**Phase II Trial of Pre-operative Bevacizumab and FOLFOX Chemotherapy in Locally Advanced Esophageal Cancer**


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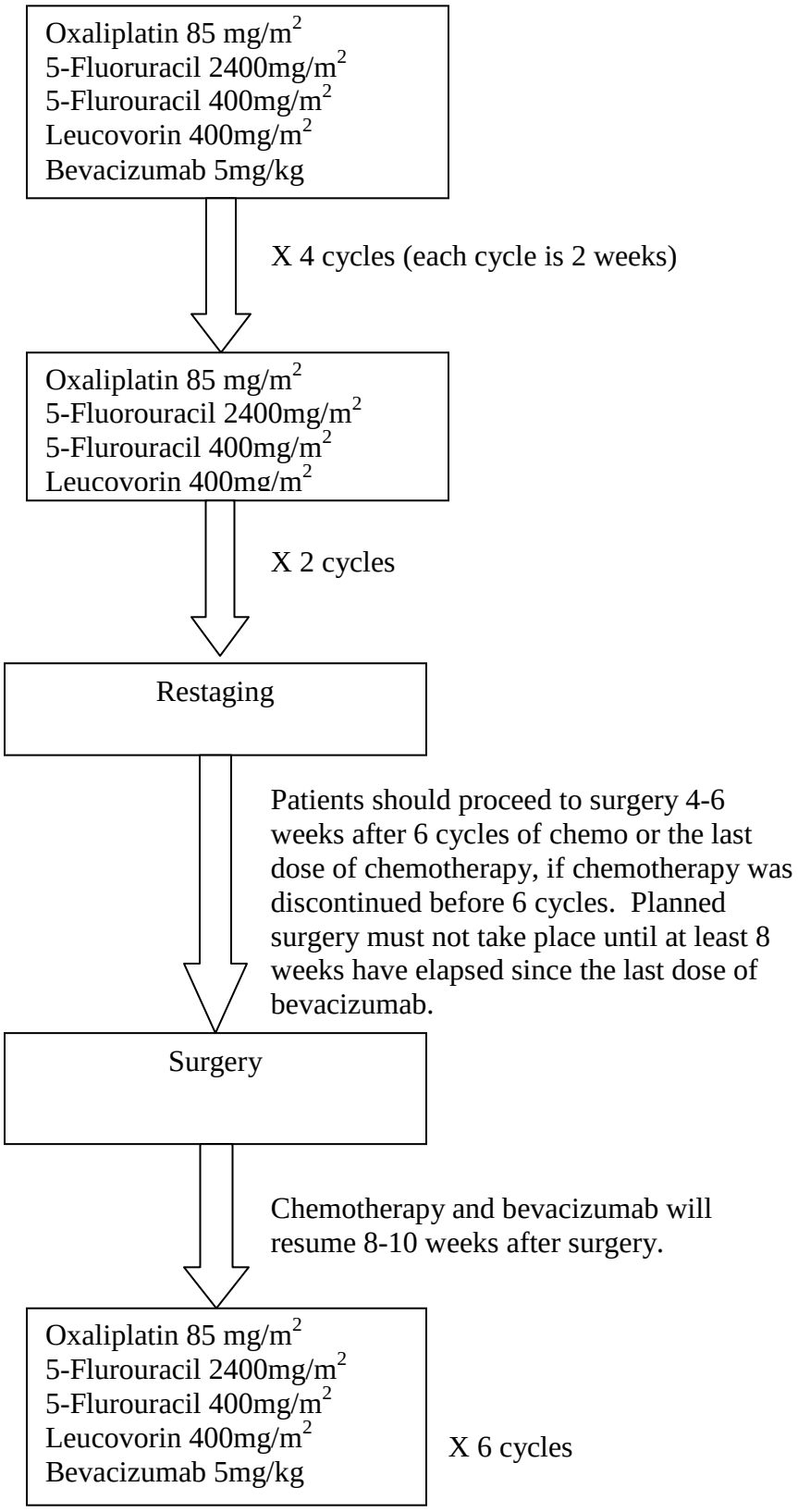





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# 1. INTRODUCTION

Cancer of the esophagus is uncommon, but lethal. The mortality rates are roughly equivalent to the incidence: 14,550 people with esophageal cancer are diagnosed in the United States each year with 13,770 deaths each year. There exists ample room for improvement over current treatment options. From the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program, the 5 year survival rate for all patients with esophageal cancer is 15 percent from 1995-2001. (1)

Surgery alone had been the standard treatment for early stage esophageal cancer. The Radiation Therapy Oncology Group studied chemoradiation verses chemotherapy in a phase III prospective randomized trial evaluating the efficacy of 5-fluorouracil and cisplatin plus 50Gy of radiation therapy compared to 64 Gy of radiation therapy alone. This was done with patients with adenocarcinoma or squamous cell carcinoma of the thoracic esophagus. 121 patients were randomized. The median survival was 8.9 months in the radiation treated patient compared to 12.5 months in the patients treated with chemotherapy and radiation. Statistically significant differences were observed in 12 month (50% vs. 33%) and 24 month (38 vs. 10%) survival ratios ($p<.001$). Concurrent therapy with cisplatin and 5 fluorouracil and radiation is superior to radiation therapy alone in patients with localized carcinoma of the esophagus. This became the standard of care for patients with inoperable disease, and the results were not notably different from those obtained in series of resectable patients. (2)

The evidence for effective radiosensitization and the ability to use a lower dose of radiotherapy raised the question of whether the pre-operative use of chemoradiation would downstage cancers to permit higher resection rates, greater success in local control with resection, and early treatment of micrometastatic disease. A series of phase II and small phase III studies have addressed this question.

A prospective randomized trial with 113 patients in Ireland was undertaken to evaluate preoperative concurrent chemoradiotherapy with surgery alone. Patients assigned to multimodality therapy received 2 courses of chemotherapy in weeks 1 & 6 (5-fluorouracil, 15mg/kg for five days, and cisplatin, 75 mg/m$^2$ on day 7) and a course of radiotherapy (40 Gy) over a 3 week period beginning with the first course of chemotherapy. The patient then had surgery. The other arm consisted of surgery with no preoperative therapy. At time of surgery, 23 out of 55 patients who had preoperative therapy (42%) had positive nodes or metastasis versus 45 of 55 (82%) for surgery alone ($p<.001$). Thirteen of 52 (25%) had a CR after chemoradiation. Median survival was longer for combined modality therapy 16 months vs. 11 months ($p=.01$). At 3 years, overall survival statistically favored the multimodality arm as compared to the surgery alone, 32% vs. 6% ($p=.01$) (5). This study has been criticized for the use of inadequate staging at baseline, a criticism that is the more to the point as survival in the surgery alone arm was markedly inferior to historical controls; however, other trials (6,7) have also supported or tended to support an advantage for preoperative chemoradiation for patients with Stage II-IVa squamous cell carcinoma or adenocarcinoma of the esophagus.

In CALGB 9781, a prospective randomized Intergroup trial of trimodality therapy versus surgery alone for the treatment of stages I-III esophageal cancer. Patients were


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randomized to surgery alone or cisplatin (100mg/$m^2$) and 5-FU (1000mg/$m^2$ x 4d) with concurrent radiation therapy followed by esophagectomy with lymph node dissection. Fifty-six of a planned 475 patients were randomized. The study was terminated because of the poor accrual; nonetheless, informative results regarding the primary endpoint of overall survival were obtained. Median survival was 4.5 years after trimodality therapy, vs. 1.8 years after surgery alone (p=.02). This randomized study demonstrated a long term survival advantage with the use of chemoradiation therapy followed by surgery in the treatment of esophageal cancer. Since this presentation, trimodality therapy has been accepted as a standard of care.

Local failure alone occurs in fewer than 10% of patients treated with trimodality therapy. The majority of patients who fail will do so at metastatic sites, and the interval development of metastatic disease is also an important cause of failure to achieve resection after neoadjuvant chemoradiation (8,9). One way to address distant metastatic recurrence is to add post-operative adjuvant therapy. A phase II trial evaluated cisplatin and 5FU combined with radiotherapy followed by esophagectomy. The objective of the trial was to determine complete pathologic response rate, survival rate, toxicity, pattern of failure and feasibility of administering adjuvant chemotherapy in patients with resectable cancer of the esophagus treated with preoperative chemoradiation. Eleven out of 29 patients enrolled on the trial achieved pathologic CR (pCR = 26%). The low pathologic CR rate may to some extent have been related to the high pre-therapy stage of patients enrolled in this study. Paclitaxel and cisplatin were given as adjuvant therapy. Of the 35 patients with potentially curative resections who were candidates for adjuvant chemotherapy, twenty-six (74%) received at least one course of paclitaxel and cisplatin, whereas 6 refused further treatment and 3 had inadequate Karnofsky performance status (60%) for further chemotherapy. Sixteen patients (62%) received 100% of the total paclitaxel dose, whereas 15 patients (58%) received 100% of the total cisplatin dose. Despite the high baseline stage of patients in this trial, and the relatively low pathologic CR rate, the 2 year survival was 62% (9). This provides some support that post-operative adjuvant therapy with a non cross resistant agent may reduce distant metastasis. The pattern of initial failure after this pre-operative approach in the study cited above and a prior study which had not included adjuvant therapy was reported with longer follow-up: local/regional alone in 6% (5 of 90), local/regional plus distant in 3% (3 of 90); distant metastases without locoregional recurrence were the initial manifestation of relapse in 47% (42 of 90) (10). The predominance of distant failure after aggressive pre-operative therapy indicates that further intensification of local therapy is unlikely to significantly improve long-term outcome for these patients, and that advances in the systemic therapy of esophagogastric therapy should be brought to bear early in the course in therapy of micrometastatic disease.

Radiation may preclude further intensification of systemic therapy. The use of perioperative regimens to surgery without radiation was examined in the MAGIC Trial. Cunningham et al assessed whether the addition of perioperative regimen of Epirubicin, Cisplatin, 5-FU (ECF) to surgery improves outcomes among patients with potentially curable gastric cancer. 503 patients were randomly assigned with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery or surgery alone. Chemotherapy consisted of 3 preoperative and 3 postoperative cycles of epirubicin, cisplatin, and fluorouracil. Primary



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end point was overall survival. The perioperative–chemotherapy group had a higher likelihood of survival (HR .75; 95% CI .6 to .93). 5 year survival favored the perioperative chemotherapy verses surgery 36 to 26% p=.09. It also favored progression free survival (HR .66, p<.001). With operable gastric or lower esophageal adenocarcinomas, the perioperative regimen of ECF decreased tumor size and stage and improved significantly progression free and overall survival (11).

The introduction of the platinoid oxaliplatin yields an active regimen in esophagogastric cancer, with somewhat less toxicity than the ECF combination. In a Phase I study, the safety and activity of radiotherapy with 5-fluorouracil, leucovorin, and oxaliplatin were assessed in 33 patients with inoperable esophageal cancer. Three cycles of oxaliplatin, 5-FU, and folinic acid with standard dose level oxaliplatin/5-FU starting on D1, D15, and D29 concomitant with 5 week's radiotherapy. An additional 3 cycles of standard FOLFOX4 were administered every 2 weeks after the end of radiotherapy. The ORR was 61% (3 CR, 14PR), median TTP 5 months (95% CI 3-6 mo) and the overall survival 9 months (95% CI 5-13 months).This showed that this regimen of oxaliplatin (85mg/m2) was well tolerated and active. (3)

Also, Mauer et al ran a phase II trial evaluating the efficacy and tolerability of FOLFOX in patients with advanced esophagus cancer. Thirty-five patients with recurrent or metastatic esophageal cancer enrolled. All were evaluated for toxicity and 34 were evaluable for response. The overall response rate was 40% (95% CI 24-57%). The overall survival was 7.1 months and th one year survival was 31%. The predominant toxicity was neutropenia, with 29% having grade 4 neutropenia. Cumulative peripheral neuropathy, grade 2 or 3, occurred in 26%. Thus, FOLFOX has favorable toxicity profile and anti tumor activity in patients with metastatic carcinoma of the esophagus (12).

In the REAL 2 trial Cunningham et al aimed to establish the use of the third generation platinum, oxaliplatin in substitution for cisplatin in advanced esophagogastric cancer. The trial objective was a non inferiority trial for survival with capecitabine compared to fluorouracil and oxaliplatin compared to cisplatin. 1002 patients were randomized in a 2x2 design. As seen in Table 1, oxaliplatin based therapy is non inferior to cisplatin based therapy (13).



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Table 1:

| OS results for Non-Inferiority (2x2 comparisons) and individual Regimens | | | |
|---|---|---|---|
| **2x2 comparisons Per Protocol** | **1 year OS (95% CI)** | **Median OS** | **HR (95% CI)** |
| **5FU: ECF + EOF** | 39.4% (35.0-43.7) | 9.6 mths | 1 |
| **Capecitabine: ECX + EOX** | 44.6% (40.1-49.0) | 10.9 mths | 0.86 (0.75-0.99)* |
| **Cisplatin: ECF + ECX** | 40.1% (35.7-44.4) | 10.1 mths | 1 |
| **Oxaliplatin: EOX + EOF** | 43.9% (39.4-48.4) | 10.4 mths | 0.92 (0.80-1.05)* |
| **Regimens ITT** | | | |
| **ECF n=263** | 37.7% (31.8-43.6) | 9.9 mths | 1 |
| **EOF n=245** | 40.4% (34.2-46.5) | 9.3 mths | 0.95 (0.79-1.15) |
| **ECX n=250** | 40.8% (34.7-46.9) | 9.9 mths | 0.92 (0.76-1.11) |
| **EOX n=244** | 46.8% (40.4-52.9) | 11.2 mths | 0.80 (0.65-0.97) ‡ |

* The Upper limit of the 95% CI excludes 1.23 we can therefore conclude non-inferiority ‡ p=0.025 comparison with ECF
There were no significant differences in response rates comparing ECF to, EOF, ECX and EOX (41%, 42%, 46%, and 48% respectively); grade 3-4 non haematological toxicity 36%, 42%, 33% and 45%; and grade 3-4 neutropaenia 42%, 30% (p=0.008), 51% (p=0.043) and 28% (p=0.001) respectively.

Alterations in neoadjuvant chemoradiation regimens have had only a modest impact on survival, but the advent of novel therapies may permit more than incremental improvement. Bevacizumab, a monoclonal antibody to VEGF, may be one such agent. Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (14).

Bevacizumab improves survival or disease-free survival in several other solid tumor malignancies, including lung cancer (15). In colorectal cancer ECOG 3200, 829 metastatic colorectal patients previously treated with a fluoropyrimidine and irinotecan assigned to one of three treatment groups. The primary end point was overall survival. Median survival treated with FOLFOX4 and bevacizumab was 12.9 months compare to 10.8 months treated with FOLFOX4 alone (HR =.75; p=.0011) and 10.2 months for bevacizumab alone. The median progression free survival for FOLFOX4 with



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bevacizumab was 7.3 months compared to 4.7 months (p<.001). The overall response rates for FOLFOX4 with bevacizumab was 22.7% and 8.6% with FOLFOX4 alone (p<.0001) (16).

The addition of bevacizumab to combination irinotecan/cisplatin chemotherapy has been evaluated in 47 patients with metastatic or unresectable esophagogastric cancer. The study aimed to demonstrate a 50% improvement in time to progression over historical values. Median time to progression was 8.3 months (95% CI 5.5 to 9.9 months). The overall response rate was 65 % (95% CI 5.5 to 9.9 months). Median survival was 12.3 months (95 % CI 11.3 to 17.2 months). The addition of bevacizumab did not increase the rate of hematologic toxicity compared with prior experience. The most common non-hematologic toxicities were fatigue and diarrhea. Thromboembolism was detected in 28% of the patients and 6% experienced perforation of the gastrointestinal tract, which occurred at the primary tumor site. The study demonstrated a striking 75% improvement in time to progression, a longer than expected overall survival, and no increase in chemotherapy side effects, although the rates of thrombotic events and bowel perforation may have been greater than with chemotherapy alone (17).

The present study aims to introduce bevacizumab into the peri-operative chemotherapy-based management of esophagogastric cancer, utilizing FOLFOX to reduce toxicity. Radiotherapy will not be included, as it was not in MAGIC, as the principal barrier to cure in these patients is distant dissemination. The study will be closely monitored for the overall disease-free survival rate.

## 2.0 OBJECTIVES

2.1 Primary: To investigate two-year disease-free survival in patients with resectable esophageal and GE junction cancer treated with perioperative bevacizumab and FOLFOX.

2.2 Secondary: To assess, by pathological examination after surgical resection, complete and partial response to neoadjuvant therapy. To characterize overall and progression free survival.

2.3 Secondary: To compare baseline and post-chemotherapy/bevacizumab tissues for biomarkers predicting response or resistance to this approach.

2.4 Secondary: To investigate safety in this setting.



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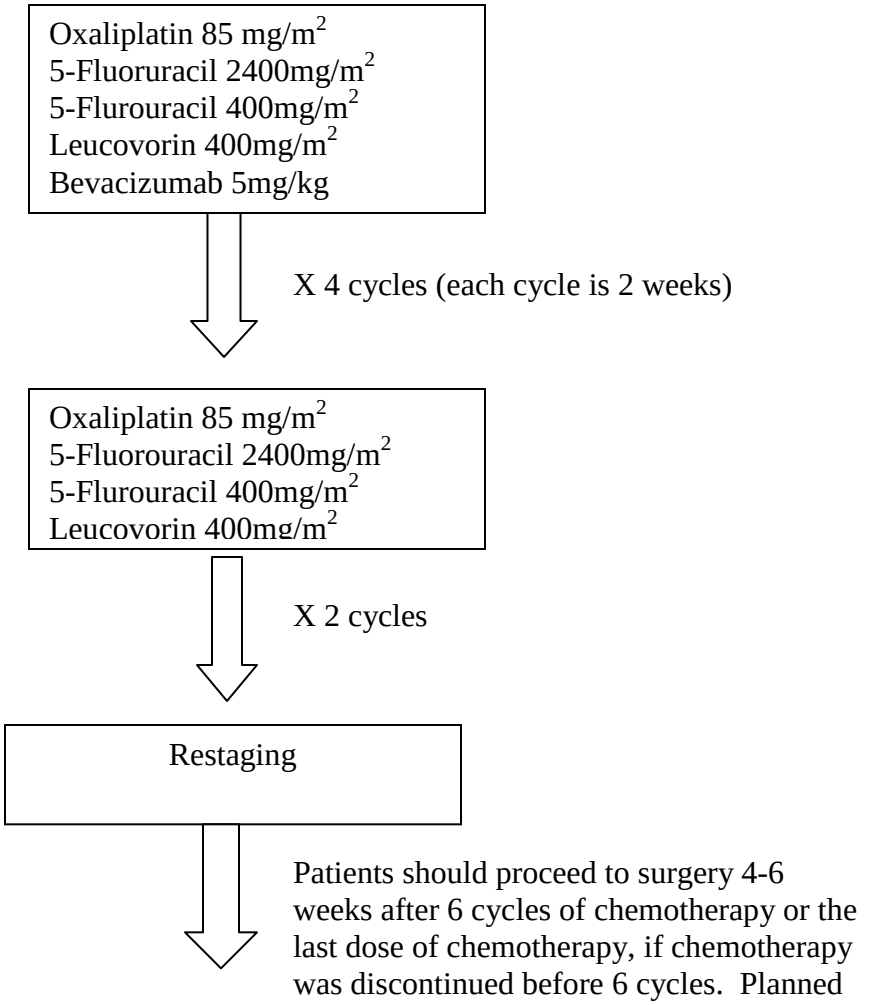
# 3.0 INVESTIGATIONAL PLAN

## 3.1 Summary of Study Design

3.1.1 This is a pilot, open-label, non-randomized, phase II study for patients with locally advanced esophageal or proximal gastric cancer. Patients must not have received prior surgery or radiation therapy. Patients must not have received prior chemotherapy. The study will be open to FCCC and the University of Pittsburgh investigators.

3.1.2 All eligible patients will receive FOLFOX with bevacizumab every 2 weeks (oxaliplatin 85mg/$m^2$, 5-fluorouracil 2400mg/$m^2$ , 5-fluorouracil 400mg/$m^2$, leucovorin 400 mg/$m^2$, and bevacizumab 5mg/kg) x 4 doses, then FOLFOX at the same doses q 2 weeks x 2. Patients will then undergo restaging, if there is no interval development of metastatic disease, the patient will be taken to resection. Patients will then complete the regimen with 6 cycles of FOLFOX plus bevacizumab.

## 3.2 Illustration of Study Design





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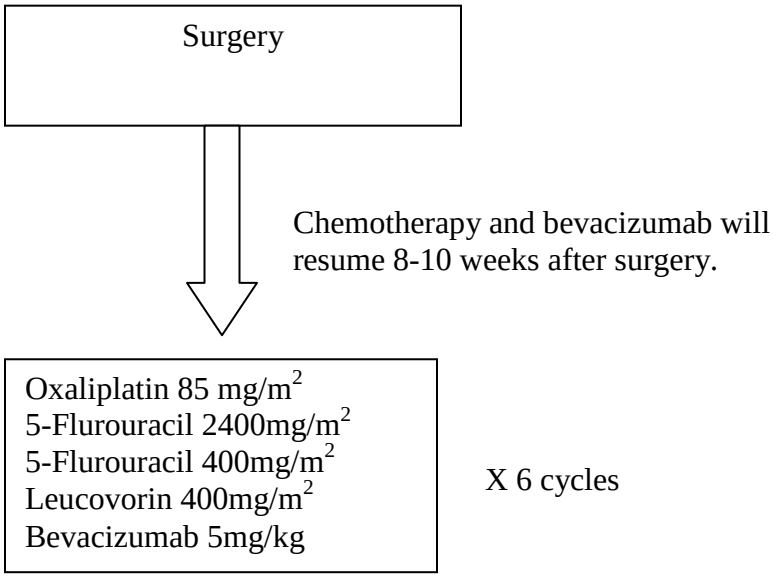
surgery must not take place until at least 8 weeks have elapsed since the last dose of bevacizumab.




## 4.0 SAFETY PLAN

4.1 A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria and routine monitoring as follows:

4.1.1 Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements (as per sections 4.1.2 and 8.0). Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see section 5.3).

4.1.2 Specific monitoring procedures are as follows:

4.1.2.1 Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.



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4.1.2.2 Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick as per guidelines in Section 8.0.

4.1.2.3 Bevacizumab should be held for 8 weeks prior to elective surgery, including the curative intent esophagectomies planned in the management of patients enrolled in this trial. In the event of emergent surgery it will be at the physician's discretion to determine risk of time since the last dose of bevacizumab and benefit of needed surgery. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 8-10 weeks after that procedure.

## 5.0 SELECTION CRITERIA

### 5.1 Eligibility Criteria

5.1.1 Patients must have biopsy proven adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma of the esophagus, GE junction and/or gastric cardia.

5.1.2 Patients must have potentially resectable disease by the thoracic, minimally invasive or transhiatal approach.

5.1.2.1 No portion of the lesion may be within 5 cm of the cricopharyngeus
5.1.2.2 Patient must be considered medically fit for surgery with average or below average risk.
5.1.2.3 T1-3 or T4 with local invasion confined to diaphragm, pleura or pericardium
5.1.2.4 –No myocardial infarction within 12 months of enrollment.

5.1.3 Patients must be $\geq$ 18 years of age.

5.1.4 Patients must have ECOG performance status 0 or 1.

5.1.5 Patients must have WBC $\geq$ 3,500/mm$^3$, platelet count $\geq$ 100,000/mm$^3$.

5.1.6 Patients must have serum creatinine (Cr) $\leq$ 1.5 mg and/or creatinine clearance $\geq$ 60cc/min.

5.1.7 Bilirubin must be < ULN unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome due to slow conjugation of bilirubin. Alkaline phosphatase must be <ULN. AST & ALT must be <ULN.



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5.1.8 Urine protein/creatinine (UPC) ratio of < 1.0 or dipstick for protein of < 2+, Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4) grade < 2. Patients with a UPC ratio ≥ 1.0 or dipstick of 2+ must undergo a 24-hour urine collection and must demonstrate < 1 gm of protein in order to participate.

5.1.9 Patients must give written informed consent and HIPAA consent

5.2 Ineligibility Criteria

5.2.1 Patients with prior chemotherapy for any malignant disorder, thoracic radiotherapy or prior surgical resection of an esophageal tumor are ineligible.

5.2.2 Patients with biopsy-proven invasion of the tracheobronchial tree or tracheo-esophageal fistula are ineligible.

5.2.3 Patients with a history of a curatively treated malignancy must be disease-free for at least two years and have a survival prognosis that is greater than five years.

5.2.4 Eligible patients of reproductive potential (both sexes) must agree to use an accepted and effective method of contraceptive during study therapy and for at least 6 months after the completion of bevacizumab. Women must not be pregnant or breast-feeding because the study drugs administered may cause harm to an unborn fetus or breastfeeding child. All females of childbearing potential must have a serum pregnancy test to rule out pregnancy within 7 days prior to registration. See further details in section 5.5.

5.2.5 Patients with a history of hypertension must measure <150/90 mmHg and be on a stable regimen of anti-hypertensive therapy. Patients with a history of hypertension who have a blood pressure of 150/90 mmHg, or greater are not eligible. Patients with a history of hypertension who have a blood pressure of < 150/90 mmHg but are not on a stable regimen of anti-hypertensive therapy, are not eligible.

5.2.6 Any prior history of hypertensive crisis or hypertensive encephalopathy.

5.2.7 New York Association (NYHA) Grade II or greater congestive heart failure.

5.2.8 Patients must not have a serious or non-healing wound, skin ulcers or unhealed bone fracture, or known HIV infection.

5.2.9 Patients with ≥ grade 2 neuropathy are not eligible.



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5.2.10 Patients must not have had significant traumatic injury within 28 days prior to randomization.

5.2.11 Patients with PT (INR) > 1.5 are not eligible. The patient may not be receiving full-dose anticoagulation. Prophylactic or full dose anticoagulation are permitted post-resection or for treatment of an intercurrent thrombotic event.

5.2.12 Patients with non-malignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude any of the study therapy drugs are not eligible. Specifically excluded are the following conditions: current symptomatic arrhythmia, symptomatic peripheral vascular disease.

5.2.13 Patients with a history of the following within 12 months of study entry are not eligible: arterial thromboembolic events, unstable angina.

5.2.14 Any history of stroke or transient ischemic attack.

5.2.15 Significant vascular disease (i.e. aortic dissection, aortic aneurysm).

5.2.16 Patients with psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude them from meeting the study requirements are not eligible.

5.2.17 Distant metastases.

5.2.18 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment.

5.2.19 Known hypersensitivity to any component of bevacizumab.

5.3 Discontinuation of Patients

5.3.1 Treatment will be discontinued for any of the following reasons

5.3.1.1 Disease progression

5.3.1.2 Administration of radiotherapy, non-protocol chemotherapy, or biological therapy.

5.3.1.3 In the Neo-adjuvant setting, excessive toxicity that requires > 2 dose reductions of <u>all</u> study treatment should not be retreated in the pre-op setting. If the investigator desires to keep the patient on study for surgery and projected post-operative therapy, this must be discussed with the PI. (Section 7.1)



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5.3.1.3 Severe co-morbidities that preclude continuation of study therapy.

5.3.1.4 Non-compliance that compromises safety of therapy.

5.3.1.5 Patient choice.

5.3.1.6 Investigator discretion (if continued treatment is no longer in the best interest of the patient).

5.3.1.7 Study closure.

5.3.1.8 Patient lost to follow up. If the patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome. All efforts to contact the patient must be clearly documented.

5.3.1.9 Clinical or symptomatic deterioration.

5.3.1.10 Patient becomes pregnant

5.3.1.11 Inability of subject to comply with study requirements.

5.3.1.12 Determination by the investigator that it is no longer safe for the subject to continue therapy.

Subjects who meet the following criteria should be discontinued from study treatment:

- Grade 4 hypertension or Grade 3 hypertension not controlled with medication
- Nephrotic syndrome
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
- Symptomatic Grade 4 venous thromboembolic event
- Any grade arterial thromboembolic event
- Grade 4 congestive heart failure
- Perforation of the large bowel
- Tracheoesophageal fistula (any grade) or Grade 4 fistula
- Unwillingness or inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- All Grade 4 events thought to be related to bevacizumab by the investigator



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Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will be followed for toxicity until resolution of the event or until the event is considered irreversible

5.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study

5.5 Pregnancy

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

The effects of this treatment on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have a negative pregnancy test within 7 days of registration prior to receiving the first dose of the investigational agent(s). If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

5.6 Baseline Pretreatment Studies

Within 21 days prior to registration:

Endoscopic esophageal ultrasound
CT scan chest
CT scan abdomen/pelvis
PET Scan



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PFTs/DLCO
Medical oncology evaluation
Surgical evaluation
Biopsies

Within 7 days prior to registration

CBC, diff, platelets
U/A
PT, PTT, INR
Comprehensive metabolic panel
UPC ratio or dipstick for protein
Serum pregnancy test

# 6 TREATMENT PLAN

## 6.1 Registration Procedures

Eligible patients will be entered on study centrally by the Fox Chase Cancer Center Office Quality Assurance (QA) Coordinator or their designee. Following registration, patients must begin protocol treatment within 7 days of registration. Issues that would cause treatment delays must be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's will be considered a screen failure or participant withdraw and will be replaced. The QA Coordinator must be notified of cancellations as soon as possible.

Participants may be registered from 9:00 am to 5:00 pm by calling the QA Coordinator at 215-728-4770. The investigator or designee will then fax the completed registration form, informed consent and HIPAA signature pages, and eligibility checklist to 215-214-1511. The QA Coordinator will notify the site when registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number assigned by the QA Coordinator prior to the initiation of treatment. The following forms must be completed at the time of registration:

- Signed and dated informed consent form
- Signed and dated HIPAA consent form
- Registration form
- Signed eligibility checklist

Exceptions to the current registration policies will not be permitted as well as:

- Late registrations (after initiation of treatment)
- Exceptions to eligibility requirements
- Participation by an institution/member not identified as eligible
- Non-Compliance with regulatory paperwork



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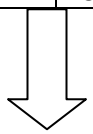
6.2 Administration Schedule - Dose calculations are based on actual body weight at the beginning of each cycle. One cycle is two treatment days every 2 weeks. Drugs are administered in the order listed in the table below.

**Phase I – Neoadjuvant therapy**

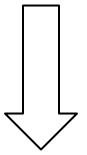
***Neoadjuvant Chemotherapy q 2 weeks x 4 Cycles**

| **Agent** | **Dose** | **Route** | **Treatment Administration** |
|---|---|---|---|
| Bevacizumab | 5 mg/kg | IV infusion over 90 minutes | Day 1 |
| Oxaliplatin | 85 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| Leucovorin | 400 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| 5 –FU | 400 mg/m$^2$ | IV bolus injection immediately following leucovorin | Day 1 |
| 5-FU | 2.4 gm/m$^2$ | IV continuous infusion over 46 hours immediately following bolus 5-FU | Days 1 and 2 |



***Neoadjuvant Chemotherapy q 2 weeks x 2 cycles (NOTE: Given after 4 Cycles of FOLFOX + Bevacizumab)**

| **Agent** | **Dose** | **Route** | **Treatment Administration** |
|---|---|---|---|
| Oxaliplatin | 85 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| Leucovorin | 400 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| 5 –FU | 400 mg/m$^2$ | IV bolus injection immediately following leucovorin | Day 1 |
| 5-FU | 2.4 gm/m$^2$ | IV continuous infusion over 46 hours immediately following bolus 5-FU | Days 1 and 2 |



**Restaging**

Patients should proceed to surgery 4-6 weeks after 6 cycles of chemotherapy or the last dose of chemotherapy, if chemotherapy was discontinued before 6 cycles.



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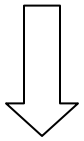
Planned surgery must not take place until at least 8 weeks have elapsed since the last dose of bevacizumab

**Surgery**



**Phase II – Adjuvant therapy 8 to 10 weeks after surgery**
***Adjuvant Chemotherapy q 2 weeks x 6 cycles**

| **Agent** | **Dose** | **Route** | **Treatment Administration** |
|---|---|---|---|
| Bevacizumab | 5 mg/kg | IV infusion over 90 minutes (see below) | Day 1 |
| Oxaliplatin | 85 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| Leucovorin | 400 mg/m$^2$ | IV infusion over 2 hours | Day 1 |
| 5 –FU | 400 mg/m$^2$ | IV bolus injection immediately following leucovorin | Day 1 |
| 5-FU | 2.4 gm/m$^2$ | IV continuous infusion over 46 hours immediately following bolus 5-FU | Days 1 and 2 |

6.3 Initial bevacizumab doses must be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 30 minutes. Again, if no adverse reactions occur, the third and subsequent doses may be administered according to institutional practice. Infusions should be run in via a volumetric infusion device. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated.

6.4 Oxaliplatin and leucovorin can be administered simultaneously using Y-line tubing provided that the leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline.

6.4.1 Supportive Care: Magnesium Sulfate 8 milliequivalent (meq) and Calcium gluconate 10 meq. Infuse at a rate and volume of solution according to your institution standards pre and post oxaliplatin



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6.5 All patients will be premedicated with Dexamethasone 10mg IV and antiemetic therapy using for example, Palonosetron .025mg IV prior to each infusion

6.6 Correlative Studies

Tissue will be collected at baseline during baseline UGI/endoscopy prior to the start of chemotherapy/Bevacizumab and at surgery. Post-treatment samples for biomarker analysis will be performed on FFPE tissue after diagnostic evaluation is completed. The research studies must not deplete diagnostic tissue so that future clinical tests would not be possible when residual disease is minimal; however, assays would be of low yield when only isolated tumor cells remain

6.6.1 Tissue will be studied for ICAM, VEGFR2 tumoral expression and ERCC1 by AQUA (18) technology at the Fox Chase Cancer Center Biosample Repository. Additional tissue-based biomarkers may be performed in the future as the state of knowledge evolves.

6.6.2 Pathology materials should be sent to:

R. Katherine Alpaugh PhD
Fox Chase Cancer Center
Protocol Support Laboratory
333 Cottman Avenue P2011
Philadelphia, PA 19111
Telephone 215 214-1634
FAX 215 214-1635
e-mail RK_Alpaugh@fccc.edu

6.6.3 Banking of Tissue

Remaining tissue will be banked in the Fox Chase Cancer Center Biosample Repository for future assessment.

Additional instructions are provided in the "Procedure for Tissue Specimen" (located in each patient case report form binder) for collection, processing and shipping blood specimens.

# 7 DOSE MODIFICATIONS

7.1 All toxicities must be graded according to the CTCAE v 4.0**.** According to the following tables, the final dose modification must be based upon the worst grade of toxicity experienced. If patients require dose reductions lower than level -2, the drug to which the adverse event is attributed will be discontinued. The remaining drugs may be continued per the protocol schema. Leucovorin and oxaliplatin must not be continued after the discontinuation of 5-fluorouracil, but 5-fluorouracil may be continued without oxaliplatin or bevacizumab and 5-fluorouracil and oxaliplatin may be continued without bevacizumab. Any dose reduction is continued for all subsequent cycles in the pre- or post-operative phase; therefore, dose re-escalation in the same



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phase of treatment is not allowed following a dose reduction. Oxaliplatin may be reintroduced at full dose post-operatively if neuropathy has resolved. Bevacizumab may be reintroduced at full dose post-operatively unless adverse event Action to be Taken column of the neo-adjuvant Dose Modification for Bevacizumab table requires permanent discontinuation. (Please see below for specific dose modifications). Missed doses will not be made up.

7.2 Dose Modifications for oxaliplatin and 5-FU Toxicity

7.2.1 There are no dose reductions for leucovorin. The dose remains fixed at 400 mg/m2. Leucovorin is discontinued only when 5-FU is discontinued.

7.2.2 Patients who require discontinuation of oxaliplatin may continue to receive 5-FU/leucovorin and bevacizumab.

7.2.3 Patients who discontinue both 5-FU and oxaliplatin may continue to receive bevacizumab, provided patient experiences no bevacizumab-related toxicities after surgery. However if patients discontinue both 5-FU and oxaliplatin during the preoperative period, surgery will be scheduled for approximately 8 weeks from the most recent dose of bevacizumab.

**Dose Levels of Oxaliplatin, 5-FU, Bevacizumab**

| | **Starting Dose*** | **Dose Level - 1** | **Dose Level - 2** |
|---|---|---|---|
| Oxaliplatin | 85 mg/m² | 65 mg/m² | 50 mg/m² |
| 5-FU Bolus | 400 mg/m² | 320 mg/m² | 200 mg/m² |
| 5-FU Infusion | 2.4gm/m² | 2 gm/m² | 1.6 gm/m² |
| Bevacizumab | 5mg/kg | - | - |

* All patients will start cycle 1 with doses listed in “Starting Dose” column.

7.3 Non-Neurologic Toxicity (Oxaliplatin and 5-FU Toxicity)

The following table describes the recommended dose modifications at the start of each subsequent cycle of therapy. All dose modifications must be based on the worst preceding toxicity.



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***NOTE: Neoadjuvant & Adjuvant Dose Modifications**

| **Toxicity NCI Grade (Value)** | **Worst interval toxicity** | **Day of treatment** |
|---|---|---|
| No toxicity | Maintain dose level | Maintain dose level |
| **Neutropenia (ANC)** | | |
| Grade 1 (ANC < LLN - 1500/mm³) | Maintain dose level | If ANC < 1000 on day of treatment, hold and check weekly until > 1000mm$^3$. Filgrastim may be utilized. PEG-filgrastim may be utilized in subsequent cycles. Then treat based on interval toxicity. If ANC < 1000 after 2 weeks, discontinue. |
| Grade 2 (ANC <1499 - 1000/mm³) | Maintain dose level | |
| Grade 3 (ANC <999 - 500/mm³) | Maintain dose level | |
| Grade 4 (ANC < 500/mm³) | Reduce 5-FU and oxaliplatin 1 dose level | |
| **Thrombocytopenia** | | If PLT < 75,000 on day of treatment, hold and check weekly until > 75,000 mm$^3$. Then treat based on interval toxicity. If PLT < 75,000 after 2 weeks, discontinue. |
| Grade 1 (PLT < LLN - 75,000/mm$^3$) | Maintain dose level | |
| Grade 2 (PLT 74,999 – 50,000/mm$^3$) | Maintain dose level | |
| Grade 3 (PLT 49,999 – 25,000/mm$^3$) | Reduce 5-FU and oxaliplatin 1 dose level | |
| Grade 4 (PLT< 25,000/mm$^3$) | Reduce 5-FU and oxaliplatin 2 dose levels | |
| Other hematologic toxicities do not require dose modification; however red blood cell transfusion should be strongly considered for hemoglobin <8 g/dl. | | |


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| Toxicity NCI Grade (Value) | Worst interval toxicity | Day of treatment |
|---|---|---|
| **Other nonhematologic toxicities (except neurologic)*,** | | |
| Grade 1 | Maintain dose level | Maintain dose level |
| Grade 2 | Maintain dose level | Hold until resolved to grade ≤1. Maintain dose level |
| Grade 3 | Reduce 5-FU and/or oxaliplatin 1 dose level** | Hold until resolved to grade ≤1. Reduce 5-FU or oxaliplatin 1 dose level |
| Grade 4 | Reduce 5-FU and/or oxaliplatin 1 dose level** | Hold until resolved to grade ≤1. Reduce 5-FU or oxaliplatin 1 dose level |

*****Exceptions: alopecia, anorexia, nausea/vomiting if can be controlled by antiemetics
**Reduce only the drug associated with the toxicity. May dose reduce both drugs if toxicity may be related to both drugs.

Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP): The hemolytic uremic syndrome should be suspected in individuals who experience unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serum creatinine.

Patients suspected of experiencing HUS or demonstrating symptoms of TTP should have the following laboratory analyses conducted: creatinine, BUN, urinalysis with microscopic evaluation, CBC with differential and platelets, PT/PTT, Fibrinogen, Fibrinogen Degradation Products (FDP), Antithrombin III (ATIII), von Wildebrand Factor (VWF), anti-nuclear antibodies (ANA), rheumatoid factor (RhF), C3, C4, CH50, anti-platelet antibodies, platelet associated IgG, circulating immune complexes.

Oxaliplatin and 5-fluorouracil should be discontinued for HUS or TTP.
With any suspicion of veno-occlusive disease (VOD) of the liver (hyperbilirubinemia, ascites, unexplained weight gain, hepatomegaly, splenomegaly, esophageal varices or other sign of portal hypertension), chemotherapy must be held. If VOD is diagnosed clinically, chemotherapy must be discontinued.


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## 7.4 Dose Modifications of Oxaliplatin for Toxicity

***NOTE: Neoadjuvant & Adjuvant Dose Modifications**

| **Neurologic Toxicity**[a] | | |
|---|---|---|
| **Paresthesias/Dysesthesias** | **1-7 day duration** | **> 7 day duration** |
| **Grade 1** – Paresthesias/dysesthesias that resolve and do not interfere with function | Maintain dose | Maintain dose |
| **Grade 2** – Paresthesias/dysesthesias interfering with function, but not activities of daily living | Maintain dose[b] | Decrease oxaliplatin one dose level[b] |
| **Grade 3** – Paresthesias/dysesthesias with pain or with functional impairment that also interfere with activities of daily living | First episode: Decrease only oxaliplatin one dose level[b]<br>Second episode: Stop oxaliplatin only | Stop oxaliplatin only |
| **+Grade 4** - Persistent paresthesias/dysesthesias that are disabling or life-threatening | Stop oxaliplatin only | Stop oxaliplatin only |
| **Laryngeal Dysesthesias** (Grading at physician's discretion) | | |
| **Grade 1** – Mild<br>**Grade 2** – Moderate | Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours | Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours |
| **Grade 3** - Severe | At physician's discretion, either stop oxaliplatin or increase duration of infusion to 6 hours | Stop oxaliplatin only |
| **Pulmonary Toxicity** | | |
| Dyspnea ≥ grade 2<br>Hypoxia ≥ grade 2<br>Pneumonitis/pulmonary infiltrates ≥ grade 2<br>Pulmonary fibrosis ≥ grade 2<br>Cough ≥ grade 3 | Hold all therapy until interstitial lung disease and pulmonary embolism are ruled out.<br>• If non-infectious interstitial lung disease is confirmed, oxaliplatin must be discontinued.<br>• If non-infectious interstitial disease is ruled out and infection (if any) has resolved, patients with persistent Grade 2 dyspnea/hypoxia or grade 3 cough can resume treatment at the physician's discretion. All others do not resume treatment with oxaliplatin. | |

**a** These toxicity descriptions should be used to determine dose modifications and delays. Use the CTCAE v4.0 to assess neurologic toxicity for adverse event reporting.
**b** Hold oxaliplatin for ≥ grade 2 neurotoxicity. When ≤ grade 1, resume treatment with dose modifications.


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If > grade 1 toxicity persists after 4 weeks' hold, discontinue oxaliplatin. Continue 5-FU + LV and bevacizumab) while oxaliplatin is held.

7.5 Dose Modifications for Bevacizumab

7.5.1 If AEs occur that require holding the bevacizumab dose, the dose will remain 5mg/kg when treatment resumes.

7.5.2 If 5-FU/LV and/or oxaliplatin are held due to chemotherapy-related AEs, bevacizumab should be continued unless the patient's medical condition precludes this, adjuvantly. If the 5-FU/LV and oxaliplatin is held prior to surgery, bevacizumab will not be continued and the patient will proceed to resection at 8 weeks following the most recent dose of bevacizumab.

If bevacizumab is held or must be discontinued before completion of chemotherapy, 5-FU/LV and oxaliplatin should be continued.

***NOTE: Neo-Adjuvant Dose Modifications for Bevacizumab**

| **Adverse Event** | **Grade CTCAE v4.0** | **Action to be Taken** |
|---|---|---|
| **Acute infusion reaction e.g., fever, chills, headache, nausea (see Syndrome-Cytokine reaction) or Allergic reaction/hypersensitivity (e.g., fever, rash, urticaria, bronchospasm)** | 1, 2 or 3 | If infusion-related or allergic reactions occur, pre-meds should be given with the next dose, but the infusion time may not be reduced for the subsequent infusion. If the next dose is well-tolerated with pre-meds, the subsequent infusion time may be reduced by 30 ± 10 min. as long as pre-meds continue to be used. If infusion-related AEs occur with the 60-min. infusion, all subsequent doses should be given over 90 ± 15 min. (with pre-meds). If infusion-related AEs occur with the 30-min. infusion, all subsequent doses should be given over 60 ± 10 min. (with pre-meds).<br><br>For patients with grade 3 reactions, the bevacizumab infusion must be stopped and not re-started on that day. At the physician's discretion, bevacizumab may be permanently discontinued or reinstituted with pre-medications and at a rate of 90 ± 15 minutes. If the reaction occurred at the 90-minute rate, initially challenge at a slower infusion rate and gradually increase to 90 minutes. When bevacizumab is re-instituted, the patient should be monitored, per physician's usual practice, for a duration comparable to duration of reaction |
| | 4 | Permanently discontinue bevacizumab. |



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| Adverse Event | Grade CTCAE v4.0 | Action to be Taken |
|---|---|---|
| **Hemorrhage**[a] | 3 | Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab.<br>All other subjects will have bevacizumab held until all of the following criteria are met:<br>• The bleeding has resolved and hemoglobin is stable.<br>• There is no bleeding diathesis that would increase the risk of therapy.<br>• Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.<br>For hemorrhage from tumor site, stop neoadjuvant bevacizumab. Bevacizumab may be resumed in the adjuvant phase. |
| | 4 | Discontinue bevacizumab.<br>For hemorrhage from tumor site, stop neoadjuvant bevacizumab. Bevacizumab may be resumed in the adjuvant phase. |
| **Thrombosis/thrombus/ embolism-venous (including vascular access device)** | 2 or 3 | Hold bevacizumab until resolution by clinical assessment or Doppler.<br>• If the planned duration of full-dose anticoagulation is < 2 weeks, hold bevacizumab until anticoagulation is complete.<br>• If the planned duration of full-dose anticoag is ≥ 2 weeks, bevacizumab may be resumed during anticoag if no grade 3 or 4 hemorrhage event occurred while on therapy<br>- If unfractionated heparin, PTT must be in therapeutic range.<br>Discontinue bevacizumab if thromboembolic events worsen or recur after resuming therapy<br>***Pre-operative setting, low molecular weight heparin will be used only, no coumadin** |
| | 4 | Permanently discontinue bevacizumab. |
| **Visceral or peripheral arterial ischemia** | 2 [b,c], 3 or 4 | Permanently discontinue bevacizumab. |
| **Cardiac ischemia/infarction** | 2 [b], 3 or 4 | Permanently discontinue bevacizumab. |
| **CNS ischemia** | 2 [b], 3 or 4 | Permanently discontinue bevacizumab. |
| **Reversible Posterior Leukoencephalopathy** | Any grade (confirmed by MRI) | Discontinue bevacizumab. |



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| Adverse Event | Grade CTCAE v4.0 | Action to be Taken |
|---|---|---|
| **GI perforation including GI leak and GI fistula** | ≥1 | Permanently discontinue bevacizumab. |
| **Intra-abdominal abscess[d]** | ≥1 | Hold Neoadjuvant therapy. Resection can be undertaken when medically safe, and no sooner than 4 weeks following the most recent dose of bevacizumab. |
| **Complication, non-infectious wound dehiscence[e]** | 1 | Hold bevacizumab for at least 1 month. If, in the physician's opinion, substantial healing has taken place within 1-3 months, bevacizumab may be resumed. If wound dehiscence recurs, permanently discontinue bevacizumab. |
| | 2, 3, or 4 | Permanently discontinue bevacizumab. |
| **Proteinuria** | UPC ratio ≤ 3.5 or dipstick 1+ | Continue bevacizumab. |
| | UPC ratio > 3.5 or dipstick > 2+ | Hold bevacizumab until it UPC recovers to ≤ 3.5 or dipstick is ≤ 2+.<br>If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab. |
| | Nephrotic Syndrome or dipstick ≥ 3+ | Discontinue bevacizumab. |
| **Hypertension** | 3 | Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician discretion. Bevacizumab mus be held for uncontrolled or symptomatic hypertension present on the day that the bevacizumab dose is to be given. If BP is not controlled with medication within 1 month, permanently discontinue bevacizumab. |
| | 4 | Permanently discontinue bevacizumab. |
| **Other clinically significant (AEs)[f]** | 3 | Hold until AE has resolved to ≤ grade 1. |
| | 4 | Permanently discontinue bevacizumab. |

**a** If coagulation disorders develop, secondary to other medical conditions, hold bevacizumab until the PT INR and PTT return to ≤ grade 1.
**b** New or worsening grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline that have not worsened.)
**c** Patients who develop brief, reversible, exercise-induced claudication (grade 2) not attributable to arterial thromboembolic events may continue on study.
**d** Refer to grading criteria listed for the appropriate adverse event in the Infection section of the CTCAE v 4.0.
**e** Refer to Injury, Poisoning, Procedural Complications section of the CTCAE v 4.0.
**f** Determination of "clinically significant" is at the physician's discretion and applies to those adverse events that can be attributed to bevacizumab and are not related to chemotherapy.


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***NOTE: Adjuvant Dose Modifications for Bevacizumab**

| Adverse Event | Grade CTCAE v4.0 | Action to be Taken |
|---|---|---|
| **Acute infusion reaction e.g., fever, chills, headache, nausea (see Syndrome-Cytokine reaction) or Allergic reaction/hypersensitivity (e.g., fever, rash, urticaria, bronchospasm)** | 1, 2 or 3 | If infusion-related or allergic reactions occur, pre-meds should be given with the next dose, but the infusion time may not be reduced for the subsequent infusion. If the next dose is well-tolerated with pre-meds, the subsequent infusion time may be reduced by 30 ± 10 min. as long as pre-meds continue to be used. If infusion-related AEs occur with the 60-min. infusion, all subsequent doses should be given over 90 ± 15 min. (with pre-meds). If infusion-related AEs occur with the 30-min. infusion, all subsequent doses should be given over 60 ± 10 min. (with pre-meds).<br><br>For patients with grade 3 reactions, the bevacizumab infusion should be stopped and not re-started on that day. At the physician's discretion, bevacizumab may be permanently discontinued or reinstituted with pre-medications and at a rate of 90 ± 15 minutes. If the reaction occurred at the 90-minute rate, initially challenge at a slower infusion rate and gradually increase to 90 minutes. When bevacizumab is re-instituted, the patient should be monitored, per physician's usual practice, for a duration comparable to duration of reaction |
| | 4 | Permanently discontinue bevacizumab. |
| **Hemorrhage[a]** | 3 or 4 | Permanently discontinue bevacizumab. |
| **Thrombosis/thrombus/ embolism-venous (including vascular access device)** | 2 or 3 | Hold bevacizumab until resolution by clinical assessment or Doppler.<br>• If the planned duration of full-dose anticoagulation is < 2 weeks, hold bevacizumab until anticoagulation is complete.<br>• If the planned duration of full-dose anticoag is ≥ 2 weeks, bevacizumab may be resumed during anticoag if no grade 3 or 4 hemorrhage event occurred while on therapy<br>- If stable dose of warfarin (or other anticoagulant), INR must be in range (usually between 2 and 3); or<br>- If unfractionated heparin, PTT must be in therapeutic range.<br>Discontinue bevacizumab if thromboembolic events worsen or recur after resuming therapy<br>***Post operatively, physician's discretion to use low molecular weight heparin or coumadin** |
| | 4 | Permanently discontinue bevacizumab. |


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| Adverse Event | Grade CTCAE v4.0 | Action to be Taken |
|---|---|---|
| **Visceral or peripheral arterial ischemia** | 2 [b,c], 3 or 4 | Permanently discontinue bevacizumab. |
| **Cardiac ischemia/infarction** | 2 [b], 3 or 4 | Permanently discontinue bevacizumab. |
| **CNS ischemia** | 2 [b], 3 or 4 | Permanently discontinue bevacizumab. |
| **GI perforation including GI leak and GI fistula** | ≥1 | Permanently discontinue bevacizumab. |
| **Intra-abdominal abscess[d]** | 3 | Hold bevacizumab until resolved. |
| | 4 | Permanently discontinue bevacizumab. |
| **Complication, non-infectious wound dehiscence[e]** | 1 | Hold bevacizumab for at least 1 month. If, in the physician's opinion, substantial healing has taken place within 1-3 months, bevacizumab may be resumed. If wound dehiscence recurs, permanently discontinue bevacizumab. |
| | 2, 3, or 4 | Permanently discontinue bevacizumab. |
| **Proteinuria** | UPC ratio ≤ 3.5 or dipstick 1+ | Continue bevacizumab. |
| | UPC ratio > 3.5 or dipstick > 2+ | Hold bevacizumab until it UPC recovers to ≤ 3.5 or dipstick is ≤ 2+<br>If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab. |
| | Nephrotic syndrome or dipstick ≥ 3+ | Discontinue bevacizumab. |
| **Hypertension** | 3 | Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician discretion. Bevacizumab should be held for uncontrolled or symptomatic hypertension present on the day that the bevacizumab dose is to be given. If BP is not controlled with medication within 1 month, permanently discontinue bevacizumab. |
| | 4 | Permanently discontinue bevacizumab. |
| **Other clinically significant (AEs)[f]** | 3 | Hold until AE has resolved to ≤ grade 1. |
| | 4 | Permanently discontinue bevacizumab. |

**a** If coagulation disorders develop, secondary to other medical conditions, hold bevacizumab until the PT INR and PTT return to ≤ grade 1.

**b** New or worsening grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline that have not worsened.)

**c** Patients who develop brief, reversible, exercise-induced claudication (grade 2) not attributable to arterial thromboembolic events may continue on study.

**d** Refer to grading criteria listed for the appropriate adverse event in the Infection section of the CTCAE v 4.0.

**e** Refer to Injury, Poisoning, and Procedural Complication section of the CTCAE v 4.0.

**f** Determination of "clinically significant" is at the physician's discretion and applies to those adverse events that can be attributed to bevacizumab and are not related to chemotherapy.


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7.6 Supportive Care

7.6.1 All supportive measures consistent with optimal patient care will be given throughout treatment.

7.7 Duration of Therapy

7.7.1 Patients will receive protocol therapy unless: Extraordinary Medical Circumstances: If, at any time, the constraints of this therapy are detrimental to the patient's health, protocol treatment should be discontinued.

7.7.2 Patients should proceed to surgery 4-6 weeks after 6 cycles of chemotherapy or if chemotherapy was stopped secondary to adverse reactions. Surgery must not take place until at least 8 weeks have elapsed since the last dose of bevacizumab.

7.7.3 Patients will continue with adjuvant chemotherapy 8-10 weeks after surgery.



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# 8 STUDY PARAMETERS

**Phase I – Neoadjuvant therapy**

| Tests | Baseline | Cycle 1 | Cycle 2[8] | Cycle 3 | Cycle 4[8] | Cycle 5 | Cycle 6[8] |
|---|---|---|---|---|---|---|---|
| H&P | X | X | | X | | X | |
| PS | X | X | X | X | X | X | X |
| CBC, plat, diff[2] | X[2] | X | X | X | X | X | X |
| Serum Cr + Mg[2] | X[2] | X | X | X | X | X | X |
| Comp Metabolic Panel[2] | X[2] | | | X | | X | |
| U/A | X[2] | | | | | | |
| CT Chest/Abd/Pelvis | X[2] | | | | | | |
| UGI endoscopy with endoscopic US | X | | | | | | |
| PET Scan | X[2] | | | | | | |
| Surgical Eval | X | | | | | | |
| Correlative Biopsies | X | | | | | | |
| PT, INR, PTT[1] | X[2] | | | | | | |
| LFTs | X[2] | X | X | X | X | X | X |
| Serum Pregnancy Test (Premenopausal)[2] | X | | | | | | |
| Vital signs (T, P, BP) | X | X | X | X | X | X | X |
| Ht[7], Wt, BSA | X | X | X | X | X | X | X |
| Urine Protein/Cr (UPC) Ratio[3] or dipstick | X[2] | | X | | X | | |
| PFT/DLCO | X[2] | | | | | | |
| Adverse Event Assessment | | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X |


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| Tests | Prior to Surgery[2, 5] | Surgery |
|---|---|---|
| H & P, VS, PS | X | |
| CBC, Plat, diff | X | |
| Serum Cr + Mg | X | |
| CT Chest/Abd/Pelvis | X | |
| PET Scan | X | |
| Surgical Eval | X | |
| PT, INR, PTT | X | |
| LFTs | X | |
| EKG | X | |
| PFTs/DLCO | X | |
| Correlative sampling | | X |
| Pathological assessment for response | | X |

**Phase II Adjuvant Therapy**

| Tests | Post Op Baseline [4] | Cycle 7 | Cycle 8[8] | Cycle 9 | Cycle 10[8] | Cycle 11 | Cycle 12[8] | 6 weeks after final Treatment | Follow Up[6] |
|---|---|---|---|---|---|---|---|---|---|
| H & P | X | X | | X | | X | | | X |
| PS | X | X | X | X | X | X | X | | |
| CBC, Plat, diff | X | X | X | X | X | X | X | X | X |
| Serum Cr + Mg[2] | X | X | X | X | X | X | X | X | |
| Compr Metabolic Panel[2] | X | | | X | | X | | X | X |
| CT Scan Chest/Abd/Pelvis | X | | | | | | | X | X |
| Surgical Eval | X | | | | | | | | X |
| PT, INR, [PTT1,] | X | | | | | | | X | |
| LFTs | X | X | X | X | X | X | X | X | |
| Vital Signs (T, P, BP) | X | X | X | X | X | X | X | X | |
| Urine Protein/Cr (UPC) Ratio or dipstick | X | | X | | X | | X | X | |
| Adverse Event Assessment | X | X | X | X | X | X | X | X | |
| Weight, BSA | X | X | X | X | X | X | X | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | |



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[1]For patients on full-dose warfarin, the PT (INR) should be monitored throughout the study treatment period per the physician's usual practice.

[2] All baseline neoadjuvant labs must be complete within 7 days of registration. All baseline neoadjuvant disease assessments must be complete within 21 days of registration. All pre-op labs and disease assessments must be completed within a timeframe defined by the surgeon. All cycle specific labs must be completed within 48 hours prior to day 1 of that cycle.

[3]UPC ratio or dipstick for protein is to be performed every other cycle. If UPC ratio is $\geq$ 1.0 or urine dipstick for protein is $\geq$ 2+, a 24-hour urine collection is required for more accurate assessment. Treatment must continue as per dose modification section during the 24 hr urine collection and can only be held according to dose modification section directions.

[4] Post-op baseline studies to be performed within 8 days prior to resumption of chemotherapy (8-10 weeks post-operatively).

[5] Studies Prior to Surgery are performed between the final cycle of pre-operative therapy and the operation, at the discretion of the treating physicians, consistent with institutional pre-operative testing guidelines, and with the CBC more than 2 weeks after the last dose of FOLFOX.

[6]Follow up:
If asymptomatic with H&P q 4 mos from the date of the last treatment x 1 yr, then q 6 mos x 2 yrs, then annually until death
Chemistry profile + CBC as clinically indicated
Chest x-ray as indicated
Radiology and endoscopy, as clinically indicated (i.e. persistent or recurrent dysphagia)
CT chest/abdomen/pelvis at 12 months and 24 months after the 6 week post final treatment timepoint
Nutritional counseling is recommended
Dilation for anastomotic stenosis as indicated

[7]Height cycle 1 day 1 only.

[8]For cycles where physician visit is not indicated, the study coordinator will collect all the assessment data (labs, PS, adverse events) and discuss with treating physician to determine treatment orders. The treating physician or designee must be available for triage visit if assessments indicate that exam/assessment by physician is needed.

[9]Only need to follow toxicities that are possibly, probably and definitely related to study treatment.


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# 9 DRUG FORMULATION AND PROCUREMENT

## 9.1 Bevacizumab

### 9.1.1 Generic Name - Bevacizumab.

### 9.1.2 Other Names

#### 9.1.2.1 NSC 704865, RhuMAb VEGF, Recombinant Humanized Monoclonal Anti-VEGF Antibody

### 9.1.3 Molecular Formula

#### 9.1.3.1 M.W. = 149 kilodaltons

### 9.1.4 Trade Name - AvastinTM (Genentech, Inc)

### 9.1.5 Classification - Antiangiogenesis agent

### 9.1.6 Action

#### 9.1.6.1 Bevacizumab binds Vascular Endothelial Growth Factor (VEGF) preventing the binding of VEGF to its receptors (Flt-1 and KDR), thus inhibiting endothelial cell proliferation and new blood vessel formation.

### 9.1.7 Dose Form

#### 9.1.7.1 Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes: Each 400 mg (25 mg/mL - 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.

### 9.1.8 Drug Procurement

#### 9.1.8.1 Bevacizumab (NSC# 704865) will be supplied by Genentech

### 9.1.9 Drug Ordering and Accountability

All study drug required for completion of this study will be provided by Genentech.

Following submission and approval of the required regulatory documents, the initial order may be placed. Drug order forms and ordering procedure will be presented at the site initiation meeting.


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It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

Amount received and placed in storage area.
Amount currently in storage area.
Label ID number or batch number.
Dates and initials of person responsible for each investigational product inventory entry/movement.
Amount dispensed to and returned by each patient, including unique patient identifiers.
Amount transferred to another area for dispensing or storage.
Non-study disposition (e.g., lost, wasted, broken).

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs.

9.1.10 Storage and Stability

9.1.10.1 Upon receipt, bevacizumab must be refrigerated (2° to 8°C). Do not freeze. Do Not Shake. Protect from light. Sterile, single-use vials contain no antibacterial preservatives. Therefore, vials must be discarded 8 hours after initial opening. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

9.1.11 Drug Preparation

9.1.11.1 The calculated dose should be placed in a sterile, empty IV bag and diluted with 0.9% sodium chloride for injection to a final volume of 100 mL. If the drug volume is greater than 100ml, the calculated dose should be placed in a sterile empty IV bag and infused undiluted. Bevacizumab should NOT be administered or mixed with dextrose solutions.

9.1.12 Dose/Administration

9.1.12.1 5 mg/kg IV infusion once every 14 days. Initial dose should be infused over 90 minutes. If no adverse reactions occur, the second dose should be administered over 30 minutes minimally. Again, if no adverse reactions occur, the third and subsequent doses should be administered over 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated.



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Infusions should be run in via a volumetric infusion device. Do NOT administer as an IV push of bolus.

9.1.13 Kinetics

9.1.13.1 Estimated half-life of bevacizumab is approximately 20 days (range 11-50 days). The clearance of bevacizumab was higher in males and in patients with a higher tumor burden.

9.1.14 Drug Interactions

9.1.14.1 Bevacizumab may increase the concentration of SN38 (the active metabolite of irinotecan) by as much as 33%. This may potentially increase the incidence of irinotecan-induced side effects such as diarrhea and leucopenia.

9.1.15Adverse Effects

9.1.15.1 In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

9.1.15.2 Allergy/Immunology: Allergic reaction/hypersensitivity. Infusion-related reactions.

9.1.15.3 Blood/Bone Marrow: Leukopenia, neutropenia, thrombocytopenia. **Neutropenia**: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

9.1.15.4 Cardiac: Hypertension/hypertensive crisis, cardiac ischemia/infarction, supraventricular arrhythmia, left ventricular dysfunction (congestive heart failure), hypotension, syncope. **Hypertension**: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive



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encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006).
There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients.
Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy must be permanently discontinued. Bevacizumab must be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

**Congestive heart failure:** In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240360 mg/m2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).
In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as CTCAE v4.0 Grade 3 or 4) in the paclitaxel bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm
No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class IIIV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.
Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.
A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to ☐ 40%) among 48 pati
cytarabine, mitoxantrone, and bevacizumab. All but 1 of these



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patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.
Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

9.1.15.5 Constitutional symptoms: Asthenia, fever, rigors/chills, weight loss

9.1.15.6 Dermatology/skin: Exfoliative dermatitis, complications with wound healing, rash, skin ulceration, urticaria. **Wound healing complications:** Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab must be discontinued in patients with severe wound healing complications.
If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure must not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

9.1.15.7 Gastrointestinal: GI perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses. Large bowel leakage, GI fistula, intestinal obstruction, intestinal necrosis, mesenteric venous occlusion, colitis, mucositis/stomatitis, nausea, vomiting, anorexia, constipation, diarrhea, heartburn/dyspepsia, dry mouth, taste disturbance. Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab must be permanently discontinued in patients who develop



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gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

9.1.15.8 Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to ☐ 1 year following
events occurring within the first 6 months of therapy. Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

9.1.15.9 Hemorrhage/Bleeding: Life-threatening or fatal pulmonary hemorrhage (primarily in lung cancer patients), CNS bleeding, GI hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, epistaxis (nose bleeds), vaginal bleeding, gum bleeding. **Hemorrhage**: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage. **Tumor-Associated Hemorrhage:** Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti rheumatic/anti inflammatory drugs, treatment with anticoagulants, prior



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radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor associated hemorrhages. Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis. **Mucocutaneous Hemorrhage:** Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly CTCAE v4.0 Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

9.1.15.10 Infection: Infection with normal ANC

9.1.15.11 Metabolic/Laboratory: Increased: alkaline phosphatase, ALT (SGPT), AST(SGOT), Bilirubin, serum creatinine. Hyponatremia and hypokalemia.

9.1.15.12 Neurology: Cerebrovascular ischemia, dizziness, abnormal gait, confusion. **Reversible Posterior Leukoencephalopathy Syndrome:** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

9.1.15.13 Ocular: Excessive lacrimation

9.1.15.14 Pain: Abdominal pain, chest/thoracic pain, headache, arthralgias, myalgias, generalized.



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9.1.15.15 Pulmonary/Upper Respiratory: Dyspnea, cough, bronchospasm/wheezing, voice changes (hoarseness)

9.1.15.16 Renal/Genitourinary: Proteinuria, nephrotic syndrome.
**Proteinuria**: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. CTCAE v4.0 Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab must be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.
Proteinuria will be monitored by urine protein:creatinine (UPC) ratio performed every other cycle. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

9.1.15.17 Vascular: Life-threatening and potentially fatal arterial thromboembolic events: cerebral infarction, transient ischemic attacks, myocardial infarction, angina. Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.
**Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis:** In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy bevacizumab.


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The incidence of CTCAE v4.0 Grade ☐ 3 venous VTE eve
one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure). In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy bevacizumab and those receiving the control chemotherapy alone. In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

**Arterial Thromboembotic Events:** An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective



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analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

9.1.15.18 Venous thromboembolic events: deep vein thrombosis, intra-abdominal thrombosis.

9.1.16 Patient Care Information

9.1.16.1 Monitor CBC and platelets. For patients taking warfarin for thrombosis, monitor PT or INR closely (weekly until two stable therapeutic levels attained). For patients on warfarin for venous access prophylaxis, routine PT monitoring.

9.1.16.2 Monitor patient closely during infusion, for infusion related events and for bleeding.

9.1.16.3 Monitor blood pressure prior to each dose to assess for development of hypertension.

9.1.16.4 Instruct patient to monitor and report signs/symptoms of : bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling)

9.1.16.5 Baseline urine protein must be performed and repeated every other cycle.. If elevated, 24-hour urine collection must be performed.

9.1.16.6 Therapy should be suspended several weeks before elective surgery and should not restart until surgical incision is fully healed.

9.1.16.7 Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.



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9.1.17 References

9.1.17.1 Bevacizumab (Avastin™) Full Prescribing Information. Genentech, Inc. 2007. Bevacizumab Investigators Brochure, Genentech, November 2009

9.2 Oxaliplatin

9.2.1 For complete instruction regarding preparation, handling, dosing and storage, please refer to the FDA-approved package insert.

9.2.2 Other Names

9.2.2.1 Eloxatin, trans-*l*-diaminocyclohexane oxalatoplatinum, cis-[oxalato(trans-*l*-1,2-diaminocyclohexane)platinum(II)].

9.2.3 Classification

9.2.3.1 Platinating agent.

9.2.4 Mode of Action

9.2.4.1 The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

9.2.5 Storage and Stability

9.2.5.1 Oxaliplatin vials are stored at room temperature between 20E and 25EC protected from light. Reconstituted solution in sterile water or 5% dextrose may be stored for 24 to 48 hours at 2E to 8EC. After further dilution in 5% dextrose, the solution is stable for 24 hours at room temperature.

9.2.6 Dose Specifics

9.2.6.1 85 mg/m² IV in 500 ml D5W.

9.2.7 Preparation

9.2.7.1 The freeze-dried powder is reconstituted by adding 10 mL (for the 50 mg vials) or 20 mL (for the 100 mg vials of Water for Injection or Dextrose 5% in Water to yield a 5 mg/mL solution. The reconstituted solution must be further diluted in an infusion solution of 250 mL to 500 mL ˍDextrose 5% in Water to give an oxaliplatin concentration between 0.2 mg/mL and 2.0 mg/mL. The reconstitution or final dilution must never be performed with a sodium chloride solution.


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9.2.8 Administration

9.2.8.1 The diluted solution of oxaliplatin is administered intravenously over 2 hours concurrent with leucovorin. Separate infusion bags and lines must be used with Yline tubing connecting the two lines before the single injection site.

9.2.9 Incompatibilities

9.2.9.1 When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion should precede that of 5-fluorouracil. Ensure the infusion lines are adequately flushed with 5% Dextrose between administration of the two drugs. Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride. Do not simultaneously administer other drugs by the same infusion line. Do not mix with alkaline solutions. Oxaliplatin is unstable under alkaline conditions. Do not use components containing aluminum for the preparation of oxaliplatin administration. There is a risk of drug degradation when in contact with aluminum.

9.2.10 Procurement

9.2.10.1 Oxaliplatin (NSC # 266046) is commercially available

9.2.11 Reported Adverse Events and Potential Risks

9.2.11.1 Allergy/Immunology: Rhinitis, Allergic/Hypersensitivity reactions (including drug fever). Can be fatal and occur with any cycle of therapy. Manifested by: urticaria, pruritus, flushing of the face, diarrhea (during infusion), shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation, and syncope.

9.2.11.2Auditory: Middle ear/hearing (ototoxicity, mild), inner ear/hearing (mild hearing loss).

9.2.11.3 Blood/Bone Marrow: decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia. Single-agent oxaliplatin produces only mild myelosuppression with minimal to severe neutropenia, anemia or thrombocytopenia. In combination, more grade 3/4 neutropenia or thrombocytopenia may be noted.

9.2.11.4 Cardiovascular (Arrhythmia): Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/bigeminy/trigeminy/ventricular tachycardia).



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9.2.11.5 Cardiovascular (General): Edema, hypertension, hypotension

9.2.11.6 Coagulation: DIC (disseminated intravascular coagulation), thrombosis/embolism(including pulmonary embolism), prolonged prothrombin time, increased INR,thrombotic microangiopathy (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome). The hemolytic uremic syndrome should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serum creatinine. Patients suspected of experiencing HUS should have the following laboratory analyses conducted:

9.2.11.6.1 Creatinine, BUN, Urinalysis with microscopic evaluation CBC with differential and platelets, PT/PTT, Fibrinogen, Fibrinogen Degradation Products (FDP),Anti-thrombin III (ATIII),Von Willebrand Factor (VWF), Anti-nuclear antibodies (ANA), Rheumatoid Factor (RhF), C3, C4, CH50, Anti-platelet antibodies, Platelet associated IgG, Circulating immune complexes

9.2.11.6.2 Oxaliplatin should be discontinued for any suspected occurrence of hemolytic uremic syndrome.

9.2.11.7 Constitutional Symptoms: Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x l09L), fatigue (lethargy. malaise, asthenia), rigors/chills, insomnia, sweating, weight gain, weight loss.

9.2.11.8 Dermatology/Skin: Erythema or skin eruptions, alopecia, hand-foot skin reaction, injection site reaction, rash/desquamation, urticaria, pruritus/itching, dry skin, nail changes, pigmentation changes.

9.2.11.9 Endocrine: Hot flashes/flushes.

9.2.11.10 Gastrointestinal: Anorexia, ascites (non-malignant), colitis, constipation, dehydration, diarrhea, dysphagia, enteritis, esophagitis, flatulence, gastritis, gastrointestinal reflux (heartburn, dyspepsia), ileus (or neuroconstipation), intestinal obstruction, nausea, odynophagia (painful swallowing), stomatitis /pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), typhilitis, ulcer, vomiting, xerostomia (dry mouth).

9.2.11.11 Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena,



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GI bleeding, rectal bleeding/hematochezia, pulmonary hemorrhage, vaginal hemorrhage, other (hemorrhage NOS).

9.2.11.12 Hepatobiliary/Pancreas: increased alkaline phosphatase, increased bilirubin, increased GGT (gamma glutamyl transpeptidase), hepatic enlargement, increased SGOT (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase), pancreatitis, hepatic veno-occlusive disease (manifested by hepatomegaly, ascites, and jaundice).

9.2.11.13 Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC <1.0 x l09L fever >38.5°C), infection (documented clinically or microbiologically with grade 3 or 4 neutropenia (ANC <1.0 x l09L), infection with unknown ANC, infection without neutropenia.

9.2.11.14 Metabolic/Laboratory: Acidosis (metabolic or respiratory), hypoalbuminemia, hypocalcemia, hyperuricemia, hyperglycemia, hypoglycemia, hypokalemia, hypophosphatemia, hyponatremia, hypomagnesemia

9.2.11.15 Musculoskeletal: Involuntary muscle contractions, trismus.

9.2.11.16 Neurology: Ataxia (incoordination, including abnormal gait), cerebrovascular ischemia, confusion, dizziness, extrapyramidal movements/restlessness, insomnia, mood alteration (depression, anxiety), neuropathy cranial (ptosis), vertigo, acute sensory neuropathy induced or exacerbated by cold (including acute laryngopharyngeal dysesthesias, Lhermitte's sign, upper extremity paresthesia), chronic peripheral neuropathy (paresthesias, dysesthesias, hypoesthesias), seizure, somnolence, speech impairment, syncope.

9.2.11.17 Ocular/Visual: Conjunctivitis, vision abnormalities including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness.

9.2.11.18 Pain: abdominal pain or cramping, arthralgia (joint pain), bone pain, chest pain (noncardiac and non- pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps).

9.2.11.19 Pulmonary/Upper Respiratory: Bronchospasm/wheezing, pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates



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(including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm, nasal cavity/paranasal sinus reactions, voice changes (hoarseness, loss or alteration in voice, laryngitis).

9.2.11.20 Renal/Genitourinary: Increased creatinine, renal failure, urinary retention, urinary urgency, dysuria.

9.2.11.21 Hemolytic Uremic Syndrome (HUS) – see coagulation.

9.2.11.22 Vascular: Phlebitis, thrombosis

9.2.11.23 Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined: tongue paralysis, anemia, aphasia, abnormal hepatic function, hyporeflexia, anxiety, depression, dysarthria, insomnia, increased sweating, rhinitis, epistaxis, gout, pancreatitis, idiopathic thrombocytopenia (5 cases), thrombocytopenia associated with hemolytic anemia (2 cases).

9.2.11.24 Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2.13 Nursing/Patient Implications

9.2.13.1 Premedicate with antiemetics (5 HT3 antagonist and steroid) to prevent severe nausea and vomiting.

9.2.13.2 Monitor for diarrhea and treat symptomatically.

9.2.13.3 Monitor for neuropathies (paresthesias of hands, feet and toes, pharynx; occasionally cramps). If they occur, tend to be brief (less than one week) during the first course but longer with subsequent courses. Advise patients to avoid cold exposure and against touching cold objects. Sensory neuropathies develop with continued treatment. Ask patient if changes in ambulation, swallowing, breathing or fine motor activity have been noted.

9.2.13.4 Prolonging the oxaliplatin infusion time to 6 hours may alleviate acute neurologic toxicities. Monitor for respiratory changes, such as shortness of breath.

9.2.13.5 The hemolytic uremic syndrome should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia, and renal failure as demonstrated by an increase in serum creatinine.



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9.2.14 References

Investigator's Brochure: Oxaliplatin. Sanofi Winthrop 1996
Prescribing Information: Oxaliplatin (Eloxatin) Sanofi-Sythelabo Inc., November 2004, Physician's Desk Reference 2010

9.3 5-Fluorouracil

9.3.1 For complete prescribing information, please refer to the approved package insert.

9.3.2 Other Names

9.3.2.1 Fluorouracil, 5-FU, Adrucil, Efudex.

9.3.3 Classification

9.3.3.1 Antimetabolite.

9.3.4 Mode of Action

9.3.4.1 Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

9.3.5 Storage and Stability

9.3.5.1 Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140EF in a water bath. Do not allow to freeze.

9.3.6 Dose Specifics

9.3.6.1 400 mg/m², then 2.4 g/m².

9.3.7 Administration

9.3.7.1 5-FU will be administered at 400 mg/m² IV bolus, followed by 2.4 g/m² continuous infusion over 46 hours on day 1 and day 2.

9.3.8 Incompatibilities

9.3.8.1 Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush



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line before giving fluorouracil. May form precipitate with fluorouracil in some concentrations.

9.3.9 Availability

9.3.9.1 Commercially available in 500 mg/10 ml ampules and vials, and 1 g/20 mL, 2.5 g/50 mL, and 5 gm/100 mL vials.

9.3.10 Side Effects

9.3.10.1 Hematologic: Leukopenia, thrombocytopenia, anemia; can be dose limiting; less common with continuous infusion.

9.3.10.2 Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.

9.3.10.3 Gastrointestinal: Nausea, vomiting, anorexia; diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.

9.3.10.4 Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia).

9.3.10.5 Cardiac: Angina, noted with continuous infusion.

9.3.10.6 Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

9.3.10.7 Hepatic: Hepatitis with hepatic infusion.

9.3.11 Nursing/Patient Implications

9.3.11.1 Monitor CBC, platelet counts.

9.3.11.2 Administer antiemetics as indicated.

9.3.11.3 Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.

9.3.11.4 Assess for stomatitis - oral care recommendations as indicated.

9.3.11.5 Monitor for neurologic symptoms (headache, ataxia).



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9.3.11.6 Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.

9.3.11.7 Inform patient of potential alopecia.

9.3.12 References

9.3.12.1 Hansen R, Quebbeman E, Ausman R, *et al*. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. J Surg Oncol 1989; 40:177- 181. Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 1988; 61:36-45.

9.4 Leucovorin

9.4.1 For complete prescribing information, please refer to the approved package insert.

9.4.2 Other Names

9.4.2.1 Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

9.4.3 Classification

9.4.3.1 Tetrahydrofolic acid derivative.

9.4.4 Mode of Action

9.4.4.1 Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

9.4.5 Storage and Stability

9.4.5.1 All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the



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drug is chemically stable for at least 24 hours at room temperature under normal laboratory light. The oral solution, 1 mg/ml, is stable for 14 days refrigerated and 7 days at room temperature.

9.4.6 Dose Specifics

9.4.6.1 400 mg/m²

9.4.7 Preparation

9.4.7.1 The 50 and 100 mg vials for injection are reconstituted with 5 and 10 mL of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/mL solution. The 350 mg vial is reconstituted with 17 mL of sterile water resulting in a 20 mg/mL solution.

9.4.8 Administration

9.4.8.1 Intravenous infusion over 2 hours, concurrent with oxaliplatin.

9.4.9 Compatibilities

9.4.9.1 Leucovorin (0.5-0.9 mg/mL) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24 and 0.96 mg/mL) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/mL) in normal saline. Leucovorin is compatible with fluorouracil and oxaliplatin.

9.4.10 Availability

9.4.10.1 Commercially available in parenteral formulations (50 mg, 100 mg and 350 mg vial).

9.4.11 Side Effects

9.4.11.1 Hematologic: Thrombocytosis.

9.4.11.2 Dermatologic: Skin rash.

9.4.11.3 Gastrointestinal: Nausea, upset stomach, diarrhea.

9.4.11.4 Allergic: Skin rash, hives, pruritus.

9.4.11.5 Pulmonary: Wheezing (possibly allergic in origin).



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9.4.11.6 Other: Headache; may potentiate the toxic, effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

9.4.12 Nursing/Patient Implications

9.4.12.1 Observe for sensitization reactions.

9.4.12.2 When given with fluoropyrimidines, monitor closely for diarrhea and stomatitis.

9.4.13 References

9.4.13.1 Arbuck SG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. Cancer 1989; 63: 1036-1044. Bleyer WA. New vistas for leucovorin in cancer chemotherapy. Cancer 1989; 63: 995-1007. Grem JL. 5-Fluorouracil plus leucovorin in cancer therapy. In: Cancer: Practices and Principles of Oncology Updates. Devita VT, Hellman S, Rosenberg SA, editors. 1988; 2(7): 1-12

# 10.0 ADVERSE EVENT REPORTING AND DEFINTIONS

## 10.1 Definitions

### 10.1.1 Adverse Events

An Adverse Event (AE) is the unfavorable and unintended sign symptom or disease temporally associated with the use of a medicinal (investigational) device or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011).*

For purposes of this clinical trial, only AEs associated (Possibly, Probably or Definitely Related) with the process of collecting breath or blood samples required by this clinical trial will be captured. The sample collections required in this clinical trial involve both blood and breath collections. Adverse Event recordability begins with the first protocol related procedure; specifically the first breath collection or Plasma, Serum and PBMC collection for banking; whichever occurs first.

### 10.1.2 Serious Adverse Events



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A Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for >24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or is a congenital anomaly/birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.1.3 Severity Rating

The investigator will evaluate the severity of each adverse event using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

- Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

10.1.4 Attribution to Study Procedure – Sample Collection

- Definite – clearly related
- Probable - likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

10.1.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources. Expected Adverse Events may include:

- Anxiety
- Dizziness



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- Cough
- Fainting

An Unexpected Adverse Event is one where the nature, severity, or frequency related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event. (see OHRP Guidance on reviewing unanticipated problems 2007)

For purposes of this clinical trial, only SAEs associated (Possibly, Probably or Definitely Related) with the process of collecting samples required by this clinical trial will be reported. Serious Adverse Event reportability begins with the first protocol related procedure; specifically the first breath collection or Plasma, Serum and PBMC collection for banking; whichever occurs first.

**10.2 Recording and Reporting Responsibilities**

10.2.1 Investigative Site Recording Responsibilities

**The following set of instructions applies to the study team / participating site.**

1. Upon identification of a recordable AE or reportable SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.
2. All AEs and SAEs that are possibly, probably or definitely related to the clinical trial sample collection procedures must be recorded on the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode. The action taken with respect to the study device, and the patient's outcome must be recorded in the CRF. All recorded events must be followed for the duration of the study, until they resolve.
3. All SAEs will be recorded on the FDA Med Watch form unless otherwise directed. After submitting the initial report it may be



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necessary to submit follow up reports to the study monitor and/or manufacturer by the investigator should the event require further investigation.

10.2.2 Investigative Site Reporting Responsibilities

1. The investigator/ site is responsible to report all SAEs to the study monitor within 24 hours of becoming aware of the event.
2. Institutional Review Board (IRB): Each investigator is responsible to report all AEs/SAEs to the IRB following guidelines set by that IRB. Fox Chase Cancer Center Quality Assurance (QA) reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent to the Regulatory Coordinator.

3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the study monitor who will confirm reportability of the event with the principal investigator.
4. If the results of an investigator review or investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
   The participating site should report events to:

   Quality Assurance Specialist/ Study Monitor
   Fox Chase Cancer Center
   333 Cottman Avenue
   Philadelphia PA 19111
   Phone: 215-214-3704
   Fax: 215-214-1511
   beth.adaire@fccc.edu

10.2.3 Sponsor Reporting Responsibilities

**This section applies to the Sponsor ONLY.**

10.2.3.1 The sponsor will report adverse events which are serious (refer to above definitions), have a causal relation to the research, and are unexpected, to all participating institutions within 48 hours of becoming aware of the event.

10.2.3.2 If the adverse event requires modification of the study protocol and informed consent, then these changes will be provided to all participating institutions in the form of an amendment from OER for each site's IRB of record along with the report of the adverse event.

10.2.3.3 SAEs that occur with commercially available agents are reportable through the Food and Drug Administration (FDA)



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MedWatch program. The timing of submissions are as directed by FDA guidelines. (http://www.fda.gov/medwatch/index.html)

10.2.3.4 OER will report events to the Study Principal Investigator, Genentech Inc. and the FDA on behalf of the reporting site as information becomes available or upon request.

Genentech, Inc.
Attn: Tarceva Clinical Trial Manager
1 DNA Way, Mailstop #443B
South San Francisco, CA 94080-4990
Tel: (650) 467-7603
Fax: 650-467-3130

Food and Drug Administration:
Telephone 1-800-FDA-1088
Fax 1-800-FDA-0178
Internet http://www.fda.gov/medwatch/report.htm

Voluntary Drug Reporting:
MedWatch
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-9787



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10.1 OER Reporting Responsibilities:

10.3 Special Warning for Bevacizumab

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.
**Hypertension**: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006).
There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved.
If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

**Proteinuria**: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTCAE v4.0 Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)


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Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 6 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

**Thromboembolic Events**: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. **Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis**: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of CTCAE v4.0 Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure).
In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.
**Arterial Thromboembotic Events:** An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab



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compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

**Gastrointestinal perforation** Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

**Fistula**: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.



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Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

**Wound healing complications:** Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone (Scappaticci et al., 2005). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

**Hemorrhage**: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

**Tumor-Associated Hemorrhage:** Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages. Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with



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occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis. This is potentially relevant because patients in this study will initially have untreated tumor present in the esophagus or GE junction, which may be at risk for bleeding.

**Mucocutaneous Hemorrhage:** Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly CTCAE v4.0Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

**Reversible Posterior Leukoencephalopathy Syndrome:** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker et al. 2006; Ozcan et al. 2006).

**Congestive heart failure:** In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m$^2$). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005). In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as CTCAE v4.0 Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.



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Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.
A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

**Neutropenia:** Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

**Additional Adverse Events:** See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

### 10.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC #704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) was developed to provide a single, complete list of reported and/or potential adverse events associated with an agent using a uniform presentation of events by body system. The subset of AEs that is used to guide expedited reporting requirements [i.e., the Agent Specific Adverse Event List (ASAEL)], as presented in the right hand column, is identified with ***bold*** and ***italic*** text. This subset contains events that are considered expected and may not need to be reported via expedited AE reporting. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" for further clarification.

## 11.0 MEASURMENT OF EFFECT

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed after neoadjuvant therapy, after surgery and about 6 weeks after final adjuvant treatment.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.



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Definitions of Measurable and Non-Measurable Disease

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

**Guidelines for Evaluation of Measurable Disease**

Measurement Methods: All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

Acceptable imaging modalities for measurable disease: CT scan (conventional and spiral), MRI, chest x-ray, and physical examination.



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Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**Measurement of Effect**

**Response Criteria**

All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.



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**Evaluation of target lesions**

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

**Partial Response (PR):** At least a 30% decrease in the sum of the diameter of target lesions, taking as reference the baseline sum.

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

(Note: the appearance of one or more new lesions is also considered progression).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters since the treatment started

**Evaluation of non-target lesions**

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

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

**Stable Disease (SD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.


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For Patients with Measurable Disease

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | SD/not evaluated | No | PR |
| PR | Non-PD/not evaluated | No | PR |
| SD | Non-PD/not evaluated | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1 Measurement of Pathologic Response

Pathologic response will be based on ypTNM staging as described. Fibrosis in the treatment sample is not expected as patients are treated with chemotherapy and a biologic rather than chemoradiation.

An additional measure of treatment effect based on histologic evaluation will be:

- Complete response: no residual cancer cells seen on H&E or with keratin stain
- Major treatment effect: estimated <20% tumor cells
- Partial treatment effect: estimated 20-50 % tumor cells
- Minor treatment effect: > 50% tumor cells seen


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# 12 DATA SAFETY MONITORING PLAN

The Study PI, biostatistician and study team will monitor toxicity and outcome on a continual basis. Early stopping rules are described in section 14.5. Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed every 6 months by the Extramural Data Safety Monitoring Committee (EDSMC). In this capacity the EDSMC will serve as an advisory committee to OER. The EDSMC will review those aspects of this trial that are outlined in the responsibilities section of the OER Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the study Principal Investigator, the Extramural Research Committee and Division Medical Director, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual, altering the accrual goals or changing the eligibility criteria for the trial.

# 13 INFORMED CONSENT

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in the site study binder or in each patient's study file.

# 14 STATISTICAL CONSIDERATIONS

## 14.1 Primary outcome / objective:

We expect to accrue 39 patients at the rate of 18 per year, for an accrual period of approximately 26 months. Because the primary endpoint is 2-year disease-free survival, we will have finished accrual before we have enough 2-year data to implement a meaningful early stopping rule for futility. A 2-year disease-free survival rate of 30% for the experimental treatment would be discouraging, and not warrant further investigation because the experimental therapy would not provide a benefit over standard therapy. A 2 year disease-free survival rate of 50% for the experimental treatment would be promising, and justify further investigation into the agent. Our decision rule will be to declare the study a success if 16 or more participants survive to 2 years. Under the discouraging rate of 30%, we would have a 9.4% chance of declaring the study a success. Under the promising rate of 50%, we would have a 90.0% chance of declaring the study a success.


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14.2. Secondary objective (from section 2.2): To assess, by pathological examination after surgical resection, complete and partial response to neoadjuvant therapy. To characterize overall and progression free survival.

Pathologic response will be based on ypTNM staging as described. Fibrosis in the treatment sample is not expected as patients are treated with chemotherapy and a biologic rather than chemoradiation.

An additional measure of treatment effect based on histologic evaluation will be:

- complete response: no residual cancer cells seen on H&E or with keratin stain
- major treatment effect: estimated <20% tumor cells
- partial treatment effect: estimated 20-50 % tumor cells
- Minor treatment effect: > 50% tumor cells seen

The analysis of response and survival outcomes will be descriptive and intended to provide information to guide future trials. We do not propose any hypothesis testing for these outcomes.

We will characterize complete and partial response to neoadjuvant therapy using proportions and 95% confidence intervals. We will use Kaplan-Meier curves to characterize overall and progression free survival.

14.3 Secondary objective (from section 2.3): To compare baseline and post-chemotherapy/bevacizumab tissues for biomarkers predicting response or resistance to this approach.

For continuous biomarkers, we will investigate the association of baseline biomarker levels and change in biomarker levels (baseline to post-chemotherapy/bevacizumab) with the binary response/resistance outcomes using Wilcoxon rank-sum tests. We will report means, medians, and standard deviations of the biomarker levels and change in biomarker levels within groups defined by response/resistance outcomes.

For binary biomarkers (patient either has biomarker or does not have it), we will use Fisher's exact tests to investigate the association of cross-sectional presence of biomarker with response/resistance outcomes. We will report proportions of patients with biomarkers within groups defined by response/resistance outcomes.

This objective is exploratory and hypothesis generating only. We do not expect to have sufficient power to detect associations of interest.

14.4 Secondary objective (from section 2.4): To investigate safety in this setting.



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This objective is descriptive only. To investigate safety in this setting, we will characterize toxicities experienced using means, standard deviations, proportions, and 95% confidence intervals.

14.5 Early stopping for toxicity

We have incorporated stopping rules to stop the study in the presence of the adverse events of unexpectedly high rates of 30-day post-surgical treatment mortality or 1-year local recurrence. If 3 or more of the first 18 patients die of any cause within 30 days of surgery the study will also be stopped. Since the 30 day post-operative mortality outcome for a patient will not be observed for several months after entry into the study (chemotherapy will be given for 12 weeks prior to surgery), we may not have 30-day post-surgery data on 18 patients by the time the 19th person enters the study. The following rules to pause accrual to ensure safety after the 19th patient is accrued will be applied.

1) When the 19th patient is accrued, and complete 30-day post-surgical mortality data are available on 16 of the first 18 patients, if zero of the 16 died from any cause within 30-days of surgery, we will not pause accrual as it will not be possible to have three 30-day post-surgical deaths among the first 18 patients.

2) When the 19th patient is accrued, if we only have complete 30-day post-surgical mortality data on 16 patients and one or two patients out of 16 died from any cause within 30 days of surgery, we will pause accrual until we have complete 30-day post-surgery data on the first 18 patients.

3) When the 19th patient is accrued, with complete 30-day surgery-related mortality data on 17 of the first 18 patients, we will not pause accrual if one or zero patients died from any cause within 30 days of surgery as it will not be possible to have three 30-day post-surgery deaths among the first 18 patients.

4) When the 19th patient is accrued, if we only have complete 30-day post-surgery mortality data on 17 patients and two out of 17 patients have died from any cause within 30 days of surgery, we will pause accrual until we have complete 30-day post-surgery data on the first 18 patients.

5) When the 19th patient is accrued, if we have complete 30-day post surgery data on all 18 of the first 18 patients accrued, we will halt the study immediately if 3 of the 18 died within 30 days of surgery.

Some characteristics of our stopping rule are described in the table below.

Characteristics of early stopping rule for 30-day treatment related mortality.

| True 30-day treatment related death rate | 5% | 10% | 15% | 20% | 25% |
|---|---|---|---|---|---|



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| | | | | | |
|---|---|---|---|---|---|
| Probability of stopping the study before the 19th patient is enrolled | 6% | 27% | 52% | 73% | 86% |

We will examine the 12-month local recurrence rate after we have data on 9 individuals (approximately month 18 of the study). If 3 or more individuals have local recurrences, we will close the study. Some characteristics of our stopping rule for local recurrence are described in the table below.

Characteristics of early stopping rule for recurrence.

| | | | | | |
|---|---|---|---|---|---|
| True local 12-month local recurrence rate | 10% | 20% | 30% | 40% | 50% |
| Probability of stopping the study before the 10th patient is enrolled | 5% | 26% | 54% | 77% | 91% |

The early stopping rules are designed to protect patients; this is necessary for 2 reasons: first, the safety and efficacy of a systemic therapy-only approach, as tested in MAGIC, may not be confirmed and second, the addition of bevacizumab in patients with an intact primary cancer of the esophagus or proximal stomach may be associated with unacceptably high rates of on-treatment toxicity or post-operative mortality.

If a patient goes off study and does not undergo surgical resection after the first 6 cycles of chemotherapy, the reason for not having surgery could be due to the inefficacy of the approach. This patient will therefore not be replaced.



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