AMENDMENT BrUOG-E/G-203

Protocol Title: BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091
Principal Investigator: Howard Safran, M.D.

Howard Safran MD
Signature T Kennedy

Date of Amendment: April 25, 2006

Amendment #4

Please replace the Title page and the informed consent form with the enclosed pages.

Section 3 Risk or Discomforts:

Side effects listed under Cetuximab in this section have been updated.

ADMINISTRATIVE CHANGE BrUOG-E/G-203

Protocol Title: BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091
Principal Investigator: Howard Safran, M.D.

Howard Safran MD
Signature

Date of Administrative Change: February 1, 2006
Administrative Change: #C

Please replace the Title page and page 29 with the enclosed pages.

Section 15.2 has been amended and now includes an increase in patient accrual to this study with the rationale for this increase as follows:

BrUOG-E/G-203 is a Brown University study piloting the regimen of cetuximab, paclitaxel, carboplatin and radiation for a proposed Radiation Therapy Oncology Group (RTOG) phase III trial. The initial protocol was to look at clinical complete response rate but RTOG and CTEP now want to see the pathological complete response rate. Only two thirds of the current 40 patients have had surgery therefore we need to increase the accrual to a total of 60 patients to get the pathological response rate to 40. Following discussions with CTEP, the RTOG and Bristol-Myers Squibb, study accrual will therefore be increased to 60 patients.

ADMINISTRATIVE CHANGE BrUOG-E/G-203

Protocol Title: BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091

Principal Investigator: Howard Safran, M.D.

Howard Safran MD
Signature T Kennedy RN. CCRA

Date of Administrative Change: October 31, 2005
Administrative Change:#B

Please replace the Title page and page 30 with the enclosed pages.

Section 15.0 has been amended and now includes an increase in patient accrual to this study with the rationale for this increase as follows:

BrUOG-E/G-203 is a Brown University study piloting the regimen of cetuximab, paclitaxel, carboplatin and radiation for a proposed Radiation Therapy Oncology Group (RTOG) phase III trial. In the CTEP review of the proposed RTOG phase III trial, it was requested that ESO-203 accrual be increased to include at least 40 patients to gather additional safety data. Following discussions with CTEP, the RTOG and Bristol-Myers, study accrual will therefore be increased to 40 patients.

AMENDMENT BrUOG-E/G-203

Protocol Title: BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091

Principal Investigator: Howard Safran, M.D.

Howard Safran MD
Signature T Kennedy RN CCRA

Date of Amendment: June 15, 2005

Amendment #3

Please replace the Title page, schema, pages 12, 15, and 19 and the informed consent form with the enclosed pages.

This protocol was designed as a pilot regimen for a national cooperative group. The decision by the cooperative group is to not use the maintenance arm with Cetuximab as it was felt that it was too difficult for patients recovering from chemoradiation and possibly surgery to continue maintenance treatment.

References to the Cetuximab maintenance arm in **sections 4.0, 4.1, 6.1, 8.1, the schema and the informed consent form have been deleted.**

AMENDMENT BrUOG-E/G-203

Protocol Title: **BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091**
Principal Investigator: Howard Safran, M.D.

Signature

Date of Amendment: February 28, 2005

Amendment #2

Please replace the Title page, page 19 and the informed consent form with the enclosed pages.

Section 11.0

In view of the reported safety update #128 of hypomagnesemia during cetuximab therapy, monitoring of serum magnesium has been added to the required data section of the protocol.

Appendix A: The possible toxicity of hypomagnesemia has been added to the consent form.

AMENDMENT BrUOG-E/G-203

Protocol Title: **BrUOG-E/G-203 CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER BMS-CA225091**
Principal Investigator: Howard Safran, M.D.

Howard Safran MD Kennedy
Signature

Date of Amendment: December 14, 2004

Amendment #1

Please replace the Title page, schema, page 11, 12 and 19, Appendix A, and Appendix B the Eligibility Checklist with the enclosed pages.

Section 3.8 and Appendix B:Tumor tissue available for assessment of EGFR status by IHC has been deleted.

Section 8.1 has been clarified by removing "weekly" in the heading over Maintainence Cetuximab

Appendix A Informed Consent has been corrected by removing chest x-ray from description under section 2 Explanation of Procedures-- Paragraph 4 as it is not required under the study parameters.

BMS-CA225091 BrUOG-E/G-203

CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER

Principal Investigator
Howard Safran, M.D.
Rhode Island Hospital and The Miriam Hospital
Hsafran@lifespan.org 401-793-7151

Co-Principal Investigator
Harold Wanebo, M.D.
Roger Williams Medical Center
Hwanebo-rwmc.org 401-456-2464

Participating Sites
Jordan Berlin M.D. Vanderbilt Ingram Cancer Center
Jordan.berlin@vanderbilt.edu 615-322-4967

Mohan Suntha M.D.
University of Maryland Cancer Center
msuntha@umm.edu 410-328-2331

Herbert Hurwitz M.D.
Duke University Medical Center
Hurwi004@mc.duke.edu 919-681-5257

Thomas DePetrillo, M.D.Rhode Island Hospital
Tdipetrillo@lifespan.org 401-444-8311

Coordinating Center
Teresa A. Kennedy, R.N., C.C.R.A.
Administrative Director
172 Cushing Street, Box G-C
Providence, Rhode Island 02912
Phone: (401) 383-3000
Fax: (401) 383-3001
Email: Teresa_Kennedy@Brown.edu

Final Protocol: 8/13/04
Administrative Correction #A: 12/6/04
Amendment #1 12/14/04
Amendment #2 2/28/05
Amendment #3 6/15/05
Administrative Change #B 10/31/05
Administrative Change #C 02/01/06
Amendment #4 4/25/06

SCHEMA BrUOG-E/G-203

CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER

TREATMENT PLAN

	DAY						
Cetuximab	1	8	15	22	29	36	
Radiation	1→5	8→12	15→19	22→26	29→33	36→38	
Paclitaxel	1	8	15	22	29	36	→ Surgery or endoscopic bx 4-7 wks post chemo/rt
Carboplatin	1	8	15	22	29	36	

Cetuximab: 400 mg/m^2 day 1 then 250mg/m^2/week on days 8, 15, 22, 29, and 36.
Radiation: External radiotherapy 50.4 Gy at 180cGy fraction/day for 28 treatments
Paclitaxel: 50 mg/m^2/week over 1 hour IV, days 1, 8, 15, 22, 29,36.
Carboplatin: AUC=2, over 30 minute IV, days 1, 8, 15, 22, 29, 36.

ELIGIBILITY CRITERIA

- Pathologically confirmed adenocarcinoma or squamous cell carinoma of the esophagus, gastroesophageal junction, or stomach.
- Patients may have mediastinal, celiac adenopathy, peri-portal and regional gastric lymphadenopathy.
- There must be no evidence of distant organ metastases.
- No prior radiation for gastric or esophageal cancer.
- Patients must be ≥ 18 years of age, and nonpregnant
- ECOG performance status 0-2.
- Patients must not have significant infection or other coexistent medical condition that would preclude protocol therapy.
- All patients must sign informed consent

Required Laboratory Data (within 15 days of treatment)

- Granulocytes ≥ 1500/μL
- Platelets ≥ 100,000/μL
- Creatinine ≤ 2 x upper limit normal (ULN
- Bilirubin ≤ 1.5 x ULN
- AST ≤ 3 x ULN

Staging:

- Chest/Abdominal CT
- Endoscopy

Exclusion Criteria

Any of the following criteria will make the patient ineligible to participate in this study:

- Acute hepatitis or AIDS.
- Active or uncontrolled infection.
- Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, and congestive heart failure.
- Prior therapy which specifically and directly targets the EGFR pathway.
- Prior severe infusion reaction to a monoclonal antibody
- Any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s).

Amendment #1 12/14/04
Amendment #3 6/15/05

TABLE OF CONTENTS

1.0 BACKGROUND INFORMATION

1.1 Introduction

The incidence of adenocarcinomas of the esophagus and gastroesophageal junction is increasing faster than any other malignancy in the United States.[1] They occur most commonly in middle age white males.[2] Barretts esophagitis appears to be a major risk factor.[3] Molecular and epidemiologic evidence suggests that adenocarcinomas of the esophagus appear to be indistinguishable from proximal gastric adenocarcinomas.[4]

Carcinomas of the esophagus and stomach carry a high mortality with surgery alone.[5] Distant metastases represent common recurrences in upper gastrointestinal cancers. Randomized trials have failed to demonstrate that chemotherapy, as a single modality, can improve survival when combined with surgical resection in esophageal and gastric cancer.[6] For example, in a randomized intergroup study, Kelsen et al showed no improvement in survival with 3 cycles of preoperative cisplatin and 5-FU followed by 2 cycles of post operative cisplatin and 5-FU as compared to surgery alone.[6] Multiple trials investigating adjuvant chemotherapy alone have not demonstrated an improvement in survival in gastric cancer.[7]

Trimodality therapy, using chemotherapy, radiation and sugery may be beneficial in esophageal and gastric cancer. For example Walsh et al demonstrated that neoadjuvant cisplatin, 5-FU and radiation followed by surgery achieved superior survival to surgery alone in adenocarcinoma of the esophagus.[8] Furthermore, a combination of adjuvant fluorouracil and radiation has improved survival in gastric cancer.[9] Preliminary studies in gastric cancer suggest that neoadjuvant chemoradiation is at least equal or more effective than adjuvant therapy.[10]

The optimal chemoradiation regimen for esophageal and gastric cancer is not known. Paclitaxel is among the most active single agents for esophageal and gastric cancer.[11] Furthermore, it is a powerful radiation sensitizer.[12] The Brown University Oncology Group has completed trials investigating the incorporation of paclitaxel into neoadjuvant chemoradiation regimens for esophageal and gastric cancer.[13,14]

In our original phase II study incorporating paclitaxel into a neoadjuvant regimen for esophageal cancer, patients received paclitaxel 60 mg/m^2, cisplatin 25 mg/m^2 and radiation.[15] Forty-one patients were entered with a mean age of 64 (43-83). Twenty-nine had adenocarcinomas of the gastroesophageal junction, 12 had squamous cancers. Ten patients had adenopathy, including six with celiac or periportal nodes. The most frequent toxicity was hematologic with 5 patients (12%) having grade 4 hematologic toxicities. Only 2 patients (5%) experienced grade 4 esophagitis defined as requiring parenteral nutrition. Patients who refused surgery and received the chemoradiation boost did not experience additional toxicity. The pathologic complete response rate was 29% and overall response rate was 71%. The 2-year progression free and overall survival rates were 51% and 54%, respectively.

We have also completed phase I/II studies of paclitaxel and radiation for locally advanced gastric cancer.[13, 14] The phase I study established the paclitaxel maximum tolerated dose as 50 mg/ m^2/ week with RT 50.4 Gy. We subsequently performed a phase II study to determine the activity and toxicity of paclitaxel and concurrent radiation for gastric cancer. Twenty-seven patients were studied. Twenty-

five had proximal gastric cancers, two had distal cancers. Eight had esophageal extension, 6 had celiac adenopathy and 7 had retroperitoneal adenopathy. Patients received paclitaxel, 50mg/m^2 by 3 hour intravenous (IV) infusion, weekly, on days 1, 8, 15 and 22 and 29. Radiation was administered concurrently to a total dose of 45.0 Gy, in 1.80 Gy fractions, for 25 treatments. Patients who were medically or surgically inoperable received a sixth week of paclitaxel with a radiation boost to 50.4 Gy.

Esophagitis and gastritis were the most important toxicities, grade 3 in four patients (15%), and grade 4 in three patients (11%). Five patients (19%) had grade 3 nausea. The overall response rate was 56%, including three patients (11%) with a complete response. The 2-year progression free and overall survival rates were 29% and 31%, respectively. This study suggested that concurrent paclitaxel and radiation demonstrates substantial local-regional activity in gastric cancer.

As described above, these regimens are well tolerated and have major activity. However, to have a substantial impact on survival, additional novel therapies are needed to prevent systemic relapses. Amplification of cellular oncogenes may, in part, underlie the aggressive behavior of adenocarcinomas of upper gastrointestinal cancers.[16] We have recently focused our research on identifying these molecular alterations and targeted them with therapeutic agents. The HER-2/*neu* gene encodes a 185-kd transmembrane glycoprotein receptor, p185^{HER2}, that has partial homology with the epidermal growth factor receptor.[17] HER-2/*neu* overexpression may transform cells by constitutive activation of signal transduction pathways. Furthermore by stimulating cell proliferation, HER-2/*neu* overexpression may promote tumor cell growth and metastasis.[18]

Antibodies directed at p185 can inhibit the growth ot tumors and of transformed cells that express high levels of this receptor.[19] As described below, clinical trials have shown that the human anti-p185^{HER2} monoclonal antibody trastuzumab has substantial activity in metastatic adenocarcinomas of the breast that overexpress HER-2/*neu*.[20-22] Furthermore trastuzumab may have synergistic activity with paclitaxel and cisplatin.[19,21]

We have completed a phase I/II study of trastuzumab with cisplatin, paclitaxel and radiation for patients with adenocarcinoma of the esophagus.[23] Eligible patients included those with T3, T4, or nodal disease. Patients with extensive loco-regional disease such as gastric extension, and adenopathy that included mediastinal, celiac, portal, and retroperitoneal disease were eligible. Patients with known metastatic disease to other organs, ascites, or peritoneal implants and those who had received prior irradiation to the planned field were ineligible. All patients received cisplatin 25 mg/m^2 and paclitaxel 50 mg/m^2 weekly for 6 weeks with radiation (RT) 50.4 Gy. HER-2/*neu* positive patients (2+/3+ by IHC) received weekly trastuzumab at dose levels of 1, 1.5, or 2 mg/kg weekly for 5 weeks after an initial bolus of 2, 3, or 4 mg/kg, respectively. Following completion of chemoradiation patients receive trastuzumab 6mg/kg q 21 days for 1 year. HER-2/*neu* negative patients received the same chemoradiation without trastuzumab as a control for toxicity. Dose limiting toxicities (DLTs) were defined as grade 3 esophageal, cardiac, or pulmonary toxicity. Sixteen of 46 screened patients (34%) overexpressed HER-2/*neu* by immunohistochemistry (ten 3+ and six 2+). Eight of 12 patients with HER-2/*neu* overexpression by IHC had an increase in the number of HER-2/neu genes, six from amplification of the HER-2/*neu* gene and two were hypderdiploid for chromosome 17. Thirty eight patients have been enrolled in the phase I/II study (16 HER-2/*neu* positive; 22 HER-2/*neu* negative controls). No increase in toxicity was seen with the addition of trastuzumab. One of 16 patients in the trastuzumab arm and 9 of 22 in the control arm had grade 3 esophagitis (p=<0.026). Mean left

ventricular ejection fraction (LVEF) for the trastuzumab group was 57% before treatment and 56% after treatment. Of the first 16 HER2 + patients, 14 had follow-up endoscopy. Eight of 14 (57%) had no residual cancer at endoscopic biopsy. Of the first 16 HER2+ patients, 2 with complete endoscopic biopsies did not undergo surgery. Twelve of 14 had a complete resection, three with path CR. These studies demonstrated that HER-2/*neu* is overexpressed in approximately one third of esophageal adenocarcinomas. Full dose trastuzumab can be incorporated with paclitaxel, cisplatin, and radiation without cardiotoxicity or increased esophagitis.

The HER-2/neu gene is overexpressed in only 33% of esophageal cancers. Expression is even less in gastric cancer. Therefore in this study we will begin to evaluate targeting to the epidermal growth factor receptor (EGFR). EGFR is overexpressed in approximately 80% of esophageal and gastric cancer.[24] Cetuximab is a mononclonal antibody that targets HER-1. We will investigate whether the addition of cetuximab to chemoradiation potentiates local control and gather preliminary data whether cetuximab can prevent the development of distant metastases.

1.2 Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor (EGFR) is a member of the erb B receptor tyrosine kinase family that includes erb B-2, erb B-3, and erb B-4. 25 It consists of an extracellular ligand-binding domain, a transmembrane region that anchors the receptor to the plasma membrane, and a cytoplasmic region containing a tyrosine kinase domain. Among the known natural ligands of EGFR include epidermal growth factor (EGF) and transforming growth factor α (TGF-α) which activate the receptor by binding to the extracellular domain and inducing the formation of receptor homodimers or heterodimers, followed by internalization of the receptor/ligand complex and auto-phosphorylation. It is now accepted that the EGFR signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis.26 In this signal network, erb B-2 is the major partner of EGFR because activated heterodimer complexes containing erb B-2 are more stable at the cell surface than complexes containing other EGFR family members.27,28 In addition erb B-2 can decrease the rate of ligand dissociation from the cognate receptor EGFR.29

1.3 EGFR Inhibition and the Cell Cycle

The effects of EGFR blockade on cell cycle progression have been investigated in several human cell types, including DiFi colon adenocarcinoma cells, non-transformed breast epithelial MCF10A cells, A431 squamous epithelial carcinoma cells, and DU145 prostatic cancer cells. These studies suggest that blocking EGFR with monoclonal antibodies such as cetuximab leads to cell cycle arrest in G1 which is accompanied by a decrease in cyclin dependent kinase (CDK) 2 activity, and an increase in the expression of CDK inhibitor p27KIP1.30, 31 In addition to inducing G1-phase arrest, EGFR blockade was also shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells.32

1.4 Cetuximab

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha.32 Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin

and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

1.5 Human Pharmacokinetics

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics.33 The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m2. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m2 as the dose increased from 20 to 200 mg/m2, and at doses >200 mg/m2, it appeared to plateau. The volume of the distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m2.

Following a 2-hour infusion of 400 mg/m2 of cetuximab, the maximum mean serum concentration (Cmax) was 184 □g/mL (range: 92-327 □g/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m2 produced a mean Cmax of 140 □g/mL (range 120-170 □g/mL). Following the recommended dose regimen (400 mg/m2 initial dose/250 mg/m2 weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

1.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-cetuximab antibodies were detected in 5% (28 of 530) of evaluable patients.33 In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anti-cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

1.7 Clinical Studies of Cetuximab

The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). Cetuximab was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single agent cetuximab was also evaluated. All

trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized, Controlled Trial

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients).34 In both arms of the study, cetuximab was administered as a 400 mg/m2 initial dose, followed by 250 mg/m2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the cetuximab plus irinotecan arm, irinotecan was added to cetuximab using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m2 every 3 weeks, 180 mg/m2 every 2 weeks, or 125 mg/m2 weekly times four doses every 6 weeks. An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.
The efficacy of cetuximab plus irinotecan or cetuximab monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with cetuximab, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.
The objective response rates (ORR) in these populations are presented in the following table.

Objective Response Rates per Independent Review

Populations	Cetuximab + Irinotecan		Cetuximab Monotherapy		Difference (95% CI[a])	
	n	ORR (%)	n	ORR (%)	%	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 – 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8, 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 – 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.

[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to cetuximab alone, patients randomized to cetuximab and irinotecan experienced a significantly longer median time to disease progression.

Time to Progression per Independent Review

Populations	Cetuximab + Irinotecan (median)	Cetuximab Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of cetuximab + irinotecan: cetuximab monotherapy with 95% confidence interval.

1.9 Single-Arm Trials

Cetuximab, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan containing regimen.35 Patients received a 20-mg test dose of cetuximab on day 1, followed by a 400-mg/m2 initial dose, and 250 mg/m2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m2 every 3 weeks or 125 mg/m2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan failure population. The median durations of response were 6.5 and 6.7 months, respectively.

Cetuximab was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen.35 Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all treated group and 14% for the irinotecan failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

1.10 EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDxTM test kit.[32] Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

1.11 Safety of Cetuximab in Clinical Studies

Anticipated Adverse Events

Except where indicated, the data described below reflect exposure to cetuximab in 633 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving cetuximab plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving cetuximab monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most serious adverse reactions associated with cetuximab were:

- Infusion reaction (3%);
- Dermatologic toxicity (1%);
- Interstitial lung disease (0.5%);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 14 (5%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving cetuximab monotherapy were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in the following table are based on the experience of 354 patients treated with cetuximab plus irinotecan and 279 patients treated with cetuximab monotherapy.

Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=279)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	49	10
Abdominal Pain	45	8	25	7
Fever[3]	34	4	33	0
Pain	23	6	19	5
Infusion Reaction[4]	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	25	3
Constipation	30	2	28	1
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
Hematic/Lymphatic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic/Nutritional				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0
Respiratory				
Dyspnea[3]	23	2	20	7
Cough Increased	20	0	10	1

Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=279)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Skin/Appendages				
Acneform Rash[5]	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab monotherapy.

[2] Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence".

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnea".

[5] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

Infusion Reactions

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 23% of patients receiving cetuximab monotherapy.

A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% (17/633) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension.

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 633 (<0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a

patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

Dermatologic Toxicity

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument.9 At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including S. aureus sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (10% Grade 3) of patients receiving cetuximab monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of S. aureus sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Cetuximab Use With Radiotherapy

In an initial study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with cetuximab, cisplatin, and radiation had a 95% incidence of rash (19% grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to cetuximab therapy should be done with appropriate caution.

Cetuximab and Radiation Increases Survival in Patients with Head and Neck Cancer

A phase III trial of 424 patients with untreated nonmetastatic squamous cell cancer of the head and neck has been reported by Bonner et al at the 2004 meetings of the American Society of Clinical Oncology.[36] This study randomized patients to cetuximab and radiation versus radiation alone. ***A dramatic improval in locoregional control and overall survival was demonstrated with the addition of cetuximab. The median survival was 54***

months treated with cetuximab/radiation versus 28 months for radiation alone. There was no increase in stomatis/esophagitis with the addition of cetuximab. We hypothesize that cetuximab may have the same benefit in patients with esophageal and gastric cancer.

1.12 Dose Rationale for Paclitaxel, Carboplatin, Cetuximab and Radiation for Esophageal Cancer:
Patiients on this clinical trial will receive paclitaxel 50mg/m^2/week, carboplatin AUC = 2/week, ceuximab 400 mg/m^2 initial dose followed by 250 mg/m^2/week and 50.4 Gy. The paclitaxel and radiation dose is the same radiation dose that was successfully utilized to incorporate trastuzumab with paclitaxel, cisplatin and radiation for patients with esophageal cancer.[23] Carboplatin will be utilized instead of cisplatin to reduce nausea and vomitting. Carboplatin has similar activity to cisplatin when used with taxanes for patients with metastatic esophageal and gastric cancer.[37] Other investigators have also successfully utilized carboplatin with chemoradiation for esophageal cancer.[38] The dose of carboplatin, AUC = 2/weekly, is the standard dose utilized with paclitaxel and radiation for lung cancer.[39,40] This study will use full dose cetuximab since the trial by Bonner et al did not show increased mucositis with cetuximab and radiation as compared to radiation alone.

2.0 STUDY DESIGN

This is a phase II study designed to determine the pathologic complete response rate, survival and safety of the combination in patients with adenocarcinoma or squamous cell carcinoma of the esophagus, gastroesophageal junction, or stomach.

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective: To determine the pathologic complete response rate by endoscopy and resection following concurrent cetuximab, paclitaxel, carboplatin and radiation in patients with esophageal and gastric cancer.

2.1.2 Secondary objectives: Secondary objectives will be to evaluate toxicities, progression-free and overall survival.

3.0 PATIENT ELIGIBILITY

3.1 Patients are required to have pathologically confirmed adenocarcinoma or squamous cell carcinoma of the esophagus, gastroesophageal junction, or stomach.

3.2 Patients may have mediastinal, celiac adenopathy, peri-portal and regional gastric lymphadenopathy.

3.3 There must be no evidence of distant organ metastases.

3.4 No prior radiation for gastric or esophageal cancer.

3.5 Patients must be $\geq$ 18 years of age, and nonpregnant

3.6 Patients must have an ANC $\geq$ 1,500/ul, platelets $\geq$ 100,000/ul, creatinine $\leq$ 2 x upper limit normal (ULN) and bilirubin $\leq$ 1.5 x ULN, and AST $\leq$ 3 x ULN.

3.7 ECOG performance status 0-2.

3.9 Patients must not have significant infection or other coexistent medical condition that would preclude protocol therapy.

3.9 Female patients, must either be not of child bearing potential or have a negative pregnancy test within 7 days of starting study treatment. Patients are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal. Pregnant or lactating females are not eligible.

3.10 All patients must sign informed consent

3.11 **Exclusion Criteria:**

Any of the following criteria will make the patient ineligible to participate in this study:

1) Acute hepatitis or AIDS.
2) Active or uncontrolled infection.
3) Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.
4) Prior therapy which specifically and directly targets the EGFR pathway.
5) Prior severe infusion reaction to a monoclonal antibody.
6) Any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s).

4.0 TREATMENT PLAN

	DAY						
Cetuximab	1	8	15	22	29	36	
Radiation	1→5	8→12	15→19	22→26	29→33	36→38	
Paclitaxel	1	8	15	22	29	36	→ Surgery or endoscopic bx 4-7 wks post chemo/rt
Carboplatin	1	8	15	22	29	36	

Cetuximab: 400 mg/m^2 day 1 then 250mg/m^2/week on days 8, 15, 22, 29, and 36.
Radiation: External radiotherapy 50.4 Gy at 180cGy fraction/day for 28 treatments
Paclitaxel: 50 mg/m^2/week over 1 hour IV, days 1, 8, 15, 22, 29,36.
Carboplatin: AUC=2, over 30 minute IV, days 1, 8, 15, 22, 29,36.

Subjects will receive paclitaxel at completion of cetuximab and prior to carboplatin

4.1 Cetuximab: 400 mg/m^2 initial dose followed by 250mg/m^2 weekly with chemoradiation.

In an effort to prevent a hypersensitivity reaction, all patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m^2 intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m^2 IV over 60 minutes. **The infusion rate of cetuximab must never exceed 5 mL/min. Patients must be continuously observed during the infusion for signs of anaphylaxis.**

Amendment #1 12/14/04
Amendment #3 6/15/05

Patients will be closely monitored for treatment-related adverse events, especially hypersensitivity reactions, during the infusion and the post-infusion observation hour. For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

4.2 Paclitaxel: 50 mg/m^2, IV over 1 hour, days 1, 8, 15, 22, 29, 36

Premedication:

- dexamethasone 20mg IV 30 minutes prior to the first cycle of paclitaxel
- ranitidine 50 mg IV (or other H_2 blocker) 30 minutes prior to the first cycle of paclitaxel
- **Note:** diphenhydramine is administered prior to cetuximab; repeat administration prior to paclitaxel is not required. The investigator should use clinical judgement to determine if the interval between the initial diphenhydramine dose prior to cetuximab and the infusion of paclitaxel requires re-administration of diphenhydramine.
- the dosages of dexamethasone and ranitidine may be reduced if no hypersensitivity reaction is observed on the first cycle.

Premedication for paclitaxel infusion may begin immediately after completion of cetuximab.

4.3 Carboplatin : AUC = 2 , IV over 30 minutes, in 250 cc D5W, days 1, 8, 15, 22, 29, 36 to be given after paclitaxel. The dose will be calculated based on the subject's **actual body weight** prior to starting chemoradiation and again on day 22. Standard IV hydration and antiemetics should be given.

The dose of carboplatin will be calculated based on the Calvert formula:

Total dose (mg) = Target AUC x (Creatinine clearance + 25)

Note:

- The carboplatin dose is calculated in mg, not mg/m^2.
- **The target AUC for carboplatin treatment in this trial is AUC=2**
- Creatinine clearance (CrCL) can either be measured or estimated based on serum creatinine using the following formula:

Cockroft-Gault formula

For males:

$$\text{CrCl (mL/min)} = \frac{\text{(140-age) x (weight in kg)}}{\text{72 x serum creatinine in mg/dL}}$$

For females:

$$\text{CrCl (mL/min)} = 0.85 \times \frac{\text{(140-age) x (weight in kg)}}{\text{72 x serum creatinine in mg/dL}}$$

Actual body weight is to be used in the calculation of doses for this study

4.4 Ancillary Therapy: Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

4.5 Concomitant Medications: Patients may receive all concomitant therapy deemed necessary to provide adequate support, with the exception of the therapies detailed below:

- No other investigational agents may be used during the study.
- No other cytotoxic agents or radiotherapy may be used during the study.

5.0 TREATMENT PLAN - RADIATION

5.1 The total dose will be 50.4 Gy in 1.80 Gy fractions given once daily, for 5 days per week for 28 fractions, on days 1-38. High energy linear accelerators ($\geq$ 6 MV) should be used.

5.2 All fields will be treated each day and portal films will be obtained of each field per week or more often if needed. Multifield techniques will be used to limit the total dose to normal structures.

5.3 Radiation Fields

The superior and inferior borders will be 5 cm. beyond the tumor and the lateral borders will be 2 cm. beyond the tumor as defined by endoscopy and radiographic studies. A barium swallow will also be obtained at the time of simulation to confirm the location of the esophagus. If the primary tumor is above the carina (proximal esophagus), the supraclavicular nodes will be included in the RT field to 50.4 Gy.

5.4 The fields must be planned with the assistance of a RT simulator.

5.5 Beam Energy: Megavoltage equipment $\geq$ 6 MV is required.

5.6 Treatment Distance: Minimal treatment distance to skin should be 80 cm. for SSD technique and minimum isocenter distance should be 80 cm. for SAD techniques.

5.7 Blocking:

a) In the case of x-ray beams, primary collimation may be used and blocking will be required only for shaping of the ports to exclude tissues that are not to be radiated.

b) In case of sloping surface such as the thoracic inlet, compensating filters are recommended.

c) If compensating filters are not available, the appropriate reductions in field size must be done at prescribed dose levels to avoid excessive radiation of a particular area.

5.8 Normal Tissue Dose:

The spinal cord dose must not exceed 45 Gy maximum. Normal lung (more than 2 cm. outside the target volume) must not receive more than 25 Gy. The maximal dose to the heart as a whole is limited to 40 Gy, but a dose as high as 45 Gy could be given to less than 50 percent of the heart.

5.9 Fractionation:

a) Each field to be treated every day.

5.10 Treatment Planning: (Use of CT strongly recommended):

a) Isodose distribution at the mid-transverse plane of the tumor should be submitted. For the purpose of the distribution, it may be assumed that the central axis passes through the mid-plane of the tumor. Doses are prescribed and calculated without tissue inhomogeneity correction.

5.11 Dose Specifications:

For the following portal arrangements, the target dose shall be specified as follows:

a) For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

b) For an arrangement of 2 or more intersecting beams: the isodense line which covers the volume at risk.

c) For a single beam: on the central ray at the center of the target area.

The dose should not vary by more than 15% over the entire target volume.

5.12 Dose Definition:

Absorbed dose is described in Centigray (cGy) to muscle tissue

1 cGy = 1 rad

5.13 Postoperative RT Course:

There is no planned postoperative RT for unresectable patients or patients with positive margins following surgery.

6.0 SURGICAL RESECTION

6.1 Two to four weeks after completing chemoradiation, patients will be reevaluated for distant metastases by physical examination and radiographic studies. If no disease progression is observed, and there are no medical or surgical contraindications, the patient may undergo surgery approximately 4-7 weeks after the last day of radiotherapy.

7.0 DOSE TOXICITIES, MODIFICATIONS AND MANAGEMENT

Adverse events should be coded according to CTCAE version 3 (Appendix D). Infusion reactions should be graded according to allergic reaction/hypersensitivity.

Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

7.1 Toxicity and Dose Modification during chemoradiation

7.1.1 Hematologic Toxicity:
The dose of paclitaxel, carboplatin, and radiation will be modified according to blood counts on the day of treatment as shown in the table below. Cetuximab will not be modified for hematologic toxicity.

Treatment Day Blood Counts		Dosage
ANC	Platelet Count	
> 1,000/µl	> 75,000/ µl	Full dosage paclitaxel, an carboplatin.
500-999/ µl	50,000 – 75,000 µl	Hold carboplatin and paclitaxe until ANC > 1,000 and Plt > 75,000 and then restarted at ful doses
< 500/ µl	< 50,000 µl	Hold XRT, carboplatin an paclitaxel; When ANC >1,00(and Plt > 75,000 resume XRT and 75% of carboplatin an paclitaxel doses. This dos reduction of paclitaxel an carboplatin is permanent Cetuximab is to be continue without interruption.

Patients who have required two dose reductions and experience a third episode of ANC <1,000/ul or Platelet < 75,000/ul may complete radiation and cetuximab on study, but will not receive additional carboplatin and paclitaxel.

7.1.2 Non-hematologic Toxicity

7.1.2.1 Cetuximab related toxities:
Cetuximab will be modified only for toxicities that are thought to be related to cetuximab such as cutaneous toxicities. Cetuximab dosage will be modified only as per section 7.2.

7.1.2.2 Chemotherapy and RT related toxicities
Carboplatin, paclitaxel, and radiation will be held for any Grade 3 or Grade 4 nonhematologic toxicity. Treatment will not be resumed until non-hematological toxicity has resolved to no greater than Grade 2. When treatment is resumed, patients will receive a 25% dose reduction of carboplatin and paclitaxel. Dose reductions are permanent. If a second episode of Grade 3 or Grade 4 nonhematologic toxicity

occurs, treatment again will be held until non-hematological toxicity has resolved to no greater than Grade 2. When treatment is resumed, patients will receive a second 25% dose reduction of paclitaxel and carboplatin. Dose reductions are permanent. If a third episode of Grade 3 or Grade 4 nonhematologic toxicity occurs, patients may complete radiation and cetuximab on study, but will not receive additional carboplatin and paclitaxel.

7.1.2.3 ANAPHYLAXIS TO PACLITAXEL

Patients who develop anaphylaxis (grade 4 hypersensitivity reaction) to paclitaxel despite appropriate premedication should not receive additional Paclitaxel. They may continue on study receiving cetuximab, carboplatin and radiation.

7.2 Cetuximab Dose Modifications

Cetuximab dose levels for toxicity:

Dose levels for cetuximab are as follows:

Table 3: Cetuximab Dose Levels

	Cetuximab
Weekly Cetuximab Dose	250 mg/m^2
Dose Level -1	200 mg/m^2
Dose Level -2	150 mg/m^2

There will be no dose level reductions below a weekly dose of 150 mg/m^2.

7.2.1 Management of Infusion Reactions

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (eg, diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, maintain the cetuximab dose and infusion rate. Consideration should be given to administration of acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) prior to the subsequent cetuximab infusion if not contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.

Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

7.2.2 Management of Pulmonary Toxicity

In the event of acute onset (grade ≥2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

7.2.3 Management of Dermatologic Toxicity

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe acneiform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

If a patient experiences a grade 3 acneiform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. If a subject experiences Grade 3 acne-like rash (acne/acneiform rash), cetuximab will be interrupted. If the rash improves and is no longer severe, treatment may be resumed without any change in dose level. The recurrence of Grade 3 acne-like rash may require further interruption of therapy, with dose reductions at re-treatment after improvement (initially to 200 mg/m2 and subsequently to 150 mg/m2) A rash that occurs only within the radiation field should be considered as radiation dermatitis and no cetuximab dose reduction is required.

Cetuximab Dose Modification Guidelines

Grade 3 Acneform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

8.0 REQUIRED DATA

8.1

	Prior to treatment	Weekly Chemorad.	Chemorad Completion	Follow-up q 6 month@
Signed Consent	X			X
History / Baseline Symptoms	X			X
Physical Examination:	X	X	X	X
Vital Signs	X	X	X	X
Toxicity Assessment		X	X	X
Laboratory: **				
CBC, Diff, Plt	X	X	X	X
Glucose, Lytes,Mg	X	X	X	X
BUN, CR	X	X	X	X
LFTs,	X	X	X	X
TP, Alb, Ca,	X			
HCG*	X			
Staging:			X	X
Chest/Abdominal CT***	X		X	
Endoscopy****	X			

*Women of childbearing potential must have a negative HCG within 7 days of starting study treatment and q3 months while on study treatment.
** Within 15 days of treatment
*** Within 4 weeks of treatment
**** Within 6 weeks of treatment
@ When off study completely follow for survival q 6 months.

9.0 DRUG AVAILABILITY, PREPARATION AND STORAGE

9.1 Cetuximab

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

9.1.1 Supplier/How Supplied

Bristol-Myers Squibb (BMS) will supply cetuximab free of charge to the patient. The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8 °C. Each vial contains the following active and inactive ingredients per 1.0 mL: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

9.1.2 Packaging and Labeling

Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

9.1.3 Handling and Dispensing of Cetuximab

Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations. Cetuximab should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients.

9.1.4 Storage Requirement/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

9.1.5 Preparation and Administration

Cetuximab must not be administered as an iv push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
2. Place the syringe into the syringe driver of a syringe pump and set the rate.
3. Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
4. Connect up the infusion line and start the infusion after priming the line with cetuximab.
5. Repeat procedure until the calculated volume has been infused.
6. Use a new needle and filter for each vial.

7. Maximum infusion rate should not exceed 5 mL/min.
8. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

9.1.6 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 866 339-4267 or 203 677-7017. Cetuximab therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

9.1.7 Cetuximab Records at Investigational Site(s)

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:

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

BMS will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

9.1.8 Drug Ordering and Accountability

Following submission and approval of the required regulatory documents, a supply of cetuximab may be ordered from BMS. Investigators must fax a completed Drug Request Form to (866 227-7229) or email (cetuximab.drug@bms.com) the order to the BMS Clinical Supply Manager.

Initial shipments will consist of 13 boxes (52 vials, each containing 100 mg of cetuximab), which will be sufficient for 8-9 weeks of treatment for 1 patient or 4 weeks of treatment for 2 patients (depending on patients' BSA). Allow 5 business days for shipment of drug from receipt of the C225 (cetuximab) Clinical Supply Shipment Request form.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Each drug box (4 vials) will contain a large label on the side of the box with the study's protocol number. It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be utilized for this study. Inside each shipping container, a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping may be included. This unit may be attached to an information card. The LCD display will show "OK" (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarms have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning or shipment contact Bristol-Myers Squibb at 800 743-9224.

Important Reorder Instructions
Reorders should be emailed directly to BMS using cetuximab.drug@bms.com for shipment within 5 days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose (~7-9 for initial dose, ~4-6 for weekly doses, dependent on patient's BSA), and that shipments may take 5 business days from BMS receipt of request. Sites may request more than 52 vials for resupply shipments only if there is adequate storage space. Quantities must be in multiples of 52.

9.1.9 Receipt of Drug Shipment
Study drug shipments may include a TagAlert™ unit and attached information card (see above for description) and a clinical supply packing list (CSPL). If included, the pharmacist/study personnel responsible for the clinical study product will need to indicate the condition of the shipment, record the TagAlert™ results, and sign the CSPL in the designated areas. The pharmacist/study personnel will keep a photocopy for the site's records, and return the original to BMS, using the enclosed, pre-addressed envelope. The TagAlert™ unit can be discarded after the reading is recorded on the CSPL.

9.1.10 Drug Destruction and Return
At the completion of the study, all unused study drugs will be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. If approved procedures are not in place, please contact Bristol-Myers Squibb at 800 743-9224 for assistance.

9.1.11 Drug Inventory Records
It is the responsibility of the Investigator to ensure that a current record of study drug disposition is maintained at each study site where the study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

9.2 Paclitaxel
Paclitaxel is commercially available under several brand names. The appropriate package insert should be consulted for information regarding formulation, preparation, storage and stability, and adverse events.

9.3 Carboplatin

Carboplatin is available as an aqueous solution for injection in single-dose vials containing 50 mg, 150 mg, 450 mg, or 600 mg or as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 100 mg, or 450 mg of carboplatin for administration by intravenous infusion. Each vial of lyophilized powder contains equal parts by weight of carboplatin and mannitol.
Commercially available supplies will be used for this study.

Preparation: Immediately before use, the content of each vial must be reconstituted with either Sterile Water for injection, USP, 5% dextrose in water, or 0.9% Sodium Chloride injection, USP, to produce a Carboplatin concentration of 10mg/ml. When prepared as directed, Carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin solutions be discarded 8 hours after dilution.

Note: Aluminum reacts with Carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Carboplatin.

Storage and Stability: Unopened vials of Carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Administration: Administer over ½ hours after completing the Paclitaxel infusion. The Calvert Equation (Dose = AUC (CCC+25) will be used to achieve the desired AUC where CCC= Wt (140-age)/72

10.0 CRITERIA FOR RESPONSE OR PROGRESSION

10.1 Measurement of Response

Response will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. 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.

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 with conventional techniques (PET, CT, MRI, x-ray) or as > 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

10.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. 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 to assess the anti-tumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

10.3 Response Criteria

Response and progression will be measured by comparing tumor size at time of study entry with measurements taken at completion of chemoradiation and every 4 months thereafter. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination.

10.4 Evaluation of target lesions-RECIST criteria

- Complete Response (CR): Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination.

11.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

A patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible.

Patients should be removed from therapy if any of the following occurs:

1. Disease progression. Every effort should be made to document objective evidence of tumor progression radiographically and not solely based on clinical and/or tumor marker suggestions of progression.
2. The occurrence of unacceptable toxicity indicating the need for cessation of treatment.
3. The physician feels it is in the best interest of the patient to stop treatment.
4. Patient refusal to continue with therapy.

5. Non-compliance by the patient with protocol requirements.
6. Patient is lost to follow-up. If a 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, if possible.
7. Termination of the study by investigator or BMS/ImClone.
8. Patient becomes pregnant.

Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. All WOCBP MUST have a negative pregnancy test within 7 days prior to receiving investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The Investigator must immediately notify BMS of this event.

12.0 PATIENT REGISTRATION AND DATA REQUIREMENTS

Eligibility Checklist (Appendix G) with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 383-3001, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed/faxed to:

Teresa A. Kennedy, R.N., C.C.R.A.
Administrative Director, BrUOG
Brown University Oncology Group,
167 Angell Street, Box G-H
Providence, RI 02912
Fax: (401) 383-3000
Phone: 401-383-3001

Response data must be clearly documented in the patient's record. Support documentation used to determine response and adverse reaction forms must be mailed or faxed as above. Severe toxicities should be confirmed with the treating physician if the grade is unclear or it is unclear whether the toxicity is related to treatment. All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form.

13.0 ADVERSE DRUG REACTION (ADR) REPORTING

13.1 Adverse Events Related To Study Conditions

BMS considers the SAE reporting period to begin with signing of the informed consent.
AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

13.2 Handling of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence that at any dose:

1. results in death,
2. is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
3. requires inpatient hospitalization or causes prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. is a congenital anomaly/birth defect,
6. results in the development of drug dependency or drug abuse,
7. is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) For reporting purposes, BMS also considers the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.

Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site. For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. Bristol-Myers Squibb will be provided with a simultaneous copy via facsimile of all

adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at:

http://www.accessdata.fda.gov/scripts/MedWatch/

MedWatch forms should be sent to the FDA online at the above internet address or at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)

All SAEs should simultaneously be faxed to Bristol-Myers Squibb at:
Global Pharmacovigilance and Labeling
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

13.3 Overdose
An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

13.4 Reporting of AE Information Following Study Completion
Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. In BMS trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

13.5 Investigators are required by Federal Regulation to report possible adverse drug reactions. See Appendix I for ADR reporting guidelines. All adverse reactions should be as per NCI Common Toxicity Criteria.

Direct questions regarding drug therapy to the Brown University Oncology Group (BrUOG) Central Office, phone: (401)-863-9139 fax: (401) 863-7735, which will in turn notify the Principal Investigator.

Reporting requirements and procedures depend upon: (1) whether investigational agents are suspected of causing toxicity, (2) whether the possibility of such a toxicity was reported in the protocol, consent form or manufacturer's literature (expected toxicity) and (3) severity or grade of the toxicity. All

reactions in a reportable category must be reported unless it is documented on flow sheets and/or follow-up forms that the treatment is definitely not responsible for the toxicity.

13.6 Types of Report

Telephone Report: Contact the Brown University Oncology Group (BrUOG) Central Office, 401-383-3000, within 24 hours of the event.

Written Report: Send the original copy of either the FDA MEDWATCH form or the NCI Adverse Drug Reaction (ADR 3500A) form whichever is applicable to the ADR Guidelines in Appendix C within 10 days of the event to the Brown University Oncology Group (BrUOG) Central Office:

Teresa A. Kennedy, R.N., C.C.R.A.
Administrative Director, BrUOG
Brown University Cancer Center
172 Cushing Street, Box G-C
Providence, RI 02912
Fax: (401) 383-3001

Report to FDA and/or Pharmaceutical Company: The BrUOG Central Office will notify by phone and/or send all drug reaction reports to the FDA and/or Pharmaceutical Company. A copy of the form will be kept by the BrUOG Central Office and a copy will be forwarded to Bristol Myers Squibb Inc.

14. 0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

The Brown University Cancer Center, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Protocol Chairman (Harold Wanebo M.D. and Howard Safran M.D.) and Brown University Cancer Center Administrative Director (Teresa Kennedy) will monitor this study. The case report forms will be monitored every 3 months for accuracy, completeness, adherence to the protocol and regulatory compliance. An audit will be performed at each of the sites every 12 months to check the case report forms against medical records to verify completeness and accuracy.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CFRs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Bristol-Myers will notify the Principle Investigator of these events.

15.0 STATISTICAL CONSIDERATIONS

15.1 Sample Size Determination

The primary objective of this phase II trial is to estimate the rate of complete pathologic response as determined by surgical resection or post treatment endoscopy (for patients not undergoing resection) for the treatment regimen being tested. A clinical meaningful pathologic response rate is 30%. A Simon two-stage design will be used in this study. The first 13 evaluable patients will be assessed for response. The trial will be terminated early if 0 or 1 complete pathologic responses are observed in these patients, and it will be concluded that the true response rate is unlikely to be ≥10%. If at least 2 complete responses are observed, accrual will continue until a total of 28 evaluable patients are enrolled. The treatment regimen will be accepted if at least 6 pathologic complete responses are observed from the 28 patients. Otherwise, the treatment will be rejected. With a significance level (i.e., the probability of accepting the new treatment when the true complete response rate is 10% or less) of 0.05 and statistical power of 85%, the probability of stopping accrual early when the true complete response rate is 10% is 0.62.

With a total accrual of 28 evaluable patients, the maximum width of the exact two-sided 95% confidence interval will be 36%.

15.2 Data Set Descriptions

The Response-Evaluable Subset is defined as all patients who received at least one dose of study medication (all treated patients). The analysis of pathological complete response will be performed on response-evaluable patients. All treated patients will be included in the analyses of progression free survival, overall survival and toxicities.

BrUOG-E/G-203 is a Brown University study piloting the regimen of cetuximab, paclitaxel, carboplatin and radiation for a proposed Radiation Therapy Oncology Group (RTOG) phase III trial. The initial protocol was to look at clinical complete response rate but RTOG and CTEP now want to see the pathological complete response rate. Only two thirds of the current 40 patients have had surgery therefore we need to increase the accrual to a total of 60 patients to get the pathological response rate to 40. Following discussions with CTEP, the RTOG and Bristol-Myers Squibb, study accrual will therefore be increased to 60 patients.

15.3 Analyses

15.3.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized using descriptive statistics for all treated patients.

15.3.2 Efficacy Analyses

The primary efficacy endpoint for this trial is pathological complete response rate, which is defined as the total number of patients with complete pathological response divided by the number of response-evaluable patients. A corresponding 95% two-sided confidence interval will also be provided.

Secondary efficacy measures include the median progression free survival (PFS) and the median overall survival and 1-year survival rate. PFS is defined as the time from start of treatment until the date of disease progression or death. A patient who has received study treatment but has neither progressed nor died will be censored on the date of the last tumor assessment. Estimates of median PFS, median survival and the one year survival rate will be calculated using the Kaplan-Meier product-limit method, along with corresponding 95% confidence intervals.

Administrative Change #C 02/01/06

15.3.3 Safety Analyses

All adverse events will be summarized without regard to causal relationship and by causal relationships to study drug, based on the Investigator's opinion. Worst toxicity grades per subject will be tabulated for adverse events and lab toxicities. Any serious adverse event or adverse event resulting in premature and permanent discontinuation of study drug will be described in detail.

BrUOG-E/G-203 is a Brown University study piloting the regimen of cetuximab, paclitaxel, carboplatin and radiation for a proposed Radiation Therapy Oncology Group (RTOG) phase III trial. In the CTEP review of the proposed RTOG phase III trial, it was requested that ESO-203 accrual be increased to include at least 40 patients to gather additional safety data. Following discussions with CTEP, the RTOG and Bristol-Myers, study accrual will therefore be increased to 40 patients.

16.0 PROTECTION OF HUMAN SUBJECTS

16.1 Informed Consent

The investigator will obtain written informed consent from all participating patients or their authorized representatives. The Brown University Oncology Group will review the proposed informed consent form from each site and will ensure the informed consent form conforms with FDA guidelines. The form must be signed, witnessed and dated. A sample consent form is contained in Appendix A. Copies of the signed document should be given to the patient and filed in the Brown University Oncology Group Central Office, as well as the patient's medical record, if in conformance with the institution's standard operating procedures.

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

16.2 Institutional Review Board

This protocol, consent procedures and any amendments must be approved by an institutional review board (IRB) operating in compliance with current regulations of the Food and Drug Administration (FDA). A letter of approval will be sent to the Brown University Oncology Group (BrUOG) Central Office prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study, as well as to any unexpected serious or unusual adverse events.

16.3 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to BMS. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.
Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

17.0 DATA SAFETY MONITORING BOARD

- All trials by the Brown University Oncology Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets three times per year with any additional meetings scheduled when needed. The responsibilities of the DSMB are as follows:
- Familiarize themselves with the research protocol(s).
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or be terminated based on these data. The DSMB reviews trial performance information such as accrual information. The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee with assurance that these have in fact been sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRBs.

18.0 REFERENCES

1. Jemal AM, Samuels A, Ghafoor A, eal al: Cancer Statistics, 2003. CA Cancer J Clin 53:5-26, 2003.

2. Hesketh PJ, Clapp RW, Doos WG, et al: The increasing frequency of adenocarcinoma of the esophag us. Cancer 64:526-530, 1989.

3. Blot WJ, Devesa SS, Kneller RW, et al: Rising incidence of adenocarcinoma of the esophagus and gastric cardia JAMA 265:1287-1289, 1989.

4.Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. Semin Oncol 1996;23:281-291.

5. Burmeister BH, Smithers BM, Fitzgerald L, et al. A randomized phase III trial of preoperative chemoradiation followed by surgery (CR-S) verus surgery alone (S) for localized resectable cancer of the esophagus. Proc ASCO: 21:130a,2002 (abstr 518).

6. Kelsen DP, Ginsberg R, Qian C, Gunderson L, Mortimer J, Estes N, Haller D, Ajani J, Kocha W, Roth J, Minsky B. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339(27):1979-84, 1998

7. Ajani JA. Chemotherapy for gastric carcinoma: new and old options. Oncology 12:44-47, 1998.

8. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335:462-467, 1996.

9. MacDonald, J.S.; Smalley, S.R.; Benedetti, J.; Hundahl, S.A.; Estes, N.C.; Stemmermann GN, Haler DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy After Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction. N. Engl. J. Med. 2001, *345*, 725-30.

10. Ajani JA: Standard chemotherapy for gastric carcinoma: Is it a myth? J Clin Oncol18:4001-4003, 2000

11. Ajani, J.A.; Ilson, D.H.; Dougherty, K.; Pazdur, R.; Lynch, P.M.; Kelsen, D.P. Activity of Taxol in Patients with Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus. J. Natl. Cancer Inst. 1994, *86*, 1086-1091.

12. Choy H, Rodriguez FF, Koester S, Hilsenbeck S, et al: Investgation of taxol as a potential radiation sensitizer. Cancer, 71:11, 3774-3778, 1993.

13. Safran H, King T, Choy H, Hesketh P, Wolf B, Altenhein E, Sikov W, Rosmarin A, Aerley W, Radie-Keane K, Cicchetti G, Lopez F, Bland K, Wanebo H. Paclitaxel and Concurrent Radiation for Locally Advanced Pancreatic an Gastric Cancer: A Phase I Study. J Clin Oncol 15:901-907, 1997.

14 . Safran H, Wanebo HJ, Hesketh PK, Akerman P, Iannitti D, Cioffi W, Dipetrillo T, Wolf B, Koness J, McAnaw R, Moore T, Chen M, Radie-Keane K. Paclitaxel and concurrent radiation for gastric cancer. Int J Radiat Oncol Biol Phys 46:889-894, 2000.

15. Safran H, Gaissert H, Akerman P, Hesketh P, Chen MH, Moore T, Koness J, Graziano S, Wanebo H. Paclitaxel , cisplatin and concurrent radiation for esophageal cancer. Cancer Invest 1:1-7, 2001.

16. Mizutani T, Onda M, Tokunaga A, Yamanaka, N, Sugisaki Y. Relationship of C-*erb*B-2 protein expression and gene amplification to invasion and metastasis in human gastric cancer. Cancer 72: 2083-2088, 1993

17. Disis ML, Cheever MA. HER-2/neu protein: A target for antigen-specific immunotherapy of human cancer. Advances in Cancer Research 341-3761, 1997

18. Lin JT, Wu MS, Shun CT, Lee WJ, Sheu JC, Wang TH. Occurrence of microsatellite instability in gastric carcinoma is associated with enchanced expression of erbB-2 oncoprotein. Cancer Res 1428-1430, 1996

19. Hancock MC, Lanagton BC, Chan T, Toy P, Monahan JJ, Mischak RP and Shawver LK: A monoclonal antibody against c-*erbB*-2 protein enhances the cytotoxicity of *cis*-diamminedichloraplatinum against human breast and ovarian tumor cell lines. Cancer Research 51, 4575-4580, September 1, 1991.

20. Shak S, Paton V, Bajamonde A., Fleming T, Eiermann W, Wolter J, Baseiga J and Norton L: Addition of Herceptin (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2+/MBC) markedly increases anticancer activity: A randomized, multinational controlled Phase III trial. Proceedings of ASCO 17: 377, 1998.

21. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, Paton V, Shak S, Lieberman G and Slamon D: Efficacy and safety of Herceptin (humanized anti-HER2 antibody) as a single agent in 222 women with HER2 overexpression who relaped following chemotherapy for metastatic breast cancer. Proceedings of ASCO 17:376, 1998.

22. Baselga J, Triapthy D, Mendelsohn J, Baughman S, Benc CC, Dantis L, Sklarin NT, Seidman AD, Hudis CA, Moore J, Rosen PP, Twaddell T, Henderson IC and Norton L: Phase II study of weekly intravenous recombinant humanized anti-p 185HER2 monoclonal antibody in patients with HER2/*neu*-overexpressing metastatic breast cancer. J Clin Oncol 14:737-744, 1996.
23. Safran H, DiPetrillo T, Nadeem A, Steinhoff M, Tantravahi U, Rathore R, Wanebo H, Hughes M, Maia C, Tsai J, Pasquariello T, Pepperell JR, Cioffi W, Kennedy T, Reeder L, Adrian A, Chak B, Choy H. Herceptin, paclitaxel, cisplatin and radiation for adenocarcinoma of the esophagus: A phase I study. In press Cancer Investigation 2004.
24. Disis ML, Cheever MA. HER-2/neu protein: A target for antigen-specific immunotherapy of human cancer. Advances in Cancer Research 341-3761, 1997
25. Mendelsohn J, Baird A, Fan Z, Markowitz SD: Growth factors and their receptors in epithelial malignancies, in Mendelsohn J, Howley PM, Israel MA, Liotta LA (eds): The Molecular Basis of Cancer. Philadelphia, PA, W.B. Saunders Company, 2001, pp 137-144.
26. Huang SM, Harari PM: Epidermal growth factor receptor inhibition in cancer therapy: biology, rationale and preliminary clinical results. Invest New Drugs 17:259-269, 1999.
27. Tzahar E, Waterman H, Chen X, et al: A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. Mol Cell Biol 16:5276-5287, 1996.
28. Lenferink AE, Pinkas-Kramarski R, van de Poll ML, et al: Differential endocytic routing of homo-and hetero-dimeric erb B tyrosine kinases confers signaling superiority to receptor heterodimers. EMBOJ 17:3385-3397, 1998.
29. Karunagaran D, Tzahar E, Beerli RR, et al: Erb B-2 is a common auxiliary subunit of NDF and EGF receptors: implications for breast cancer. EMBO J 15:254-264, 1996.
30. Chou JL, Fan Z, DeBlasio T, Koff A, Rosen N, Mendelsohn J. Constitutive overexpression of cyclin D1 in human breast epithelial cells does not prevent G_1 arrest induced by deprivation of epidermal growth factor. *Breast Cancer Res Treat.* 1999; 55:267-283.
31. Fan Z, Shang BY, Lu Y, Chou JL, Mendelsohn J. Reciprocal changes in $p27^{KIP1}$ and $p21^{CIP1}$ in growth inhibition mediated by blockade or overstimulation of epidermal growth factor receptors. *Clin Cancer Res.* 1997; 3:1943-1948.
32. Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. *J Clin Invest.* 1995; 95:1897-1905.
33. ERBITUX™ (cetuximab) package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company. 2004. ER-B0001-02-04.
34. Cunningham D, Humblet Y, Siena S, et al. Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC). *Proc Amer Soc Clin Oncol.* 2003;22:252. Abstract 1012/oral presentation.
35. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II Trial of Cetuximab (C225, Erbitux™) in Patients with Refractory Colorectal Cancer that Expresses the Epidermal Growth Factor Receptor. (manuscript accepted for publication by *J Clin Oncol*).
36. Bonner Ja, Harari PM, Giralt J, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: A phase III study of high dose radiation therapy with or without cetuximab. Proc Am Soc Clin Oncol 22:2004 abstract 5507
37. Tsai J, Berkenblit A, Akerman P, Ahmed N, Rathore R, Harrington D, Roye D, Stuart K, Kennedy T, Safran H. Phase I/II study of docetaxel, capecitabine and carboplatin in metastatic esophagogastric cancer. Proc Am Soc Clin Oncol 22:2004 (abstr 4035)
38. Gray, J.R.; Meluch, A.A.; Kalman, L. Neoadjuvant Paclitaxel/Carboplatin/5-FU/Radiaiton Therapy for Localized Esophageal Cancer: Update of a Minnie Pearl Cancer Research Network Phase II Trial. Proc. Am. Soc. Clin. Oncol. 18:1999.

39. Choy H, Akerley W, Safran H, Clark J, Rege V, Papa A, Glantz M, Puthawala Y, Soderberg C, Leone L. A phase I trial of concurrent weekly taxol administered as a 3 hour infusion and radiation therapy for advanced non-small cell lung cancer. J Clin Oncol 12:2682-2686, 1994.
40. Choy H, Akerley W, Safran H, Graziano S, Chung C, Williams T, Cole B, Kennedy T. Multi-institutional phase II trial of paclitaxel, carboplatin and concurrent radiation therapy for locally advanced non-small cell lung cancer. J Clin Oncol 16;3316-33322, 1998.

APPENDIX A

Suggested Consent Form

BrUOG-E/G-203

CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER

You are being asked to take part in a research project. All research projects carried out at _____ institutions are covered by the rules of the Federal Government as well as rules of the State and each institution. Under these rules, the researcher will first explain the project and then ask you to participate. You will be asked to sign this agreement which states that the project has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the project. He or she will explain how the project will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the project. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research project. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the project, please sign this form in front of the person who explained the project to you. You will be given a copy of this form to keep.

1. Nature and Purpose of the Project

You have been asked to take part because you have esophageal or stomach cancer. Previous studies have evaluated the use of radiation therapy and chemotherapy (anticancer drugs) in esophageal and gastric cancer. To try to improve on these results, cetuximab will be given in addition to the chemotherapy drugs paclitaxel and carboplatin and radiation therapy. Cetuximab is an antibody that attaches to the epidermal growth factor receptor on cancer cells. Cetuximab in combination with radiation increases lifespan for patients with inoperable head and neck cancer. This is one of the first studies using cetuximab with radiation for patients with esophageal and gastric cancer. The main objectives of this study are to determine the effectiveness of the combination of cetuximab, paclitaxel, carboplatin and radiation as a treatment for patients with esophageal and stomach cancer.

Your doctors are studying the combination of cetuximab, carboplatin, and paclitaxel in an effort to improve the treatment of patients with espophageal and gastric cancer. This trial

is supported by Bristol Myers Squibb (the maker of cetuximab, carboplatin and paclitaxel) through the Brown University oncology Group (BrUOG).

2. Explanation of Procedures

You will receive cetuximab, paclitaxel and carboplatin with radiation for six weeks. You will get radiation treatments five days a week for 28 treatments. Radiation treatments take about 10 minutes and are given as an outpatient. Starting the same day as your first dose of radiation, you will be given cetuximab, carboplatin and paclitaxel by vein as an outpatient. You will get decadron, diphenhydramine and ranitidine by vein over 30 minutes before each dose of chemotherapy to lower the risk of an allergic reaction to the paclitaxel and cetuximab. You will get cetuximab over 1-2 hours. Then you will receive paclitaxel over one hour and carboplatin over 30 minutes. When you receive chemotherapy, you will get medicines to prevent nausea. You will get cetuximab paclitaxel, and carboplatin once a week for six weeks with the radiation.

Blood tests, taking about two teaspoons of blood, will be done each week to check your blood counts before the chemotherapy is given. If your blood counts are too low, the dose of paclitaxel and carboplatin will be decreased or a dose of chemotherapy will be omitted; if your blood count is very low, radiation may also be stopped temporarily until the blood count rises.

Three weeks after the paclitaxel, carboplatin and radiation are completed your physicians will evaluate you for surgery with additional blood tests, a CAT scan of your chest and abdomen and an endoscopy. You and your doctors will decide whether you will have surgery 4-6 weeks after completion of chemotherapy and radiation to try to remove the cancer.

Following completion of all of your treatments you will have a CT scan of the chest and abdomen and blood tests every 6 months to find out if and when your cancer starts to grow again. These tests are not experimental and are part of routine check-ups of patients with your disease.

Cetuximab will be supplied at no charge by Bristol Myers Squibb.

Because of potential harm to the unborn child, if you are a woman of childbearing potential, you must agree to use adequate birth control measures before the start of the trial and throughout your participation in this trial. If you are a man, you should avoid fathering children, while receiving treatment on this study. If you become pregnant or father a child while participating in this study, you will need to notify your physician immediately.

If you have any questions regarding this study, you may contact the Dr. Howard Safran at (401) 793-7151.

3. RISKS OR DISCOMFORTS

You will receive radiation and three drugs in this study, paclitaxel, carboplatin and cetuximab, that may cause the following side effects; some are common (occurring in more than 10% of people) and some are uncommon (occurring between 1-10%) and rare (occurring in less than 1%).

Paclitaxel: (Taxol)

Common (more than 10% of patients are expected to have these side effects):

- Low blood counts, susceptibility to infection and/or bleeding with possible need to a blood transfusion. If you develop a fever or other signs of infection when your blood counts are low, you may need to be hospitalized to get intravenous antibiotics to help your body fight the infection; infections in patients with low blood counts are dangerous and potentially fatal.
- Nausea and vomiting, loss of appetite, and weight loss. You will be given medicine to help avoid these.
- Hair loss: You may lose some or all of your hair about three weeks after the first dose of chemotherapy. It will grow back after chemotherapy is stopped. Hair color will not change, but sometimes hair is curlier.
- Flu-like symptoms: fever, chills, muscle aches, fatigue. Tylenol is helpful in relieving these symptoms.
- Intestinal irritation with mild diarrhea
- Mouth ulcers
- Abnormalities in liver function tests, which are usually temporary
- Numbness, pain and tingling of hands and feet that sometimes worsens with additional treatment and may not disappear after the drug is stopped
- Joint pain
- Mild allergic reaction including skin rash, itching, flushing.
- Changes in blood pressure

Uncommon (1-10%):

- Fainting
- Irregular heart beats or a decreased heart rate
- Severe allergic reaction including chest pain, a rapid heart rate, difficulty breathing and low blood pressure

Rare (Less than 1%):

- Seizures
- Neurologic abnormalities including rare occurrence of flashing light, blurry vision, confusion and disorientation
- Inflammation of the pancreas

- Rare occurrence of bowel ischemia (lack of oxygen supply to the bowel) or typhlitis (severe infection of the large bowel)
- Liver failure
- Death has been reported in patients receiving paclitaxel

Carboplatin

Common:

- Nausea, vomiting, and loss of appetite. You will be given medicine to help avoid these side effects.
- Low of blood counts. Low white blood cell counts may increase your risk of infection. If you develop a fever or other signs of infection when your blood counts are low, you may need to be hospitalized to get intravenous antibiotics to help your body fight the infection. Low platelets may increase the risk of bleeding or bruising.
- Hair loss. You may lose some or all of your hair beginning about three weeks after your first treatment. Your hair will grow back after treatments stop.
- Mouth and throat sores. These can be treated with a soothing mouth rinse.

Uncommon:

- Allergic reactions. These are usually mild with a skin rash or itching.
- Abnormalities of liver function tests. This is usually temporary.
- Diarrhea.

Rare:

- Hearing loss.
- Neurologic abnormalities including weakness, blurred vision or dizziness
- Kidney damage. This may be permanent and sometimes can be associated with loss of magnesium and potassium in the urine.

Cetuximab:

Common:

- Acne-like rash. Especially on the face, upper chest and back. This occurs in 9 of 10 patients. The acne-like rash is often pustular. There may be skin drying and cracking. In about 1 in 20 patients the rash can be very severe. The rash generally gets better over 1-2 months and almost never results in permanent scarring. The rash can be itchy or painful and sometimes can become infected and need antibiotics to treat. If the rash is severe, the dose of cetuximab will be reduced or held until the rash gets better.
- Weakness.
- Nausea.
- Vomiting.
- Diarrhea **which can be severe**.
- Weight loss.
- Fever with or without chills.
- A decrease in the number of red blood cells, which may make you short of breath, weak and fatigued.

- Headache.
- Mouth sores that may result in difficulty swallowing.

Uncommon:

- Nail disorder in which the folds on the sides of your nails, especially thumbs and big toes, will swell.
- Mild allergic reaction, which occurs, while receiving cetuximab or up to 1 hour after getting cetuximab and includes chills, shaking and lowered blood pressure.
- Loss of appetite.
- A decrease in the number of platelets, which may result in easy bruising or bleeding for a longer time.
- A decrease in the number of white blood cells, which may cause you to get an infection.
- Dizziness.
- Feeling of prickling or tingling on your skin.
- Mild rise in the value of blood tests that measure liver function.
- Difficulty breathing.
- Flushing.
- Pain in your muscle or joints.
- Hives
- **Low Magnesium**
- **Infusion reaction at site of injection**

Rare:

- **Kidney failure**
- Inflammation in your brain, which may cause you to have a headache, **confusion**, fever or stiff neck.
- Severe allergic reaction, which may cause you to have trouble breathing, hives and/or low blood pressure (making you feel faint or dizzy **or could be fatal**).
- Inflammation and scarring of the lung which can give shortness of breath and be serious and result in death.
- **Cardiac arrest which can be fatal.**

Radiation Therapy – Side effects which have been observed in some patients undergoing radiation therapy include pain, difficulty swallowing and difficulty eating. You may develop redness or peeling of the skin (like a sunburn) in the area receiving radiation. Other side effects include fatigue, nausea and vomiting, diarrhea, increases in temperature and pulse rate, a drop in blood pressure, rash, hair loss, and loss of appetite. There is also a possibility of inflammation of the lungs, and a decrease in the white blood cell count, and/or red blood cell count and/or platelet count which may cause an increased risk of infection, fever, chills, bruising, bleeding or anemia.

Antiemetic (anti-Nausea Medication): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache,

restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

Venipuncture (inserting a needle into a vein to obtain blood or give medication) may cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein there is slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

A number of established chemotherapeutic agents have an inherent risk of causing secondary cancers and/or leukemias. Whether cetuximab, paclitaxel or carboplatin causes secondary malignancies is unknown. Certain agents in use today, not currently known to be associated with this risk may be shown at a later time to result in the development of these secondary cancers and/or leukemia.

There may be other side effects that have not been reported. If you have any unusual symptoms you will report them immediately to your doctor or nurse or go to the nearest Emergency Care Facility. Your doctors will be carefully monitoring your condition to minimize any possible risks. If your doctors feel that the side effects are too severe in your particular case, they will lower the dose of the chemotherapy drugs or even stop them.

For women of childbearing age, if you become pregnant, you cannot participate in this research study. You must use a form of birth control approved by your doctor while you participate in this study. If you become pregnant, you must tell your doctor immediately.

Surgery – You will sign a separate consent form for the surgery.

4. Benefits

Cetuximab, paclitaxel, carboplatin and radiation are given to try to decrease the size of your esophageal or stomach cancer. The addition of the cetuximab may or may not be beneficial to you. There may or may not be direct medical benefits for you. How well and how long your esophageal or stomach cancer will respond to this treatment are not known.

5. Alternative Therapies

Other treatments include surgery alone or treatment with radiation therapy alone, or treatment with a combination of chemotherapy and radiation therapy. There is no clear evidence that other treatments are significantly more effective than those used in this study.

6. **Confidentiality**

All of your records from this study will be treated as private health care records. The records will be protected according to the rules of _____ institutions. The _____ institutions privacy practices and policies are based on the rules about protection of private health care information contained in Rhode Island law and in the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations ("HIPAA").

A record of your progress with treatment will be kept in a confidential form at the _____institution and at the headquarters of the Brown University Oncology Group.Signing the informed consent allows access to the patients records by _____institution staff and affiliates, regulatory agencies such as the FDA, and Bristol Myers Squibb) There is a possibility that your medical records may be inspected or photocopied by the Food and Drug Administration, Brown University Oncology Group, a federal or state Governmental agency, and Bristol Myers Squibb, or its designees, in the ordinary course of carrying out their respective functions.

The results of this trial may be published. If they are published, the identity of individual patients will remain confidential in these publications.

As required by HIPAA, you will be given a separate Research Authorization Form that will be tell you the people and organizations that may use, receive and share information learned about you during the Study. Signing the Authorization Form means you give permission for your health care information to be used and shared for the Study purposes.

You should also know that there are times when the law might require or permit _____ institutions to release your health information without your permission. The Privacy Notice explains when this might happen. To give you some examples, State law requires health care workers to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

7. **Refusal/Withdrawal**

You decide whether or not, you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study.

If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study.

8. **Medical Treatment/Compensation in Case of Injury**

We do not expect that you will be hurt by taking part in this research study. However, if you are hurt as a result of taking part in this study, _____ institutions will provide without charge to you, what it feels is fair and proper treatment. _____ institutions does not however, have any plan or money set aside to pay you (for "pain or suffering") if you are hurt. Signing this agreement does not lessen or take away any of your lawful rights. For more facts about these terms, please contact _____ in the Office of Research Administration at _____phone.

9. Rights and Complaints

If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact_____ in the _____ institutions Office of Research Administration at _____phone.

Signatures

I ACKNOWLEDGE THAT I HAVE READ THE ABOVE EXPLANATION OF THIS PROJECT THAT ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I AGREE TO PARTICIPATE IN THIS RESEARCH PROJECT.

_____ _____

Signature of participant/authorized representative* Date

I ACKNOWLEDGE THE PROCESS AND/OR SIGNATURE OR STATEMENT SET FORTH ABOVE.

_____ _____

Signature of witness (required if consent is presented orally or at the request of the IRB) Date

I CERTIFY THAT I HAVE EXPLAINED FULLY TO THE ABOVE PATIENT THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH PROJECT.

_____ _____

Signature of researcher or designate Date

Consent form copy: participant☐ medical record☐ researcher☐ other(specify)☐

*If signed by agent other than participant, please explain below

Amendment #1 12/14/04

Amendment #2 2/28/05

Amendment #3 6/15/05

Amendment #4 4/25/06

SUGGESTED RESEARCH AUTHORIZATION FORM FOR PARTICIPATION IN BrUOG TRIALS

_____ _____

Committee # **Name of Study Volunteer**

_____

Name of Principal Investigator

(Insert study title here)

You have agreed to participate in a research study. A researcher has already explained the purpose of the study to you. The purpose of this form is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. However, as part of the research process, as has already been explained a little bit in the research study consent form, some of this information will need to be used and shared. We want you to understand and feel comfortable with this process. Please read this form very carefully and ask questions about anything you do not understand. IF YOU SIGN THIS FORM YOU ARE GIVING US PERMISSION TO USE AND SHARE YOUR PERSONAL HEATH INFORMATION IN THE WAYS DESCRIBED IN THIS FORM.

A representative of [Hospital] must fill in this form completely before providing it to you. DO NOT SIGN A BLANK FORM. You or your authorized representative should read the descriptions below before signing this form.

You will be given a copy of this form to keep. Please put it in a safe place so you can re-read it if you want.

UNDERSTANDINGS AND NOTIFICATIONS

We are asking you to give permission to use and/or release the information described below in connection with the research study called [insert complete title]_____ (the "Study"). The Study was explained to you during the informed consent process and is described in the research consent form that you already signed. Very briefly, the general purpose of the Study is: [insert brief description of study]. The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information."

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, nor the payment for your health care, nor your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant

If you sign this permission form, you may cancel it in writing at any time. If you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action, may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to [insert name of Principal Investigator/Researcher].

Optional Statement: You will not be allowed to see or copy the information described on this form as long as the research is in progress. You may see and copy the information upon completion of the research in accordance with (insert institutions name) policies.

You have a right to receive a copy of this form after you have signed it. If after you have signed this form you have any questions relating to your rights, please contact [*insert relevant contact information*].

USES AND RELEASES COVERED BY THIS AUTHORIZATION (PERMISSION)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- Every research site for this study, including this hospital, and including each site's research staff and medical staff
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
- The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: _____
- The United States Food and Drug Administration, Department of Health and Human Services, Office of Inspector General, Office of Civil Rights.
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
- Principal Investigator and other Investigators
- Study Coordinator

- Additional members of the Research Team
- The patient advocate or research volunteer protector: _____
- Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
- Data and Safety Monitoring Boards and others that monitor the conduçt of the Study, for example a Clinical Events Committee
- The members and staff of the hospital's affiliated Privacy Board (if such a board is used)
- Others (as described below)_____

_____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

What personal health information will be used or released? The appropriate boxes should be checked below and the descriptions should be in enough detail so that you (or any organization that must release information to carry out this authorization) can understand what information may be used or released.

☐ The entire research record and any medical records held by the hospital may be used and released.

☐ The following information:

_____

_____

SIGNATURE

I have read this form and all of my questions about this form have been answered. By signing below, I give my permission for the described uses and releases of information

_____ _____

Signature of Study Volunteer or Authorized Representative Date

_____

Print Name of Study Volunteer or Authorized Representative

_____

Description of Authorized Representative's Authority

I also confirm that I have been given a copy of the (insert institutions name) Privacy notice

_____

Signature of Study Volunteer or Authorized Representative

CONTACT INFORMATION

The contact information of the study volunteer or authorized representative who signed this form should be filled in below.

Address:

_____

_____

_____

_____

Telephone:

_____ (daytime)

_____ (evening)

Email Address (optional):

_____

THE STUDY VOLUNTEER OR HIS OR HER AUTHORIZED REPRESENTATIVE MUST BE PROVIDED WITH A COPY OF THIS FORM AFTER IT HAS BEEN SIGNED.

Privacy Officer/Designee Approval: By signing below, I certify that this Research Authorization complies with the hospital's policy *Use and Disclosure of Protected Health Information for Research Purposes* and with the Health Insurance Portability and Accountability Act of 1996 and implementing regulations.

_____

Print Name of Privacy Officer or Designee,

_____

_____

Signature of Privacy Officer or Designee Date

BrUOG-E/G-203-CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER

ELIGIBILITY CRITERIA: ALL MUST BE YES FOR THE PATIENT TO BE ELIGIBLE FOR PROTOCOL

____1. Pathologically confirmed adenocarcinoma or squamous cell carinoma of the esophagus, gastroesophageal junction, or stomach. Patients may have mediastinal, celiac adenopathy, peri-portal and regional gastric lymphadenopathy

State Date Dx: _____State Disease Site: _____State Cell Type:_____

____2. There must be no evidence of distant organ metastases.

____3. No prior radiation for gastric or esophageal cancer.

____4. Patients must be ≥ 18 years of age ECOG performance status 0-2.. and not pregnant

State age in years_____Date of Birth_____ ECOG PS: State Numerical Value_____

____5. Women of childbearing potential must have a negative pregnancy test within 7 days prior to start of therapy. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least three months thereafter. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential).

Beta HCG: State results:_____ Date of test_____

_____6. Patients must not have significant infection or other coexistent medical condition that would preclude protocol therapy.

_____ 7 Patients with Acute hepatitis or AIDS are not eligible

_____8. Patients with Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, and congestive heart failure. are not eligible

_____9. Patients with Prior therapy which specifically and directly targets the EGFR pathway. are not eligible

_____10.Patients with Prior severe infusion reaction to a monoclonal antibody are not eligible

____ 11.The following minimum required **laboratory data done within 15 days of treatment** should be present for eligibility upon study:

Test; Absolute Neutrophil Count ≥ 1500/μL **Numerical value_____ Date of test_____**
Test; Platelet count ≥ 100,000ul **Numerical value_____ Date of test_____**
Test: Total Bilirubin ≤ 1.5 x ULN
Numerical value_____ institution ULN_____ Date of test_____
Test: Creatinine ≤ 2 x upper limit normal (ULN
Numerical value_____ institution ULN_____ Date of test_____
Test: SGOT < 3 x ULN
Numerical value_____ institution ULN_____ Date of test_____

_____12. Any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s).

Test: Chest/Abdomen: Date test obtained_____

_____14. Required Pre treatment evaluations within 6 weeks of treatment)

Test: Endoscopy Date test obtained_____

_____15. Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

_____16. The support documentation, per the requirements under the study parameters section of each individual protocol, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

a. Signed Consent Form	Enclosed _____	Not Enclosed _____	Not Applicable _____
b. On-Study Form (applies to outside institutions)	Enclosed _____	Not Enclosed _____	Not Applicable _____
c. Pathology Report(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
d. Lab Report(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
e. Bone Scan Report(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
f. Cat Scan Report(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
g. MRI Report(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
h. Upper GI Series	Enclosed _____	Not Enclosed _____	Not Applicable _____
i. Barium Swallow	Enclosed _____	Not Enclosed _____	Not Applicable _____
j. Barium Enema	Enclosed _____	Not Enclosed _____	Not Applicable _____
k. Quality of Life Form(s)	Enclosed _____	Not Enclosed _____	Not Applicable _____
l. Protocol Diagrams	Enclosed _____	Not Enclosed _____	Not Applicable _____

m. Radiation Quality Assurance Documentation _____
(Please indicate where patient is being treated.)

n. Data Manager notified Radiation Therapy Department to send RT Quality Control material Yes ____
No _____

o. Specimens (as applicable) Date Sent _____ Type of Specimen _____ Sent To _____

p. Other _____ Enclosed ____ Not Enclosed _____

IRB approval date of protocol: _____ Hospital where patient will be treated: _____

Date patient will begin treatment: _____ Primary Physician: _____

The patient (full name) _____ has met the above protocol criteria on _____

and is assigned BrUOG sequence number _____

Your signature: _____

PLEASE FAX THESE FORMS TO THE BrUOG CENTRAL OFFICE, (401) 383-3001, TO REGISTER THE PATIENT.

Amendment #1 12/14/04

BrUOG ELIGIBILITY CHECKLIST FOR PATIENT REGISTRATION
APPENDIX –B

BrUOG-E/G-203-CETUXIMAB, PACLITAXEL, CARBOPLATIN AND RADIATION FOR ESOPHAGEAL, GASTROESOPHAGEAL JUNCTION AND GASTRIC CANCER

ELIGIBILITY CRITERIA: ALL MUST BE YES FOR THE PATIENT TO BE ELIGIBLE FOR PROTOCOL

____1. Pathologically confirmed adenocarcinoma or squamous cell carinoma of the esophagus, gastroesophageal junction, or stomach. Patients may have mediastinal, celiac adenopathy, peri-portal and regional gastric lymphadenopathy

State Date Dx: _____State Disease Site: _____State Cell Type:_____

____2. There must be no evidence of distant organ metastases.

____3. No prior radiation for gastric or esophageal cancer.

____4. Patients must be ≥ 18 years of age ECOG performance status 0-2. and not pregnant

State age in years_____Date of Birth_____ ECOG PS: State Numerical Value_____

____5. Women of childbearing potential must have a negative pregnancy test within 7 days prior to start of therapy. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for at least three months thereafter. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential).

Beta HCG: State results:_____ Date of test_____

____6. Tumor tissue available for assessment of EGFR status by IHC

____7. Patients must not have significant infection or other coexistent medical condition that would preclude protocol therapy.

____8. Patients with Acute hepatitis or AIDS are not eligible

____9. Patients with Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, and congestive heart failure. are not eligible

____10. Patients with Prior therapy which specifically and directly targets the EGFR pathway. are not eligible

____11.Patients with Prior severe infusion reaction to a monoclonal antibody are not eligible

____12.The following minimum required **laboratory data done within 15 days of treatment** should be present for eligibility upon study:

Test; Absolute Neutrophil Count ≥ 1500/μL **Numerical value_____ Date of test_____**
Test; Platelet count ≥ 100,000ul **Numerical value_____ Date of test_____**
Test: Total Bilirubin ≤ 1.5 x ULN
Numerical value_____ institution ULN_____ Date of test_____
Test: Creatinine ≤ 2 x upper limit normal (ULN
Numerical value_____ institution ULN_____ Date of test_____
Test: SGOT < 3 x ULN
Numerical value_____ institution ULN_____ Date of test_____

____13. Any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s).

Test: Chest/Abdomen: Date test obtained_____

_____15. Required Pre treatment evaluations within 6 weeks of treatment)

Test: Endoscopy Date test obtained_____

_____16. Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

_____17. The support documentation, per the requirements under the study parameters section of each individual protocol, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

a. Signed Consent Form Enclosed _____ Not Enclosed _____ Not Applicable _____
b. On-Study Form (applies to outside institutions) Enclosed _____ Not Enclosed _____ Not Applicable _____
c. Pathology Report(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
d. Lab Report(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
e. Bone Scan Report(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
f. Cat Scan Report(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
g. MRI Report(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
h. Upper GI Series Enclosed _____ Not Enclosed _____ Not Applicable _____
i. Barium Swallow Enclosed _____ Not Enclosed _____ Not Applicable _____
j. Barium Enema Enclosed _____ Not Enclosed _____ Not Applicable _____
k. Quality of Life Form(s) Enclosed _____ Not Enclosed _____ Not Applicable _____
l. Protocol Diagrams Enclosed _____ Not Enclosed _____ Not Applicable _____
m. Radiation Quality Assurance Documentation _____
(Please indicate where patient is being treated.)

n. Data Manager notified Radiation Therapy Department to send RT Quality Control material Yes ____
No _____

o. Specimens (as applicable) Date Sent _____ Type of Specimen _____ Sent To _____

p. Other _____ Enclosed ____ Not Enclosed _____

IRB approval date of protocol: _____ Hospital where patient will be treated: _____

Date patient will begin treatment: _____ Primary Physician: _____

The patient (full name) _____ has met the above protocol criteria on _____

and is assigned BrUOG sequence number _____

Your signature: _____

PLEASE FAX THESE FORMS TO THE BrUOG CENTRAL OFFICE, (401) 383-3001, TO REGISTER THE PATIENT.

APPENDIX: C
MEMORANDUM

TO: BrUOG Physicians
Clinical Research Nurses
Clinical Research Associates

FROM: Teresa A. Kennedy, R.N., C.C.R.A.
Administrative Director
Brown University Oncology Group

RE: Adverse Reaction Reporting Guidelines

Attached are Adverse Reaction reporting guidelines which have been adopted from the FDA/NIC guidelines to be utilized for all patients on BrUOG protocols. Included are guidelines for:

Commercial Agents
Investigational Agents: Phase II and III protocols
Investigational Agents: Phase I protocols
Reporting of Secondary Primary Cancers

All Adverse Reaction reporting should be based on the Common Toxicity Criteria. **It is the responsibility of the physician to notify his/her protocol office when a reportable toxicity occurs and to grade and sign the report.**

NOTE: Just for your information, hospitalization for a patient on protocol does not necessarily in itself require an ADR form to be filled in. It is the type and grade of toxicity for which the patient is hospitalized that determines if an ADR form is completed.

Adverse Event Definitions

An Adverse Event is any new, undesirable medical experience or change of an existing condition which occurs during or after treatment, whether or not considered product-related.

Life Threatening Adverse Event is any adverse event that places the patient or subject in view of the investigator, at the immediate risk of death from the reaction.

A Serious Adverse Event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity or causes a congenital anomaly/birth defect.

The definition of serious adverse event (experience) also includes *important medical event.* Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience.

BrUOG Guidelines for Adverse Reaction Reporting

The following guidelines should be followed in reporting adverse reactions to the BrUOG Central Office.

ADR Reporting should be based on Common Toxicity Criteria. The BrUOG Central Office will report all toxicities to the NCI, pharmaceutical companies, and BrUOG Physicians, Clinical Research Nurses, and Clinical Research Associates as applicable.

Commercial Agents:

Instructions	Grade 1 - 5 unexpected[1]	Death due to Rx or within 30 days of Rx[2]
ADR Form to BrUOG Central Office within 10 days	X	X
Copy will be sent to NCI by BrUOG Central Office	X	X
Notify local IRB within 10 days	X	X

1 Any unexpected toxicity not reported in the literature or the package insert must be reported.

2 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.
MedWatch Form is acceptable. This form must be signed by the treating physician.

Non-Treatment Related Toxicities
If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the BrUOG Flow Sheets.

Investigational Agents: Phase II and III

Instructions	Grade 2-3 unexpected[1]	Grade 4-5 unexpected[1]	Grade 4 expected[2]	Death due to Rx or within 30 days of Rx[3]
Call BrUOG Central Office within 24 hours		X		X
ADR Form to BrUOG Central Office within 10 days	X	X	X	X
BrUOG Central Office will send report to NCI within 10 days	X	X	X	X
BrUOG Central Office will send report to drug manufacture within 10 days as applicable	X	X	X	X
Notify local IRB within 10 days	X	X	X	X

1 Any unexpected toxicity not reported in the literature or the package insert must be reported.

2 Grade 4 expected myelosuppression need not be reported but should be documented on flow sheets.

3 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

These ADRs are to be reported on the Adverse Reaction (ADR) Form for Investigation Drugs
The form must be signed by the treating investigator.

Non-Treatment Related Toxicities

If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the BrUOG Flow Sheets.

Investigational Agents: ADR Reporting Phase I Studies

Instructions	Grade 1 - 5 first occurrence of previously unknown clinical event[1]	Grade 4	Death due to Rx or within 30 days of Rx[2]
Call BrUOG Central Office within 24 hours	X	X	X
BrUOG Central Office will notify NCI within 24 hours	X	X	X
BrUOG Central Office will call drug sponsor within 24 hours	X	X	X
Investigational Agent ADR Form to BrUOG Central Office within 10 days.	X	X	X
BrUOG Central Office will send ADR Form to NCI within 10 days	X	X	X
BrUOG Central Office will send ADR Form to drug manufacture within 10 days	X	X	X
Notify local IRB within 10 days	X	X	X

1 Any unexpected toxicity not reported in the literature or the package inset must be reported.

2 Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended, but which is felt to be treatment related, must be reported.

These ADRs are to be reported on the Adverse Reaction (ADR) Form for Investigational Drugs. The form must be signed by the treating investigator.

Non-Treatment Related Toxicities

If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the BrUOG Flow Sheets.

Appendix –D

NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of a CTCAE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An "Em dash" (—) indicates a grade not available

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	Short Name	1	2	3	4	
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Dea
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	De
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis; Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	De
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	De
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	De

AUDITORY/EAR

Adverse Event	Short Name	Grade 1	2	3	4	5
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing (patients with/without baseline audiogram and enrolled in a monitoring program)[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing (patients without baseline audiogram and not enrolled in a monitoring program)[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing (patients with/without baseline audiogram and enrolled in a monitoring program)[1]; Hearing (patients without baseline audiogram and not enrolled in a monitoring program)[1].						
Otitis, middle ear (non-infectious)	Otitis	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

Adverse Event	Short Name	Grade 1	2	3	4	
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing (patients with/without baseline audiogram and enrolled in a monitoring program)[1]; Hearing (patients without baseline audiogram and not enrolled in a monitoring program)[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Deat

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurre first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater thresho shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of Am 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New Yo American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

Adverse Event	Short Name	Grade 1	2	3	4	De
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	De
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	De
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	De
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	De
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	De
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	De
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	De
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	De
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts <5%)	RAEB or RAEB-T (marrow blasts >5%)	De
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	De
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	De
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	De
Blood/Bone Marrow – Other (Specify, ___)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	De

CARDIAC ARRHYTHMIA

Adverse Event	Short Name	Grade 1	2	3	4	
Conduction abnormality/ atrioventricular heart block – *Select*: –Asystole –AV Block-First degree –AV Block-Second degree Mobitz Type I (Wenckebach) –AV Block-Second degree Mobitz TypeII –AV Block-Third degree (Complete AV block) –Conduction abnormality NOS –Sick Sinus Syndrome –Stokes-Adams Syndrome –Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	De
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	De
ALSO CONSIDER: Ventricular arrhythmia – *Select*.						
Supraventricular and nodal arrhythmia – *Select*: –Atrial fibrillation –Atrial flutter –Atrial tachycardia/Paroxysmal Atrial Tachycardia –Nodal/Junctional –Sinus arrhythmia –Sinus bradycardia –Sinus tachycardia –Supraventricular arrhythmia NOS –Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) –Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	De

CARDIAC ARRHYTHMIA

Adverse Event	Short Name	Grade 1	2	3	4	
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Dea
Ventricular arrhythmia – *Select* –Bigeminy –Idioventricular rhythm –PVCs –Torsade de pointes –Trigeminy –Ventricular arrhythmia NOS –Ventricular fibrillation –Ventricular flutter –Ventricular tachycardia	Ventricular arrhythmia	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Dea
Cardiac Arrhythmia – Other (Specify, ___)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Dea

CARDIAC GENERAL

Adverse Event	Short Name	Grade 1	2	3	4	
NAVIGATION NOTE: Angina is graded as Cardiac Ischemia/Infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	De
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	De
Cardiac Ischemia/Infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	—
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS Ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (>24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	De
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

Adverse Event	Short Name	Grade 1	2	3	4	
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	De
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	De
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	De
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac Ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	De
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	De
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	De
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	De
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	De

CARDIAC GENERAL

		Grade				
Adverse Event	Short Name	1	2	3	4	
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Deat
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Deat
Cardiac General – Other (Specify, ___)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Deat

COAGULATION

Adverse Event	Short Name	Grade 1	2	3	4	
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	De
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	De
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select*.						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select*.						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	De
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	De

CONSTITUTIONAL SYMPTOMS

Adverse Event	Short Name	Grade 1	2	3	4	5
Fatigue (lethargy, malaise, asthenia)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI >40 kg/m^2	Death
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	Death
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report*, Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	Death
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight Loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, ___)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

Adverse Event	Short Name	Grade 1	2	3	4	
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Dea

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select*' is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	1	2	3	4	5
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	Death

DERMATOLOGY/SKIN

Adverse Event	Short Name	Grade 1	2	3	4	5
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

Adverse Event	Short Name	Grade 1	2	3	4	5
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
Gynecomastia	Gynecomastia	Mild	Pronounced or painful	Pronounced or painful and operative intervention indicated	—	—
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	Death
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic; intervention not indicated	Symptomatic; intervention indicated	—	—	Death
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic; intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, ___)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	2	3	4	5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic; medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	2	3	4	5
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	Death
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	Death
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic; interfering with GI function	—	Death
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 2	3	4	5
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately ailment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	Death
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as **Stricture/stenosis** (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic; pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhilitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

Adverse Event	Short Name	Grade 1	2	3	4	5
Fistula, GI – *Select*: –Abdomen NOS –Anus –Biliary tree –Colon/cecum/appendix –Duodenum –Esophagus –Gallbladder –Ileum –Jejunum –Oral cavity –Pancreas –Pharynx –Rectum –Salivary gland –Small bowel NOS –Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

Adverse Event	Short Name	Grade 1	2	3	4	5
ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying).						
ALSO CONSIDER: Constipation; Nausea; Obstruction – *Select* in the GASTROINTESTINAL CATEGORY; Vomiting.						
incontinence, anal	Incontinence, anal	Requires occasional use of pads required	Requires daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
leak (including anastomotic), GI – *Select* –Biliary tree –Esophagus –Large bowel –Leak NOS –Pancreas –Pharynx –Rectum –Small bowel –Stoma –Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anastomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to ailment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	2	3	4	5
Mucositis/stomatitis (clinical exam) – *Select:* –Anus –Esophagus –Large bowel –Larynx –Oral cavity –Pharynx –Rectum –Small bowel –Stomach –Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Mucositis/stomatitis (functional/symptomatic) – *Select:* –Anus –Esophagus –Large bowel –Larynx –Oral cavity –Pharynx –Rectum –Small bowel –Stomach –Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately alimentor hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	2	3	4	5
Necrosis, GI – *Select*: –Anus –Colon/cecum/appendix –Duodenum –Esophagus –Gallbladder –Hepatic –Ileum –Jejunum –Oral –Pancreas –Peritoneal cavity –Pharynx –Rectum –Small bowel NOS –Stoma –Stomach	Necrosis, GI – *Select*	—	—	Inability to ailment adequatety by GI tract, (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: –Cecum –Colon –Duodenum –Esophagus –Gallbladder –Ileum –Jejunum –Rectum –Small bowel NOS –Stoma –Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	2	3	4	5
Perforation, GI – *Select*: –Appendix –Biliary tree –Cecum –Colon –Duodenum –Esophagus –Gallbladder –Ileum –Jejunum –Rectum –Small bowel NOS –Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Stricture/stenosis (including anastomotic), GI – *Select*: –Anus –Biliary tree –Cecum –Colon –Duodenum –Esophagus –Ileum –Jejunum –Pancreas/pancreatic duct –Pharynx –Rectum –Small bowel NOS –Stoma –Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Hemorrhage, GI – *Select*.

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ulcer, GI – *Select*: –Anus –Cecum –Colon –Duodenum –Esophagus –Ileum –Jejunum –Rectum –Small bowel NOS –Stoma –Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, ___)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysidesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, ___)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemorrhage, GI – *Select*: –Abdomen NOS –Anus –Appendix –Biliary tree –Cecum/appendix –Colon –Duodenum –Esophagus –Ileum –Jejunum –Liver –Lower GI NOS –Oral cavity –Pancreas –Peritoneal cavity –Rectum –Stoma –Stomach –Upper GI NOS –Varices (esophageal) –Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemorrhage, GU – *Select*: –Bladder –Fallopian tube –Kidney –Ovary –Prostate –Retroperitoneum –Spermatic cord –Stoma –Testes –Ureter –Urethra –Urinary NOS –Uterus –Vagina –Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: –Bronchopulmonary NOS –Bronchus –Larynx –Lung –Mediastinum –Nose –Pharynx –Pleura –Respiratory tract NOS –Stoma –Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	Short Name	1	2	3	4	5
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, ___)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

Adverse Event	Short Name	Grade 1	2	3	4	5
NAVIGATION NOTE: Biliary tree damage is graded as **Fistula, GI – *Select***; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin.						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

Adverse Event	Short Name	Grade 1	2	3	4	5
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhilitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).						
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	2	3	4	5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin; Encephalopathy.						
Infection – Other (Specify, ___)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – SELECT

AUDITORY/HEARING
- –External ear (otitis externa)
- –Middle ear (otitis media)

CARDIOVASCULAR
- –Artery
- –Heart (endocarditis)
- –Spleen
- –Vein

DERMATOLOGY/SKIN
- –Lip/perioral
- –Peristomal
- –Skin (cellulites)
- –Ungual (nails)

GASTROINTESTINAL
- –Abdomen NOS
- –Anal/perianal
- –Appendix
- –Cecum
- –Colon
- –Dental-tooth
- –Duodenum
- –Esophagus
- –Ileum
- –Jejunum
- –Oral
- –Oral cavity-gums (gingivitis)
- –Peritoneal cavity
- –Rectum
- –Salivary gland
- –Small bowel NOS
- –Stomach

GENERAL
- –Catheter-related
- –Foreign body (e.g., graft, implant, prosthesis, stent)
- –Wound

HEPATOBILIARY/PANCREAS
- –Biliary tree
- –Gallbladder (cholecystitis)
- –Liver
- –Pancreas

LYMPHATIC
- –Lymphatic

MUSCULOSKELETAL
- –Bone (osteomyelitis)
- –Joint
- –Muscle (infection myositis)
- –Soft tissue NOS

NEUROLOGY
- –Brain (encephalitis, infectious)
- –Brain + Spinal cord (encephalomyelitis)
- –Meninges (meningitis)
- –Nerve-cranial
- –Nerve-peripheral
- –Spinal cord (myelitis)

OCULAR
- –Conjunctiva
- –Cornea
- –Eye NOS
- –Lens

PULMONARY/UPPER RESPIRATORY
- –Bronchus
- –Larynx
- –Lung (pneumonia)
- –Mediastinum NOS
- –Mucosa
- –Neck NOS
- –Nose
- –Paranasal
- –Pharynx
- –Pleura (empyema)
- –Sinus
- –Trachea
- –Upper aerodigestive NOS
- –Upper airway NOS

RENAL/GENITOURINARY
- –Bladder (urinary)
- –Kidney
- –Prostate
- –Ureter
- –Urethra
- –Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- –Cervix
- –Fallopian tube
- –Pelvis NOS
- –Penis
- –Scrotum
- –Uterus
- –Vagina
- –Vulva

LYMPHATICS

Adverse Event	Short Name	Grade 1	2	3	4	5
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	Death
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to ailment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	Death
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	Death
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	Death
Lymphatics – Other (Specify, ___)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	Death
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	Death
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	Death
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	Death
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	Death
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia) Ionized calcium	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	2	3	4	5
Calcium, serum-high (hypercalcemia) Ionized calcium	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholestremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	Death
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	Death
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, ___)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	2	3	4	5
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia; Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	—
ALSO CONSIDER: Induration/fibrosis skin; Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy-motor; Neuropathy-sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication-device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light object)	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM)*, Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: –Extraocular –Extremity-upper –Extremity-lower –Facial –Left-sided –Ocular –Pelvic –Right-sided –Trunk –Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK; Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	2	3	4	5
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	Death
Soft tissue necrosis – *Select*: –Abdomen –Extremity-upper –Extremity-lower –Neck –Pelvic –Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately ailment or hydrate orally	—	—
NAVIGATION NOTE: Wound-Infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-Infectious is graded Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	Death
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy-cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness/tremor	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	Death
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: –Agitation –Anxiety –Depression	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	2	3	4	5
Neuropathy: cranial – *Select:* –CN I Smell –CN II Vision –CN III Pupil, upper eyelid, extra ocular movements –CN IV Downward, inward movement of eye –CN V Motor-jaw muscles; Sensory-facial –CN VI Lateral deviation of eye –CN VII Motor-face; Sensory-taste –CN VIII Hearing and balance –CN IX Motor-pharynx; Sensory-ear, pharynx, tongue –CN X Motor-palate; pharynx, larynx –CN XI Motor-sternomastoid and trapezius –CN XII Motor-tongue	Neuropathy : cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select.* ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select.*						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision or restraints indicated	Harmful to others or self; life-threatening consequences	Death

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY						
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	Death
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	Death
REMARK: Eyelid dysfunction includes madarosis, eythema, thickening, telangiectasis, trichiasis, canalicular stenosis, symblepharon, ectropion, and entropion. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	symptomatic and interfering with adl; operative intervention indicated	Perforation or blindness (20/200 or worse)	Death
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface diseases	Ocular surface diseases	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	Death
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	Death
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	Death
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	Death
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	Death
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	Death

OCULAR/VISUAL

Adverse Event	Short Name	Grade 1	2	3	4	5
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	Death
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	Death
Vision-blurred vision	Blurred Vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Vision-flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	Death
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, ___)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

Adverse Event	Short Name	Grade 1	2	3	4	5
Pain – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	Death
Pain – Other (Specify, ___)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	Death

PAIN – *SELECT*

AUDITORY/HEARING
- –Ear/external
- –Ear/middle

CARDIOVASCULAR
- –Cardiac/heart
- –Pericardium

DERMATOLOGY/SKIN
- –Face
- –Lip
- –Oral-gums
- –Scalp
- –Skin

GASTROINTESTINAL
- –Abdomen NOS
- –Anus
- –Dental/teeth/peridontal
- –Esophagus
- –Oral cavity
- –Peritoneum
- –Rectum
- –Stomach

GENERAL
- –Pain NOS
- –Tumor pain

HEPATOBILIARY/PANCREAS
- –Gallbladder
- –Liver

LYMPHATICS
- –Lymph node

MUSCULOSKELETAL
- –Back
- –Bone
- –Buttock
- –Extremity-limb
- –Intestine
- –Joint
- –Muscle
- –Neck
- –Phantom (pain associated with missing limb)

NEUROLOGY
- –Head/headache
- –Neuralgia/peripheral nerve

OCULAR
- –Eye

PULMONARY/UPPER RESPIRATORY
- –Chest wall
- –Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- –Larynx
- –Pleura
- –Sinus
- –Throat/pharynx/larynx

RENAL/GENITOURINARY
- –Bladder
- –Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- –Breast
- –Ovulatory
- –Pelvis
- –Penis
- –Perineum
- –Prostate
- –Scrotum
- –Testicle
- –Urethra
- –Uterus
- –Vagina

PULMONARY/UPPER RESPIRATORY

Adverse Event	Short Name	Grade 1	2	3	4	5
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to ailment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select;* Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection – *Select;* Obstruction/stenosis of airway – *Select;* Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity reaction; Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	Death

PULMONARY/UPPER RESPIRATORY

Adverse Event	Short Name	Grade 1	2	3	4	5
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy-motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: –Bronchus –Larynx –Lung –Oral cavity –Pharynx –Pleura –Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	Death
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse ox <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
Obstruction/stenosis of airway – *Select:* –Bronchus –Larynx –Pharynx –Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support) indicated	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea; Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC ≤1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

Adverse Event	Short Name	Grade 1	2	3	4	5
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis (radiographic changes)	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy.						
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, ___)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: –Bladder –Genital tract-female –Kidney –Ureter –Urethra –Uterus –Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	Death
Leak (including anastomotic), GU – *Select*: –Bladder –Fallopian tube –Kidney –Spermatic cord –Stoma –Ureter –Urethra –Uterus –Vagina –Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

Adverse Event	Short Name	Grade 1	2	3	4	5
Obstruction, GU – *Select*: –Bladder –Fallopian tube –Prostate –Spermatic cord –Stoma –Testes –Ureter –Urethra –Uterus –Vagina –Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: –Bladder –Fallopian tube –Kidney –Ovary –Prostate –Spermatic cord –Stoma –Testes –Ureter –Urethra –Uterus –Vagina –Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select*; Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

Adverse Event	Short Name	Grade 1	2	3	4	5
Stricture/stenosis (including anastomotic), GU – *Select*: –Bladder –Fallopian tube –Prostate –Spermatic cord –Stoma –Testes –Ureter –Urethra –Uterus –Vagina –Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	Death
ALSO CONSIDER: Acidosis; Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, ___)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

Adverse Event	Short Name	Grade 1	2	3	4	5
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	Short Name	1	2	3	4	5
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

Adverse Event	Short Name	Grade 1	2	3	4	5
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness ALSO CONSIDER: Pain – *Select*.	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	Death
Sexual/Reproductive Function – Other (Specify, ___)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

Adverse Event	Short Name	Grade 1	2	3	4	5
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, Intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, ___)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, ___) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – SELECT

AUDITORY/HEARING
- Inner ear
- Middle ear
- Outer ear-Pinna
- Outer ear NOS

CARDIOVASCULAR
- Heart
- Spleen
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid

ENDOCRINE *(continued)*
- Pituitary
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Neck NOS
- Nasal cavity
- Nasopharynx
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Anal sphincter
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity

GASTROINTESTINAL *(continued)*
- Rectum
- Stoma (GI)
- Small bowel NOS
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreatic duct
- Pancreas

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-upper
- Extremity-lower
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- Brachial plexus

NEUROLOGY *(continued)*

NERVES:
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Nerve-lingual
- Nerve-long thoracic
- Nerve-recurrent laryngeal
- Nerve-peripheral sensory NOS
- Nerve-peripheral motor NOS
- Nerve-sciatic
- Nerve-thoracodorsal
- Sacral plexus

OCULAR
- Conjunctiva
- Cornea

OCULAR *(continued)*
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Trachea
- Thoracic duct
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An Acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity reaction (including drug fever); Bronchospasm; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

Adverse Event	Short Name	Grade 1	2	3	4	5
"Retinoic acid syndrome"	Retinoic acid syndrome	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, ___)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	

VASCULAR

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	Death
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	Death
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis, or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/embolism	—	Deep vein thrombosis, or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: –Aorta –Carotid –Extremity-lower –Extremity-upper –Lower extremity –Other NOS –Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vessel injury-vein – *Select:* –Extremity-upper –Extremity-lower –IVC –Jugular –Other NOS –SVC –Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial) ALSO CONSIDER: CNS cerebrovascular ischemia.	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

APPENDIX E

ECOG PATIENT PERFORMANCE STATUS

STATUS	SCALES KARNOFSKY	ZUBROD-ECOG-WHO	STATUS
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536.