THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase IIB Study of Trimodality Management of clinical T1bN0M0 cancers of the esophagus
2010-0333

Core Protocol Information

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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Objectives: To assess the efficacy (pathologic complete response) and safety of Trimodality management (chemoradiotherapy followed by esophagectomy) in patients with clinically staged T1bN0M0 cancer of the esophagus or gastroesophageal junction.

Primary endpoint: Pathologic Complete Response (PCR) rate

Secondary Objectives:
1. Time to disease progression or death
2. Evaluation of preoperative toxicity and postoperative morbidity/mortality
3. Evaluation of feasibility of pretreatment and posttreatment/preoperative deoxyribonucleic acid (DNA) methylation biomarkers in tumor and blood as predictor of pCR rate

2.0 Rationale

1. *The Need to Improve the outcomes for T1b esophageal cancer*

Esophagectomy or endoscopic mucosal resection is the most standard approach for the management of stage I esophageal cancers. Early stage T1N0 disease can be defined as disease that is confined to the superficial mucosal layer (T1a) or that which has invaded to the submucosal layer (T1b). Multiple single institutional experiences documenting the outcomes of patients treated with esophagectomy for stage I esophageal cancers have demonstrated a less than optimal outcomes for patients with T1b disease. From M.D. Anderson, Cen et al. have reported the results of 99 consecutive patients with T1 adenocarcinoma who have underwent esophagectomy/lymphadenectomy, of which 51 patients have T1b disease (1). The investigators reported a much better 5-year overall survival (OS) for patients with T1a tumors (88%) than those with T1b tumors (62%) ($p=0.001$). Patients with evidence of lymphovascular invasion (LVI) and/or nodal metastasis (LNM) had a worse 5 year OS (≤37%) compared to those without either risk factors (88%, $p<0.001$). Also from M.D. Anderson, Liu et al reviewed the pathologic correlate of LVI or LNM to the clinical stage of patients (2). They found that T1b stage is significantly associated with LNM (44% versus 12% for T1a, $p<0.001$), larger tumors (>75% have >1.2 cm tumors versus ~30% for T1a tumors, $p<0.001$), and LVI (73% versus 18% for T1a, $p<0.001$). These investigators found that both LNM and LVI were prognostic for tumor recurrence, but only LVI was prognostic for overall survival. Tumor recurrence was more frequent in T1b disease (40% at 5 years) than T1a disease (0% at 5 years), resulting in 5 year OS of 58% for T1b and 91% for T1a disease (2). These findings have been confirmed in another large cohort study of 100 patients with T1 esophageal cancers receiving primary esophagectomy (3). They also found that LNM was significantly associated with T1b disease (27% vs. 7% for T1a). Although the 5 year OS for the entire cohort was 62%, and the 3 year DFS was 80%, this rate was significantly lower for patients with N1 disease (5 year OS is 35% N+ vs 70% N-, $p=0.0057$). These and other surgical series have demonstrated the poor outcomes of surgery alone for T1b disease due to the high propensity of these tumors to exhibit poor prognostic features such as LVI, TNM, and larger tumors, which has also been demonstrated to be an independent prognostic factor (4).

From these surgical series, it is also apparent that neither endoscopic mucosal resection (EMR) nor endoscopic submucosal resection (ESR) are adequate treatments for T1b esophageal cancers. Limited resection is very effective treatment for T1a disease, which has been demonstrated by the low risk features of this stage of disease based on these surgical series as well as institutional experiences utilizing EMR for management of early esophageal cancers. However, even in the most experienced centers, R0 resection is still only 75%, with high incidence of recurrences (30%) (5, 6). Even in the most selective group of patients (<2cm tumors, T1a, no LVI, histologic grades 1 to 2), as reported by a series of 100 patients in Germany, the lateral positive margin was still 34% (6). During the median 33 month follow-up, recurrence or metachronous disease was found in 11% of patients. All recurrences were salvageable, yielding a 3 year OS of 98%. However, this treatment approach wouldn't be appropriate for T1b cancers because the unpredictably high rates of LNM and LVI would not be adequately addressed by a mucosal or submucosal limited resection. Recently, Barbour et al (2010) (34) produced a stratification scheme based on 85 T1 patients treated with surgical resection alone. The patients were analyzed based on three risk factors: T1b status, tumor grade, and presence of LVI. While patients with T1a disease or T1b disease with Grades 1 or 2 and negative LVI had fairly good survival (5 yr overall survival of 95% and 85%, respectively), patients with T1b disease and grade 3 or any patients with LVI had 5 year survival of 50% and 30%, respectively.

So while esophagectomy is the standard of care for T1b esophageal cancers, multiple surgical series have demonstrated that this disease carries high rate of unsuspected lymph nodal metastasis (LNM) (27-45%) (2, 3, 7, 8) and lymphovascular invasion (LVI) (1, 2). The presence of such features portends to a poorer recurrence risk and overall survival as that seen for more locally advanced disease (stage II-III), where trimodality management with chemotherapy with radiation followed by surgical resection is the standard of care in the United States. This is based on numerous trials (9-11) and a meta-analysis (12) demonstrating survival benefit with preoperative chemoradiation compared to surgery alone.

2. *Non-surgical management for T1b cancers*

The only curative measure for esophageal cancers without a surgical resection is definitive chemoradiation. Definitive chemoradiation has been demonstrated to be curative for around 20-25% locally advanced esophageal cancer patients in a large randomized trial of unresectable patients (13). Whether definitive chemoradiation will yield better outcomes in early stage esophageal cancers (exclusively squamous cell cancers) was evaluated by investigators in Japan. In an earlier experience, Yamada and colleagues tested the role of definitive chemoradiation in 63 T1N0M0 squamous cell cancers of the esophagus (T1a=23, T1b=40) (14). The chemoradiation employed a median dose of 59.4 Gy with concurrent cisplatin/5FU, followed by 10-12 Gy HDR brachytherapy. They found high rates of control for T1a disease at 84.4%, but the 5 year disease free survival was 50.5% for T1b disease. Seven patients developed metastatic disease, all of which were patients with T1b disease. Local failures were seen in 15 patients (11 local only, 4 local + distant metastasis), with salvage therapies successful in saving 5 of 11 local recurrence only patients. In a separate phase II study investigating the efficacy of definitive chemoradiation for exclusively T1bN0 patients, cisplatin and 5FU were concurrently administered with a split course regimen of 60 Gy of radiotherapy (one

week break in between 30 Gy radiation) (15). Since the primary endpoint of the study was clinical complete response (cCR) rate, each of the 72 patients enrolled in the study was evaluated for clinical response at 4 weeks after chemoradiation with an EGD and biopsy. A clinical CR was defined as EGD evidence without tumor except for flat erosion, a negative biopsy, and no evidence of new lesions. Although they found a cCR rate of 87.5%, the 4 year recurrence free survival was only 52.8%, similar to the previously reported retrospective study. Of the 36 patients who developed recurrence or achieved less than a CR after chemoradiation, 16 had endoscopic resection as salvage therapy, and 6 that failed within the treatment port underwent esophagectomy as salvage. However of the 14 patients who couldn't be salvaged, 6 patients had distant metastasis and 8 patients had regional lymph node involvement. All 14 patients died of disease, resulting in a 4 year OS of 80.5%.

Although these studies demonstrated the feasibility and relative safety of performing non-surgical management for T1b esophageal cancers, the high risk of recurrence from these studies highlights the need for more aggressive therapies. Also, all the patients treated in these two Japanese studies had squamous cell cancers and so the applicability of this to patients treated in the United States where adenocarcinomas are prevalent is unknown. From these two reports, around 10-15% of non-salvageable recurrence is due to regional LNM. If upfront esophagectomy and lymphadenectomy clears the residual disease left in the primary site or regional lymph nodes after chemoradiation, approximately a 10-15% improvement in survival should be expected.

3. *The importance of pathologic complete response in predicting prognosis in esophageal cancer patients after preoperative chemoradiation*
Pathologic response rate after preoperative chemoradiation is an important prognostic factor for survival in locally advanced patients (16). This generally ranges from 25-45% in most series of locally advanced cancers managed with the trimodality therapy (9-11). There is currently no experience what the pCR rate is for stage I patients since trimodality therapy has not been evaluated for this stage of disease. Utilizing a treatment regimen where that could be systematically assessed will be important to determine the potential of an organ preservation approach for T1b patients in the future.

4. *Preoperative chemoradiation may improve outcomes in T1b patients*
Since patients with submucosal disease (T1b) tend to have high risk for nodal metastasis and LVI, with the 5 year survival rates for the T1b patients with these features nearly comparable to locally advanced cancers (stage II-III), preoperative or adjuvant therapies may be necessary to improve outcomes of these patients. Adding adjuvant therapies after upfront surgery is an option for these patients, but postoperative therapies incorporating radiation or chemotherapy alone have not shown to improve outcomes in multiple randomized trials in locally advanced cancers after surgical resection (17). Although postoperative chemoradiation have been shown to improve outcomes of patients with gastric/GE junction tumors based on the U.S. Intergroup 0116 study (18), which randomized gastric (80%) or GE junction (20%) tumors to surgery alone or postoperative chemoradiation, there are several disadvantages of using postoperative chemoradiation. Radiation fields after surgery tends to be larger since it must cover not only the pretreatment surgical bed but also the areas of dissection. The dose used postoperatively is higher and will vary depending on the surgical margin status. Oxygenation tends to be poorer in a dissected area, and therefore may decrease the efficacy of radiotherapy (and the reason for the need of higher doses of radiation). With higher doses of radiation, toxicity is likely to also be higher. In the area of the upper abdomen where sensitive structures such as the stomach, small bowel, and liver reside, doses above 45 to 50 Gy will be very difficult to administer without causing severe gastrointestinal side effects (nausea/vomiting, strictures, fistulas, small bowel obstruction).

Preoperative chemoradiation is an accepted standard in the United States for locally advanced stage II-III esophageal cancers. The basis of this was first established by an Irish study that randomized 113 patients with adenocarcinomas of the esophagus to 2 cycles of preoperative cisplatin/5FU and concurrent radiation to 40 Gy in 15 fractions or to surgical resection alone (9). The pCR rate for preoperative chemoradiation is 25%. There was a significant improvement in the 3 year overall survival (32% versus 6%) and median survival (16 months versus 11 months) ($p=0.01$) for the preoperative chemoradiation group. Many with a pCR (85%) were alive and disease free at 2 to 43 months. However the surgical resection group had an unusually poor 3 year survival rate of 6%, especially when historical surgical series demonstrate a 3 year survival of 20-25%. Many would argue that preoperative chemoradiation made up for the poor outcomes of surgery in this series of patients. At around the same time, Arlene Forastiere and colleagues in the United States were also studying the role of preoperative chemoradation, first as a phase II study that demonstrated promising results compared to historical controls of surgery alone, and later as a prospective randomized study of 100 patients (10, 19). This latter study randomized patients to preoperative chemoradiation with 5FU/Cisplatin/Vinblastine plus radiation (45 Gy) or surgery alone. The pCR rate was 28%. There was an improved local control rate in the chemoradiation group (81% versus 60%, $p=0.04$), but because of the small size of the study, there was only a trend to improved survival for the chemoradiation group (30% versus 16%) (10). Although technically a negative study, this trial is largely viewed as a positive trial demonstrating the superiority of preoperative chemoradiation since the survival rate in the neoadjuvant group is similar to the Walsh et al. study and that the surgery alone arm had survival rates that was largely equivalent to historical rates. These results were further corroborated by the recent publication of the results of CALGB 9781, a phase III study that closed to poor accrual with only 56 patients enrolled out of the planned 475 patients (11). Patients were randomized to preoperative cisplatin/5FU and radiation to 50.4 Gy or surgery alone. The pCR rate was 40%, and the median survival was better in the chemoradiation group (4.5 years versus 1.8 years) as well as the 5 year overall survival (39% versus 16%). However, trials done through the EORTC (Europe) and the TTROG (Australia) testing the role for preoperative chemoradiation have been largely negative studies, with only a benefit of disease free survival but not overall survival for patients treated with preoperative chemoradiation (20, 21). A meta-analysis of 10 randomized trials comparing preoperative chemoradiation versus surgery (1209 patients) found better hazard-ratio for mortality (0.81), corresponding to a 13% absolute 2-year survival benefit. The benefit was seen for both squamous and adenocarcinoma histologies (12).

Our experience at M.D. Anderson also favors the trimodality approach. We have analyzed our experience in 132 consecutive stage II-III patients treated at M.D. Anderson between 1990 to 1998 (22). We found that preoperative chemoradiation was better than definitive chemoradiation alone for 5 year loco-regional control (67.1% vs 22.1%, $p<0.000$), disease-free survival (40.7% vs 9.9%, $p<0.000$), and 5-year overall survival (52.6% vs 6.5%, $p<0.000$). There was no difference in distant metastastic free survival between the two groups, however. There may been some negative selection bias for the definitive chemoradiation group since these patients tended to be older, have more squamous cell carcinoma, located at upper thoracic or

cervical locations, and have more T4 tumors, but on both univariate and multivariate analysis, surgical resection remained a significant independent predictor of outcomes.

The importance of adding surgical resection after chemoradiation remains controversial since two European randomized trials demonstrated only an improvement in local control but not overall survival (23, 24). One major caveat of these studies is that the potential survival benefit of surgery was offset by the high rates of postoperative morbidity/mortality. We expect that the benefits of surgery should be seen at high volume centers where the morbidity and mortality rates are expected to be lower (25). Since surgical resection is the expected standard for T1b esophageal cancers where the postoperative complication rates are low (3), it is therefore important to assess the toxicity of trimodality treatment of T1b patients before adopting it for widespread use.

5. *Biomarker predictors for pathologic response*
It is a fact that definitive chemoradiation can cure select patients (26), particularly those who achieves a pCR after treatment. Clinical predictors for pCR using PET response or EDG biopsy results posttreatment are correlative, but are not sensitive enough to predict pCR (27). Tumor biomarkers may be a more sensitive way to determine which tumors are likely to respond to treatment. Ajani and colleagues have utilized expression microarray to identify three markers (PERP, S100A2, and SPRR3) that have allowed discrimination of pCR from <pCR with high sensitivity and specificity (28). This is currently being validated in larger clinical sets.

Promoter CpG island DNA methylation is a cancer-specific mechanism to turn-off tumor-suppressor genes. Since DNA is a stable molecule that is easily amplifiable from small amounts of materials, detection of residual cancer specific DNA methylation changes in small amounts of tissue or body fluids may be a promising approach to assess treatment response after chemoradiation (29, 30).

3.0 Patient Eligibility

Inclusion criteria:

1) Histologically documented adenocarcinoma or squamous cell carcinoma of the thoracic esophagus or gastroesophageal junction that are staged as T1b using endoscopic ultrasound (EUS) or from a large biopsy (either criteria # 1 or #2 can be met for eligibility).
2) Patients who undergo a diagnostic Endoscopic Mucosal Resection (EMR) and have a diagnosis of T1b stage established.
3) Performance score Karnofsky Performance Scale (KPS) 80-100.
4) Patients should be surgical candidates for esophagectomy and should have no contraindications for chemotherapy or radiation.
5) Negative pregnancy test for women of child bearing potential. They must agree to adequate contraception.
6) Complete blood count (CBC) and complete metabolic panel (chemo-14: Glucose, Calcium, Albumin, Total Protein, Sodium, Potassium, CO2, Chloride, Blood Urea Nitrogen (BUN), Creatinine, Alkaline Phosphatase, ALT (SGPT), AST (SGOT), and Bilirubin) to assess adequate hematologic, renal and hepatic functioning will be obtained. The values are as follows: Adequate hematologic (White Blood Count (WBC) >2,500/uL, platelets > 75,000/uL), renal (creatinine clearance > 50 mL/min), and liver function (bilirubin <=1.5 fold the upper limit of normal and liver enzymes < 3 fold the upper limit of normal).
7) Based on the risk factors and propensity of

LNM and poorer survivals seen in retrospective studies as discussed in the introduction, only patients with any one (1) of high risk features such as LVI, tumors >1.2 cm, and high grade will be enrolled (Grade is the pathologic term defining the degree of differentiation. Grade 1 is well differentiated, Grade 2 is moderately differentiated, and Grade 3 is poorly differentiated).

Exclusion criteria:

1) Prior radiation to the chest
2) Previous or concomitant cancers other than 1) curatively treated carcinoma in situ of cervix, basal cell of the skin, curative treatment for transitional cell carcinoma of the bladder, and early stage cancers at another non-overlapping site that was treated more than 3 years ago for cure.
3) Pregnant or breast-feeding females
4) Clinically significant uncontrolled major cardiac, respiratory, renal, hepatic, gastrointestinal or hematologic disease but not limited to:
   a) active uncontrolled infection
   b) Symptomatic congestive heart failure, unstable angina, or cardiac dysarrhythmia not controlled by pacer device
   c) no myocardial infarction within 3 months of registration
5) Known hypersensitivity to docetaxel, 5-fluorouracil, polysorbate-80, or any component of the formulation.

4.0 Pretreatment evaluation

4.1. Pretreatment evaluation:

A complete history and physical to include performance status, recent weight loss, percent of weight loss, usual weight, and concurrent non-malignant disease and its therapy must be recorded. Laboratory studies will included CBC with differential, platelet count, Liver function tests (LFTs), electrolytes, and creatinine within 3 weeks.

Computed tomography (CT) of chest with contrast and Positron emission tomography/ computed tomography (PET/CT) scans are required workup components that should be done within 3 months prior to starting chemoradiation. Pulmonary function tests (PFTs) should be updated within 3 months prior to starting treatment. Esophagogastroduodenoscopy (EGD) with EUS +/- biopsy at M.D. Anderson are required to confirm staging.

Patients are evaluated independently by the thoracic surgeon, the medical oncologist, and the radiation oncologist.

Quality of life (QOL) during treatment will be assessed at baseline, during treatment, and at followup. The QOL scale used are the FACT E (Appendix A), the FACT TS-G (Appendix B), and the Mayo (Appendix C). These will be administered at various

times pretreatment and throughout the course of treatment and at followup. The questionnaire to be administered and the time line of when these will be administered is detailed in the Appendix D.

5.0 Evaluation During Study

5.1 Treatment Schematic

The following demonstrates the treatment schematic for each week of therapy until radiotherapy is complete (approximately 5.5 weeks).

Table 1: Phase 2 Treatment Schematic

Day	1	2	3	4	5	6	7
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
	Docetaxel					Holiday	Holiday
	5-FU	5-FU	5-FU	5-FU	5-FU	Holiday	Holiday
	Radiotherapy	Radiotherapy	Radiotherapy	Radiotherapy	Radiotherapy	Holiday	Holiday

Docetaxel and Fluorouracil (5-FU)

Docetaxel and 5-FU should be prepared and administered in accordance with the prescribing information approved by the Food and Drug Administration (FDA) or other regulatory agencies where docetaxel and 5-FU are commercially available.
See Table 2: Therapy Dose and Schedule below for additional information regarding the dose and schedules for docetaxel, and 5-FU.

Table 2: Therapy Dose and Schedule

Drug	Dose	Schedule
Docetaxel	20 mg/m^2	1-hour IV infusion
5-FU	300 mg/m^2/day	24-hour continuous IV infusion by portable pump

*We will premedicate with dexamethasone 10 mg IV 30 minutes prior to weekly docetaxel administration.

Docetaxel and 5-FU

Although commercial supplies of 5-FU and docetaxel will be utilized, records should, when possible, document manufacturer, supplier, and lot numbers for each vial administered to each patient. Any remaining or unused 5-FU or docetaxel should be handled according to the institution's guidelines for handling and disposing of antineoplastic agents.

5.2 Study Drug Handling and Disposal

Docetaxel and 5-FU

Docetaxel and 5-FU should be disposed of in accordance with the prescribing information approved by the Food and Drug Administration (FDA) or other regulatory agencies where docetaxel and 5-FU are commercially available. See the docetaxel and 5-FU Product Information Sheets for details regarding handling and disposal.

5.3 Radiation Therapy

Participating institutions must utilize 3-D CT based planning and must be able to comply with the criteria described below.

5.3.1 Dose Specifications

- The daily prescription dose will be 1.8 Gy to be delivered to the periphery of the planning target volume (PTV). The isodose line (generally 93-98%) chosen will encompass at least 95% of the PTV.
- The maximum point dose, minimum point dose, and mean dose to PTV will be reported.
- The total dose will be 50.4 Gy (1.8G/Fx/day) prescribed to the periphery of the PTV.

5.3.2 External Beam Equipment

For Photons, megavoltage equipment is required with effective photon energies >6 MV. Proton beam therapy (PBT) will also be allowed for this trial.

5.3.3 Treatment Planning Imaging and Localization Requirements

- A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV) and planning target volume (PTV). For this study, the local regional nodes (whether clinically positive or negative) will be included in the clinical target volume (CTV). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, 3-5 mm thickness of the regions, harboring gross tumor and 8-10 mm thickness of the remaining regions, are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include lungs, skin, heart, spinal cord, esophagus, and liver. A measurement scale for the CT image shall be included.

- For cervical primaries (defined as tumors above the carina), the bilateral supraclavicular nodes need to be included. For mid-esophageal primaries (at or below the carina), the paresophageal nodes need to be included—not the supraclavicular or celiac. For distal/gastroesophageal primaries, the field should include the celiac nodes and left gastric nodes.

- Barium swallow during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the outline of the esophagus.

- Optimal immobilization is critical for this protocol. Alpha cradle or approved alternative immobilization system is required. Patients may be placed on the supine or prone position. In general, supine is recommended for proximal and distal primaries whereas prone is recommended for mid-esophageal.

5.3.4 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

- *Gross Tumor Volume (GTV)* is defined as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary (GTV-P) only. Note: ICRU Report #50 also defines a clinical target volume (CTV) that includes the area of subclinical involvement around the GTV. For this protocol, we have chosen to define the CTV a minimum of 4 cm proximal and distal and 1 cm lateral beyond the GTV delineated by CT scan and /or endoscopy (endoscopy is preferable). The final CTV may be larger since for cervical primaries, the supraclavicular nodes need to be included, and for distal primaries, the celiac nodes need to be included in the treatment fields. CTV must be determined by the treating physician, and with CT based planning, must respect anatomic boundaries of potential microscopic disease spread.

- *Planning Target Volume (PTV)* will provide margin around the CTV to compensate for variability in treatment set up, breathing, or motion during treatment. A margin around the CTV will define the PTV. The PTV volume must include a minimum of 1 cm and a maximum of 2 cm around the CTV. Therefore, the superior and inferior margins will be approximately 5 cm beyond the GTV, and the lateral margins will be approximately 2 cm beyond the GTV. Once again, the final PTV may be larger since for cervical primaries, the supraclavicular nodes need to be included, and for distal primaries, the celiac nodes need to be included in the treatment fields. If daily verification imaging is done, a 0.5cm expansion for the PTV is allowed.

5.3.5 3D Planning

- For photon based radiation, both 3D conformal and Intensity Modulated Radiation Therapy (IMRT) techniques can be used. For PBT, either passive scattering PBT or Intensity Modulated Proton Therapy (IMPT) can be used. The techniques and modality utilized will be at the discretion of the treating physician.

- Normal Tissue Volume and Tolerance. The normal tissues in the table below are to be contoured in their entirety.

- The following organs and doses are guidelines for the treatment plan (see Table 3: Normal Tissue Volume and Tolerance). Physician/ Dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 1.8 Gy/Fx (uncorrected).

Table 3: Normal Tissue Volume and Tolerance

Incidence of Pneumonitis (%)					
Quartile	**GTV *(cc)***	**Mean Dose *(Gy)***	**% of Ipsilateral Lung Receiving > 20 Gy**	**% of Total Lung receiving > 20 Gy**	**V_{ef}**
≥ Grade 2					
1st	32	20	7	8	0
2nd	12	21	10	23	23
3rd	27	25	38	29	25
4th	27	29	42	33	45
> Grade 3					
1st	11	10	7	8	0
2nd	6	11	0	0	5
3rd	3	8	21	19	14
4th	20	24	25	27	26

Tolerance Dose			
Organ	**Volume**	**TD 5/5**	**End Point**
Lung *(See Table 1)*	*(Table 1)*	*(Table 1)*	Clinical Pneumonitis
Spinal Cord	5 cm	50 Gy	Myelitis
	10 cm	50 Gy	Myelitis
	20 cm	47 Gy	Myelitis
Heart	1/3	50 Gy	Clinical Pericarditis
	2/3	45 Gy	Clinical Pericarditis
	3/3	40 Gy	Clinical Pericarditis
Liver	1/2	35 Gy	Clinical Hepatitis
	2/2	30 Gy	Clinical Hepatitis

- It is expected that the dose to the lungs, heart, spinal cord, and liver will be the primary dose-limiting structures. Every effort should be made to keep the total lung dose to a minimum.

- When planning the beam arrangement to the PTV, the lungs, heart, spinal cord, and liver should be out of the field to the greatest extent possible. The dose per fraction to the lungs, heart, and spinal cord should be maintained at 2 Gy or less per fraction to the greatest extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangement should be used.

5.3.6 Treatment Verification

At least twice weekly (at least 48 hours apart) verification films or images of the orthogonal views (anterior to posterior and lateral projection) must be reviewed by the treating physician. If daily orthogonal films are taken, the PTV margin can be reduced to 0.5 cm expansion from the CTV. The required accuracy of patient positioning and the use of multi-leaf collimator apertures suggest the daily use of on-line imaging may be desirable.

5.3.7 Therapy Interruptions

- If interruption of therapy (up to 2 weeks) becomes necessary, radiation therapy should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.

- If the patient develops ≥Grade 3 RT-related toxicity, RT, and chemotherapy (docetaxel and 5-FU) should be withheld. Treatment can resume once RT-related toxicity is <Grade 3 (e.g. Grade 1 or 2 or pre-therapy baseline).

5.3.8 Criteria for Toxicity

- Toxicities related to radiation therapy include: fatigue, myleosuppression, skin erythema, subcutaneous fibrosis, esophagitis, carditis, myelits, acute radiation pneumonitis and late pulmonary fibrosis, and esophageal stricture.

- Acute toxicity monitoring: Acute (< 90 days from RT start) side effects of radiation therapy will be documented and graded according to the NCI-CTCAE version 4.0.

- Late toxicity monitoring: Late (> 90 days since start or persisting beyond 90 days) post-treatment complications will be evaluated and graded according to the RTOG Late Effects Radiation Morbidity Criteria.

5.3.9 Dose Delays and Dose Modifications for Toxicity

Treatment with docetaxel, 5-FU, and radiation therapy may be delayed, up to 2 weeks (14 days), to allow for resolution of toxicity.
Treatment must be delayed and/or modified if any of the following apply:

Table 4: Dose Delays and Modifications for Toxicity

TOXICITY/ NCI-CTCAE GRADE	ACTION TAKEN
DLTs (hematologic or non-hematologic)	
Except for serum troponin	**Step 1:** Interrupt treatment until the toxicity has resolved to ≤Grade 1 or pre-therapy baseline, up to 2 weeks (14 days). **Step 2:** Restart treatment at reduced dose (docetaxel should be reduced by 15 mg/m^2, 5-FU reduced by 50 mg/m^2, monitor as clinically indicated.
Serum Troponin	
Chemistries	
• Total bilirubin is greater than the ULN • AST and/or ALT is >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN	**Step 1:** Interrupt treatment until the toxicity has resolved to ≤Grade 1 or pre-therapy baseline, up to 2 weeks (14 days). **Step 2:** Restart treatment; monitor as clinically indicated.

Hematologic	
• Neutrophil count is <1500 cells/ mm^3	**Step 1:** Interrupt treatment until the toxicity has resolved to ≥1500 cells/mm^3 or pre-therapy baseline, up to 2 weeks (14 days). **Step 2:** Restart treatment; monitor as clinically indicated.
• Grade 4 neutropenia (<500 cells/mm^3) lasting 7 days or more • Grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C	**Step 1:** Interrupt treatment until resolved to Grade 0-1, up to 2 weeks (14 days). **Step 2:** Restart treatment at reduced dose (docetaxel should be reduced by 15 mg/m2, 5-FU reduced by 50 mg/m2, and monitor as clinically indicated. **Note:** If toxicity does not resolve, consult Ascenta Therapeutics' Medical Monitor, to determine if it is in the best interest of the patient to continue in the study. GCSF may be administered following the subsequent course)
• Grade 3 platelets (25,000-50,000 cells/mm^3)	**Step 1:** Interrupt treatment until resolved to Grade 0-1, up to 2 weeks (14 days). **Step 2:** Restart treatment; monitor as clinically indicated
• Grade 4 platelets (≤25,000 cells/mm^3)	**Step 1:** Interrupt treatment until resolved to Grade 0-1, up to 2 weeks (14 days). **Step 2:** Restart treatment at reduced dose (docetaxel should be reduced by 15 mg/m2, 5-FU reduced by 50 mg/m2, monitor as clinically indicated. **Note:** If toxicity does not resolve, consult Ascenta Therapeutics' Medical Monitor, to determine if it is in the best interest of the patient to continue in the study.
Any other Grade 2 or 3 Toxicity	
If clinically significant	**Step 1:** Interrupt treatment up to 2 weeks (14 days), until toxicity resolves to ≤Grade 1. **Step 2:** Restart treatment at reduced dose (docetaxel should be reduced by 15 mg/m2, 5-FU reduced by 50 mg/m2, and monitor as clinically indicated.
Recurrent Grade 2 or 3 Toxicity	
If clinically significant	Discontinue treatment and follow-up per protocol.

5.4 Post-treatment evaluation:

Four to six weeks after chemoradiation patient will be brought back for restaging studies using contrast enhance CT of chest and PET-CT, as well as repeat EGD with biopsy to assess for clinical response to therapy. Once patients are deemed eligible for surgical resection, surgery should begin no later than 8 to 10 weeks after completing chemoradiation.

5.5 Surgery

Transhiatal or transthoracic approaches (left thoractomy or Ivor Lewis) will be left to the discretion of the surgeon.

5.6. Biomarker study

One of the secondary objectives is evaluation of feasibility of pretreatment and posttreatment/preoperative DNA methylation biomarkers in tumor and blood as predictor of pCR rate. Patient will be consented for blood draw for assessing DNA methylation biomarkers on protocol LAB09-0307, an approved protocol that consents patients being treated with radiation for blood draws at various times before, during, and after treatment. Tumor biomarkers will be assessed using tissue collected at the time of diagnosis either as fresh frozen or paraffin-embedded samples. The protocol to allow for use of this tissue is LAB09-0856.

6.0 Statistical Considerations

6.1 Preliminaries. This is a single-arm phase IIB trial of chemo-radiation followed by surgery for patients with early stage grade T1b esophageal cancer. This trial is motivated by the idea that adding chemo-radiation to surgery in this patient subgroup will improve their clinical outcome. The primary endpoint will be pathologic CR (PCR). Secondary endpoints will include T = disease-free survival (DFS) time, defined as the time to disease progression or death, pre-surgery toxicity (PreTox), defined as any NCI grade 4 non-hematologic toxicity observed during the 10-week period beginning at the start of chemo-radiation and ending at the time of surgery, and post-surgery mortality (PostDeath), defined as death due to any cause during the 30-day period following surgery.

6.2. Outcomes and Stopping Rules. The design will include three early stopping rules: (a) A futility rule based on PCR that stops the trial if it is unlikely that an improvement in
Prob(PCR), from the historical rate of .25 to a targeted rate of at least .45, will be achieved; (b) A safety rule based on PreTox that stops the trial if it is likely that a probability of this event higher than the historical probability of .30 will occur (c) A safety rule based on PostDeath that stops the trial if it is likely that a probability of this event higher than the historical probability of .026 will occur. A maximum of 30 patients will be treated with a follow up of 1 year after the last patient is accrued. An accrual rate of 6 patients per year will be assumed.

6.3. **Futility Monitoring**. The following futility monitoring rule, as described in Thall and Sung (31) will be used. We assume that the historical PCR probability qPCR,0 ~ beta (50, 150), reflecting an historical rate of 25% based on approximately 200 patients, and that for the corresponding probability using the experimental treatment modality in the trial, qPCR,E ~ beta(.25, .75), reflecting the same prior mean of 25% but with an effective sample size of 1 patient. That is, the prior qPCR,E on is non-informative. Since the binary PCR outcomes will be obtained based on tissue samples taken at surgery, PCR will be monitored continuously and the trial will be stopped for futility if Pr(qPCR,0 + .20 < qPCR,E | data) < .025. This translates into the following decision boundaries: The trial will be stopped for futility if [# patients with PCR]/[# patients evaluated] is less than or equal to 0/5, 1/10, 3/15, 4/20, or 6/25.

6.4. Safety Monitoring. Since neoadjuvant chemo-radiation is used as conventional treatment for esophageal cancer patients with more advanced disease but surgery alone is standard therapy for T1b stage esophageal cancer patients, the following adverse events (AEs) will be monitored to ensure a safe trial. The method of Thall, Simon and Estey (32) will be used. The historical rates of PreTox and PostDeath that will be used to construct monitoring rules are .30 for q1 = Prob(PreTox) and .026 for q2 = Prob(PostDeath), where the latter is computed as the weighted average .02*.70 + .04*.30 = .026 to reflect the prior experience using chemo-radiation that the PostDeath rates are 2% in patients who do not experience PreTox and 4% in patients who do experience PreTox. Indexing the four possible elementary AE outcomes by 1 = (No PreTox, No PostDeath), 2 = (PreTox, No PostDeath), 3 = (No PreTox, PostDeath), 4 = (PreTox, PostDeath), and their respective probabilities by w1, w2, w3, w4, it follows that q1 = w2 + w4 and q2 = w3 + w4. Indexing the experimental regimen (neoadjuvant chemo-radiation + surgery) by E and the historical standard experience by S, we assume a non-informative Dirichlet prior with parameters (.6818, .2922, .0182, .0078) for wE = (wE1, wE2, wE3, wE4) under E and corresponding informative Dirichlet standard historical prior with parameters (681.8, 292.2, 18.2, 7.8) for the corresponding historical probability vector wH. The marginal AE probabilities are qE1 = wE2 + wE4 and qE2 = wE3 + wE4 for E and similarly qS1 = wS2 + wS4 and qS,2 = wS3 + wS4 for S. The two early stopping rules are as follows. The trial will be stopped early

6.4.1 due to an excessively high PreTox rate if Prob(q1S < q1E | data) > .97, or

6.4.2 due to an excessively high PostDeath rate if Prob(q2S < q2E | data) > .95

These rules will be applied after each cohort of 5 patients has been treated and evaluated. The early stopping bounds determined by these probability criteria are as follows: Stop the trial due to an excessive PreTox rate if [# patients with PreTox]/[# patients scored] is greater than or equal to the upper bound 4/5, 7/10, 9/15, 11/20, 13/25. Stop the trial due to an excessive PostDeath rate if [# patients with PostDeath]/[# patients scored] is greater than or equal to the upper bound 2/5, 2/10, 3/15, 3/20, 3/25.

6.5 Simulation Study. Each case was simulated 1000 times, assuming an accrual rate of 6 patients per year (0.5 per month). The overall stopping probability under each scenario was computed as pSTOP = 1 – (1- $p_{STOP, T}$)*(1- $p_{STOP, TOX-DEATH}$) where $p_{STOP, T}$ = stopping probability due to the futility rule and $p_{STOP, TOX-DEATH}$ = stopping probability due to the two safety rules, assuming independence. Note that the only desirable scenario among the six scenarios considered is that where the true event probabilities are Pr(T >2 yrs) = .92, Prob(PreTox) = .30 and Prob(PostDeath) = .026.

		True Event Probabilities			
Description		Pr(T >2 yrs)	Prob(PreTox)	Prob(PostDeath)	P_{STOP}
No Improvement In DFS	Historical PreTox and Post Surgery Rates	.82	.30	.026	.61
No Improvement In DFS	Too Toxic		.50	.026	.83
No Improvement In DFS	High Post Surgery Death Rate		.30	.126	.86
Improvement In DFS	Historical PreTox and Post Surgery Rates	.92	.30	.026	.18
Improvement In DFS	Too Toxic		.50	.026	.64
Improvement In DFS	High Post Surgery Death Rate		.30	.126	.71

6.6 Data Analyses.

The rates of pathologic CR, PreTox and Postdeath will be tabulated and their possible relationships to baseline covariates assessed by logistic regression (32). Unadjusted progression free survival time will be estimated by the method of Kaplan and Meier (33) and its possible relationship to baseline covariates assessed by survival regression modeling (32).

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