelvis with and without contrast, or (2) PET/CT from the skull base to mid-thigh. Baseline imaging must be after surgery, and within 42 days of starting adjuvant chemotherapy.
6. Procedures are to be repeated at the beginning of each cycle and can be assessed up to 2 days in advance of D1 for each cycle. These cycles are 14 days long if FOLFOX used and 21 days long if CAPEOX used.
7. Three month interval begins from the end of completion of chemotherapy, and continues until 36 months after surgery (unless patient comes off study, per Section 6). These assessments can be +/- 14 days from planned date. Imaging assessments during follow-up can occur every 3-6 months, per investigator's standard practice. If subject has disease recurrence, follow-up will stop.

15.2 ARM 2: Node-Positive, Adjuvant Chemoradiation.

Study Procedures	Screening & Baseline (1)	Arm 2: Chemo alone, Cycle 1 28-day cycle (6)	Arm 2: ChemoRT, 5 weeks Schedule is for each week					Arm 2: Chemo alone, Cycle 2 28-day cycle (6)	Arm 2: Chemo alone, Cycle 3 28-day cycle (6)	Post-Treatment Surveillance, every 3 months (7)
			W 1	W 2	W 3	W 4	W 5			
Informed Consent	X									
History & Physical Exam; Vitals (2); ECOG PS	X	X	X	X	X	X	X	X	X	
CBC + differential + platelets	X	X	X	X	X	X	X	X	X	
CMP: Serum Chemistries (3)	X	X	X	X	X	X	X	X	X	
AE Assessment		X	X	X	X	X	X	X	X	
Pregnancy Test	X									
Tumor for genetic profile (4)	X									
Imaging (5)	X								X	
Chemo, Adjuvant		X	X	X	X	X	X	X	X	
Concurrent XRT			X	X	X	X	X			
XRT Treatment Report (8)							X			
Survival Status, Recurrence									X	

1. Screening procedures must be obtained within 28 days of registration, with the exception of radiographic studies and tumor samples for baseline profiles.
2. Vital signs includes blood pressure, respiratory rate, height, and weight.
3. Serum chemistries to include: liver enzymes (AST, ALT, alkaline phosphatase), blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, calcium, bicarbonate), total protein, albumin, total bilirubin, glucose.
4. Tumor samples from diagnostic biopsy (before neo-adjuvant chemo) and surgery (after neo-adjuvant chemo) should be obtained (after subject consents to participate).
5. Can be either (1) CT of the chest with contrast and CT of the abdomen/pelvis with and without contrast, or (2) PET/CT from the skull base to mid-thigh. Baseline imaging must be after surgery, and within 42 days of starting adjuvant chemotherapy.

6. Procedures are to be repeated at the beginning of each cycle and can be assessed up to 2 days in advance of D1 for each cycle.
7. Three month interval begins from the end of completion of chemotherapy, and continues until 36 months after surgery (unless patient comes off study, per Section 6). These assessments can be +/- 14 days from planned date. Imaging assessments during follow-up can occur every 3-6 months, per investigator's standard practice. If subject has disease recurrence, follow-up will stop.
8. XRT treatment is reported once, at the completion of chemoXRT.

16.0 APPENDIX II: ECOG PERFORMANCE STATUS SCALE

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

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: *Toxicity And Response*