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**SWOG**

**A RANDOMIZED, PHASE III STUDY COMPARING CARBOPLATIN/PACLITAXEL OR  
CARBOPLATIN/PACLITAXEL/BEVACIZUMAB WITH OR WITHOUT CONCURRENT  
CETUXIMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER  
(NSCLC)**

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**STUDY COORDINATORS:**

Roy S. Herbst, M.D., Ph.D. (Medical Oncology)  
Yale Cancer Center  
Section of Medical Oncology  
333 Cedar Street, PO Box 208028  
New Haven, CT 06520-8028  
Phone: 203/785-6879  
FAX: 203/785-4116  
E-mail: roy.herbst@yale.edu

Edward S. Kim, M.D. (Medical Oncology)  
Levine Cancer Institute  
Carolinas Healthcare System  
1021 Morehead Medical Dr., Suite 3100  
Charlotte, NC 28204  
Phone: 980/442-3105  
FAX: 980/442-3101  
E-mail: edward.kim@carolinashealthcare.org

David R. Gandara, M.D. (Lung Committee Chair)  
Professor of Medicine  
UC Davis Cancer Center  
4501 X Street, Ste 3017  
Sacramento, CA 95817  
FAX: 916/734-7946  
E-mail: david.gandara@ucdmc.ucdavis.edu

Thomas J. Semrad, M.D. (Medical Oncology)  
UC Davis Cancer Center  
4501 X Street, Ste 3016  
Sacramento, CA 95817  
Phone: 916/734-3771  
FAX: 916/734-7946  
E-mail: thomas.semrad@ucdmc.ucdavis.edu

Fred R. Hirsch, M.D., Ph.D. (Translational Medicine)  
University of Colorado CC  
PO Box 6511, MS 8117  
Aurora, CO 80045  
Phone: 303/724-3858  
E-mail: fred.hirsch@ucdenver.edu

**AGENTS:**

IND-Exempt Agents:  
Bevacizumab (rhuMab VEGF) (Avastin)  
(NSC-704865)  
Carboplatin (CBDCA) (NSC-241240)  
Cetuximab (IMC-C225) (Erbix<sup>®</sup>) (NSC-714692)  
Paclitaxel, Taxol<sup>®</sup> (NSC-673089)

**BIostatisticians:**

Mary Redman, Ph.D.  
James Moon, M.S.  
SWOG  
Statistical Center  
1100 Fairview Ave N, M3-C102  
PO Box 19024  
Seattle, WA 98109  
Phone: 206/667-4623  
FAX: 206/667-4408  
E-mail: mredman@fhcrc.org  
E-mail: jmoon@fhcrc.org

**ENDORsING GROUPS**

**NCCTG:**

Alex A. Adjei, M.D., Ph.D.  
Roswell Park Cancer Institute

**CALGB:**

Michael Perry, M.D.  
University of Missouri/Ellis Fischel Cancer Center

**PARTICIPANTS**

**ALLIANCE**/Alliance for Clinical Trials in Oncology  
**ECOG-ACRIN**/ECOG-ACRIN Cancer Research Group  
**NRG**/NRG Oncology  
**SWOG**/SWOG

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

**Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical [appendix](#).**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [www.ctsu.org](http://www.ctsu.org).
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical [appendix](#) for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted via the OPEN Registration System. Refer to the CTSU logistical [appendix](#) for specific instructions.
- Data management will be performed by SWOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to SWOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by SWOG. Please send query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

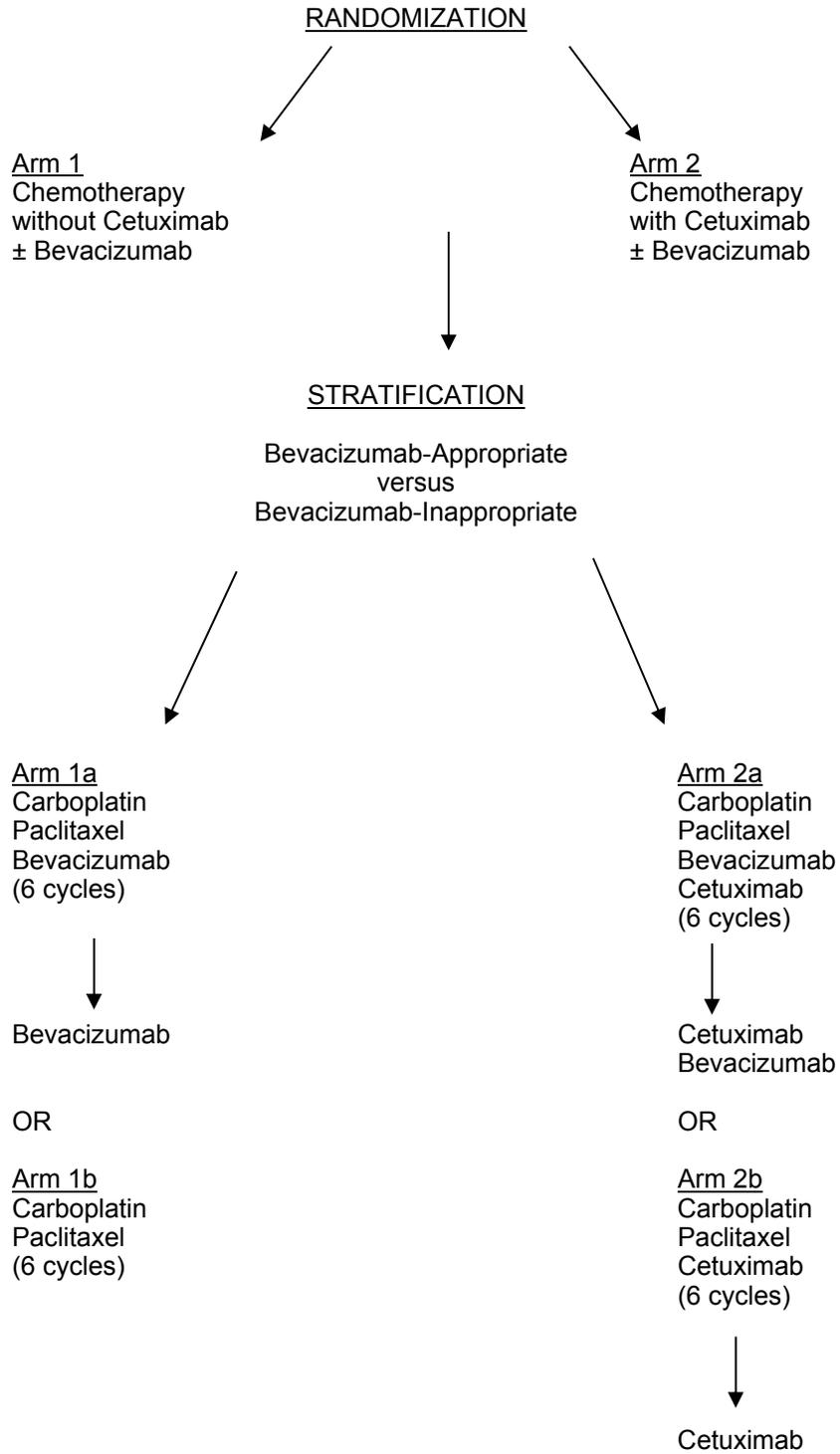
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS  
AND CONTACT INFORMATION

<b>To submit site registration documents:</b>	<b>For patient enrollments:</b>	<b>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</b>
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206</p>	<p>Please refer to the patient enrollment section for instructions on using the OPEN system.</p>	<p><u>Online Data Submission:</u> Institutions participating through CTSU are required to submit and amend their data electronically via Online Data submission. Access the SWOG Workbench using your CTSU User ID and password at the following url: <a href="https://crawb.crab.org/TXWB/ctsulogon.aspx">https://crawb.crab.org/TXWB/ctsulogon.aspx</a>.</p> <p><u>Exceptions:</u> Data items that are not available for online submission (operative and pathology reports, patient completed forms, scan reports, etc.) may be submitted by FAX at 800/892-4007.</p> <p>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</p>
<p><b>For treatment-related questions</b> contact the Study PI of the Coordinating Group.</p>		
<p><b>For eligibility or data submission questions</b> contact the SWOG Data Operations Center at 206/652-2267.</p>		
<p><b>For questions unrelated to patient eligibility, treatment, or data submission</b> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctscontact@westat.com">ctscontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><b>The CTSU Public Web site is located at: <a href="http://www.ctsu.org">www.ctsu.org</a>.</b></p>		
<p><b>The CTSU Registered Member Web site is located at <a href="http://www.ctsu.org">www.ctsu.org</a></b></p>		

CTSU logistical information is located in [Appendix 18.7](#)



**SCHEMA**



## 1.0 OBJECTIVES

### 1.1 Primary Objective

In patients with advanced NSCLC treated with carboplatin, paclitaxel and bevacizumab (if appropriate) with or without cetuximab, the primary objective of this study is to compare:

- a. Overall survival (OS) in the entire study population,
- b. Progression-free survival (PFS) by institutional review in EGFR FISH-positive patients.

### 1.2 Secondary Objectives

a. In patients with advanced NSCLC treated with carboplatin, paclitaxel and bevacizumab (if appropriate) with or without cetuximab, the secondary objectives are to compare:

1. OS and PFS by centralized review in EGFR FISH-positive patients,
2. PFS by centralized image review and by institutional review in the entire study population.

b. To compare the response rate (confirmed plus unconfirmed, complete and partial responses) in the subset of patients with measurable disease in:

1. EGFR FISH-positive patient,
2. the entire study population.

c. To assess the toxicities of these treatment regimens.

d. To prospectively test EGFR FISH as a predictive marker for the selection of patients for cetuximab plus chemotherapy.

e. To evaluate the role of KRAS mutations in terms of cetuximab efficacy.

f. To compare the results of EGFR FISH with KRAS mutations, EGFR mutations, EGFR IHC and other purported EGFR-related biomarkers.

### 1.3 Tertiary Objectives

The tertiary objectives of this study are:

a. To compare PFS in patients with advanced NSCLC with an IHC score > 200 treated with carboplatin, paclitaxel, and bevacizumab (if appropriate) with or without cetuximab,

b. To compare OS in patients with advanced NSCLC with an IHC score > 200 treated with carboplatin, paclitaxel, and bevacizumab (if appropriate) with or without cetuximab.

## 2.0 BACKGROUND

Rationale for selected approach and trial design.

Lung cancer is the most frequent cause of cancer death in the United States, with only 15% of patients surviving 5 years after diagnosis. Poor survival reflects, in part, the fact that almost 50% of cases present with advanced stage disease, for which effective systemic therapies are limited. However, recent development of novel molecular therapies, such as inhibitors of the epidermal growth factor receptor (EGFR), offer considerable promise for patient subsets sensitive to these agents. The EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib were the first molecular targeted agents to demonstrate benefit in patients with advanced non-small cell lung cancer (NSCLC). Early studies defined patient characteristics of those most likely to respond as: female sex, adenocarcinoma or bronchioloalveolar cell carcinoma (BAC) histology, never-smoker and Asian. BR.21, an NCI-Canada trial comparing erlotinib to placebo as 2<sup>nd</sup> line therapy in unselected patients, was the first demonstration of survival benefit for any targeted agent in NSCLC. A similar placebo-controlled study with gefitinib, the ISEL study, did not show a survival benefit, perhaps due to differences in patient eligibility criteria. Even in BR.21, the response rate to erlotinib was < 10% and the overall impact on survival was modest, prompting research efforts to define molecular biomarkers predictive of clinical benefit, especially improved survival. (1) Although a number of potential EGFR biomarkers have been proposed, including EGFR protein expression, mutation status, and gene copy number defined by FISH, EGFR FISH was most effective in predicting survival benefit in the two placebo-controlled randomized trials: hazard ratio (HR) for EGFR FISH-positive patients of 0.44 in the BR.21 study and 0.61 in ISEL. (2-4)

The presence of certain EGFR tyrosine kinase domain (TKD) mutations defines an NSCLC patient subset in which dramatic responses to EGFR TKIs are often seen, but outside of Asian populations, this biomarker is not clearly associated with prolonged survival from EGFR TKI therapy. This discrepancy perhaps reflects the low incidence of these TKD mutations in western populations of NSCLC. For example, there was no improvement in survival in patients with EGFR mutations in the BR.21 trial, despite an association with improved response rates. (2-3) In terms of prognosis, i.e., independent of therapy, studies performed to date suggest that EGFR mutations are actually associated with a good prognosis and more indolent course. In the TRIBUTE study of chemotherapy ± erlotinib as 1<sup>st</sup> line therapy, patients with EGFR mutated tumors had a better survival independent of therapy. (5) There are at present no published patient data regarding EGFR mutations under the influence of cetuximab-based therapy. However, preclinical data suggest that in contrast to the TKIs, NSCLC cell lines harboring EGFR mutations do not exhibit hypersensitivity to cetuximab. (6)

The prognostic and predictive value of EGFR protein expression by immunohistochemistry (IHC) has been studied in a relatively large number of reports, with mixed results, perhaps accounted for by heterogeneity in the patient populations studied as well as variability in methodologies. In a meta-analysis by Meert, et al., using an eight-study subset, expression by IHC was modestly associated with a poor prognosis, HR 1.13, 95% confidence intervals 1.00-1.28). (7) In BR.21, using the DAKO EGFR Pharm Dx kit which defines positivity as > 10% of tumor cells staining, 57% of tumors tested were positive. EGFR protein expression defined in this manner was not a strong prognostic factor. (2-3) However, there was predictive value. In IHC-positive patients receiving erlotinib, the HR for survival was 0.68 (p=0.02), without a significant interaction coefficient (p=0.25). (2) The ISEL study of gefitinib versus placebo showed a HR=0.77 (0.56, 1.08) with a borderline significant interaction coefficient (p=0.05). (4) In the BR.21 study there was no difference in survival between erlotinib versus placebo in IHC-negative patients, while in the ISEL study IHC-negative patients had a tendency to shorter survival with gefitinib (HR=1.57 (0.86, 2.87). No similar data regarding EGFR protein expression are yet available for cetuximab-based therapy in NSCLC.

EGFR FISH appears to have both *prognostic* and *predictive* implications in NSCLC. The concept of EGFR FISH as a *predictive* biomarker for EGFR TKIs originated with SWOG investigators, and the Colorado group, who also developed the assay classification system that has been commonly used, as previously reported in SWOG efforts such as **S0126** (a Phase II trial of gefitinib in advanced BAC). (8-10) EGFR FISH has previously demonstrated predictive value for efficacy of the EGFR TKIs gefitinib and erlotinib in advanced NSCLC in a number of clinical studies, including BR.21 and ISEL, in which the Colorado scoring criteria was used, either by the Colorado group themselves, or by other investigators. No such data regarding EGFR FISH as a predictive marker exist for the monoclonal antibody cetuximab plus chemotherapy until now, as described in our recent report discussed below. (11)

Limited studies performed to date suggest that EGFR FISH is associated with a poor *prognosis* in NSCLC. Hirsch et al. first studied the *prognostic* association of EGFR gene copy number in surgically resected NSCLC. In this study, increased gene copy number was associated with reduced survival ( $p=0.13$ ). When combined with EGFR protein expression, the combination group with high EGFR FISH and high protein expression score ( $> 300$  by H-score [= intensity  $\times$  % positive cells]) had the worst survival ( $p=0.01$ ). (9) The prognostic associations of EGFR FISH can also be derived from the two large randomized placebo-controlled studies, BR.21 and ISEL. In the ISEL study with gefitinib versus placebo, the median survival in the placebo arm was 4.5 months in the FISH-positive group versus 6.2 months in the FISH-negative group (interaction test,  $p=0.004$ ). (4) In the BR.21 study of erlotinib versus placebo the median survival in the placebo arm was estimated to be 4.5 months for the EGFR FISH-positive group versus 5.5 months for the FISH-negative group (interaction test,  $p=0.10$ ). (2) A recent update of the BR.21 study by Zhu, et al., shows that only EGFR FISH-positive status was prognostic for worse survival ( $p=0.025$ ) and predictive of differential survival benefit from erlotinib ( $p=0.005$ ). (3) Thus, both ISEL and BR.21 point to EGFR FISH-positivity as a poor prognostic factor, in the absence of EGFR TKI therapy. Others have also reported a poor prognosis in EGFR FISH-positive patients with NSCLC, particularly in squamous cell histology. (12) An association of EGFR FISH with poor prognosis has been reported in head and neck cancer as well. (13) In NSCLC patients treated with chemotherapy alone, (pertinent to interpretation of the **S0342** data) there were no differences in outcomes between EGFR FISH-positive and FISH-negative groups for PFS ( $p=0.39$ ) or OS ( $p=0.82$ ). (14) Taken together, these data suggest that EGFR FISH positivity portends a relatively poor prognosis in NSCLC (we believe an analogy may be drawn to HER2 FISH positivity in breast cancer).

**S0342** was a recently completed Phase II selection design study of chemotherapy (paclitaxel-carboplatin) with either sequential or concurrent cetuximab (see [figures](#) below), conducted to determine whether one schedule or the other was preferable for subsequent Phase III testing against chemotherapy alone (current **S0819** proposal). Two hundred twenty-nine patients with advanced NSCLC were enrolled in the study. EGFR FISH was performed in 76 patients with available tumor tissue, and classified as positive according to the Colorado scoring criteria. (11) This FISH patient cohort had no significant differences in clinical characteristics or outcomes when compared with the overall study group. As described here, SWOG translational medicine investigators observed a striking and unprecedented finding that increased EGFR gene copy number by FISH was associated with clinical benefit from cetuximab plus chemotherapy. (11) Objective response (CR/PR) was numerically higher in FISH-positive patients (45%) versus FISH-negative patients (26%,  $p=0.14$ ), while disease control rate (CR/PR plus stable disease) was statistically superior (81% versus 55%,  $p=0.02$ ). Patients with FISH-positive tumors had a median progression-free survival of 6 months versus 3 months for FISH-negative patients ( $p=0.0008$ ). Median survival was 15 months for FISH-positive patients versus 7 months for those who were FISH-negative ( $p=0.04$ ). Furthermore, survival favored FISH-positive patients receiving concurrent therapy, and was statistically positive only in the concurrent arm. These results are the first to suggest that EGFR FISH is a predictive factor for selection of NSCLC patients for cetuximab plus chemotherapy. We believe these preliminary data are encouraging for all efficacy parameters and warrant further prospective testing.

Figure 1: S0342 Phase II Selection Design Schema

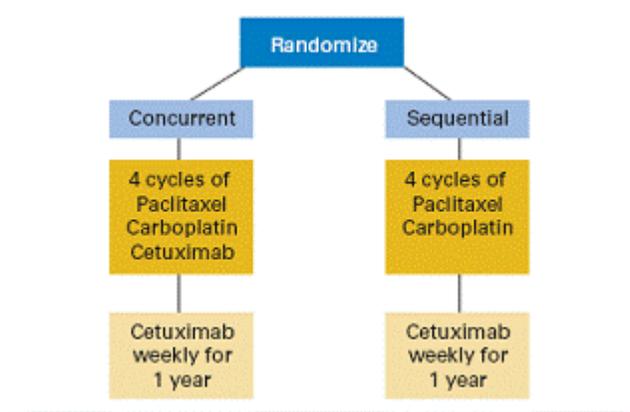
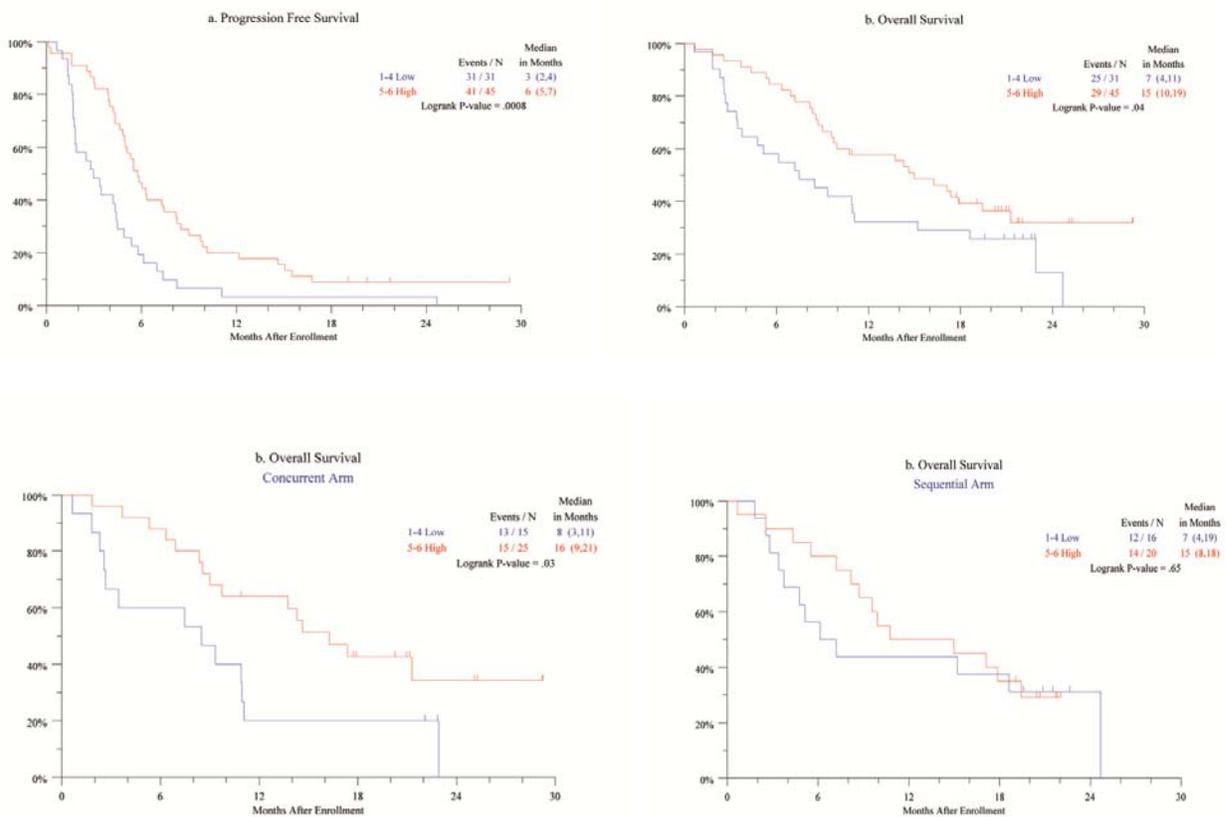


Figure 2: S0342 Analysis by EGFR FISH



As can also be discerned from these recently published data and as noted in our paper, the improved outcomes with EGFR FISH positivity in **S0342** appear even more interesting when the underlying poor prognosis of this group is taken into account. (11) We hypothesize that this observation does represent a treatment effect, perhaps similar to that of trastuzumab improving survival of HER2 FISH-positive breast cancer patients, a poor prognosis subgroup. However, we acknowledge that due to the relatively small sample size and retrospective nature of the data, that our observations in **S0342** are only hypothesis-generating. Nevertheless, these concepts are addressable in **S0819**.

Even more recently, SWOG completed a Phase II trial (**S0536**) in 99 patients testing the combination of carboplatin, paclitaxel, bevacizumab and cetuximab. This study, for which the primary endpoint was incidence of hemorrhagic toxicity, has shown this 4-drug regimen to be safe for future study with an acceptable toxicity profile when compared with either our **S0342** results or the **E4599** results. Specifically, the incidence of toxicity  $\geq$  Grade 4 was 31.5% in **S0342** versus 29.4% in **S0536**. The rate of Grade 4 or worse hemorrhagic toxicity was 2%. Fatal toxicities occurred in 3/85 (3.5%) patients on **S0536**, exactly the same rate as in E4599. Thus, the toxicity profile of the **S0536** regimen (paclitaxel/carboplatin/bevacizumab/cetuximab) appears acceptable when compared with either **E4599** (paclitaxel/carboplatin/bevacizumab) or a paclitaxel/carboplatin/cetuximab regimen.

Secondary endpoints of **S0536** included PFS and OS. Realizing that **S0536** is a single arm Phase II trial, PFS of 7 months and OS of 14 months surpass the efficacy of any prior SWOG trial, by 2-3 months for each endpoint.. Most importantly, there is no hint of a negative efficacy signal, the concern raised by the panitumumab trial in colorectal cancer. Therefore, we conclude that **S0536** has demonstrated both safety (the primary objective) and promising efficacy.

#### **KRAS mutation**

KRAS mutations, typically associated with tobacco-induced carcinogenesis in NSCLC, have been correlated with a poor *prognosis*, independent of therapeutic intervention. However, in surgically resected early stage NSCLC, a recent report from the BR.10 trial showed no significant prognostic association. (23) Studies with EGFR TKIs in NSCLC have also shown that patients with KRAS mutations respond poorly to EGFR TKIs. The update from the BR.21 study shows a significant survival benefit with erlotinib in patients with wt KRAS (median survival 7.5 months (HR=0.69, p=0.03). Patients with KRAS-mutated tumors had a median survival of 3.7 months (HR=1.69, p=0.3). (3) In the recently presented INTEREST study (gefitinib versus docetaxel) there was no statistically significant association between KRAS mutation and outcome. (15)

KRAS mutations in colon cancer have recently been reported to be a negative selection factor for patients receiving cetuximab-based therapy. In the Crystal study presented at ASCO 2008, adding cetuximab to FOLFIRI in metastatic colorectal cancer led to a significant increase in PFS (HR=.85, p=0.048). However, the benefit of cetuximab plus FOLFIRI was much greater in patients with KRAS wild-type tumors (HR=0.68, p=0.017). (16) In Cairo2, a randomized trial of capecitabine, oxaliplatin and bevacizumab with and without cetuximab, although response rates, disease control rates and OS were identical between the two study arms, PFS was 10.7 months in the control arm versus 9.6 months with cetuximab, p=0.018. (24) PFS in the two study arms was similar in KRAS wt tumor patients, but decreased with cetuximab in KRAS mutant tumor patients, 12.5 versus 8.6 months, p=0.043. OS in patients with KRAS mutant tumors was 18.1 months with cetuximab versus 24.9 months without, p=0.35. These data suggest a significant impact of KRAS mutation on cetuximab efficacy in colorectal cancer.

We submit that colorectal cancer and NSCLC are fundamentally different in several aspects pertinent to this issue, including molecular epidemiology of KRAS mutation (smoking-related in NSCLC), heterogeneity of histology in NSCLC (incidence of KRAS mutation 40-50% in colorectal cancer versus 20% overall in NSCLC, about 30% in adenocarcinomas), underlying EGFR-related biology (lack of EGFR mutations in colon cancer), and comparative activity of EGFR-directed

therapies (low activity of EGFR TKIs in colon cancer). Thus, the implications of the recent colon data in regard to the current proposal are uncertain. There are currently no published data correlating KRAS mutation and patient outcomes with cetuximab-based therapies in NSCLC, although we do now have limited data from **S0342**, as detailed below.

In **S0342**, a smaller number of analyzable tumor specimens remained for KRAS testing after initial EGFR pathway testing, limiting interpretation of the analysis. Determination of KRAS mutation in tumor DNA shed into plasma by scorpion-ARMS technology was performed to supplement the tissue analysis. Shown below are results in tissue alone versus tissue plus plasma. In these limited data sets, response rates and disease control rates appear similar between patients with wild type and mutant KRAS tumor, as does PFS (median 4 months in both wild type and mutant KRAS patients).

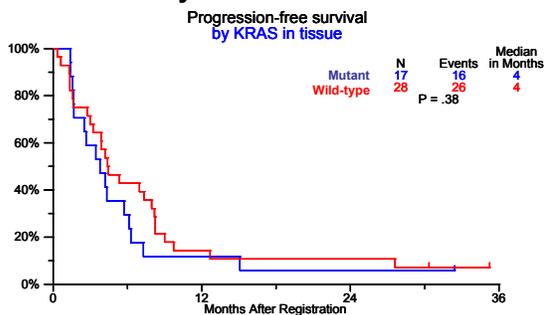
**S0342 KRAS Analysis for Response: Tissue alone**

	Wild type N=28	Mutant N=17	p-value
Response	5 (18%)	5 (29 %)	0.47
Disease control	17 (61%)	12 (71%)	0.54

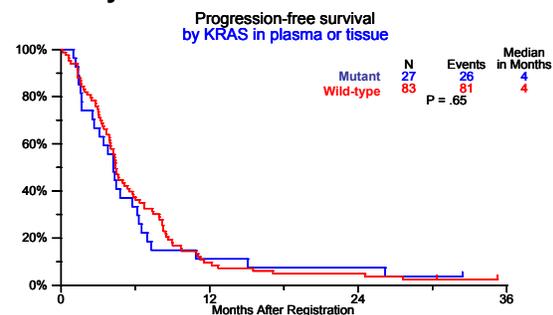
**S0342 Analysis for Response: Tissue + Plasma**

	Wild type N=83	Mutant N=27	p-value
Response	22 (27%)	9 (33 %)	0.62
Disease control	61 (73%)	19 (70%)	0.81

**S0342 Analysis for PFS: Tissue Alone**

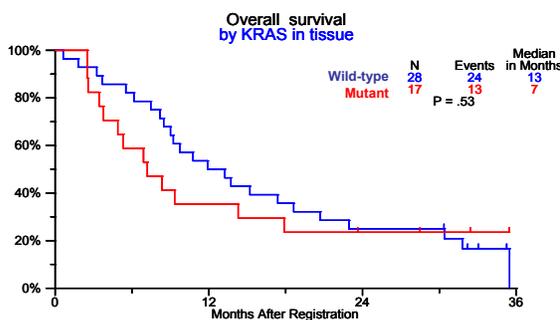


**S0342 Analysis for PFS: Tissue + Plasma**

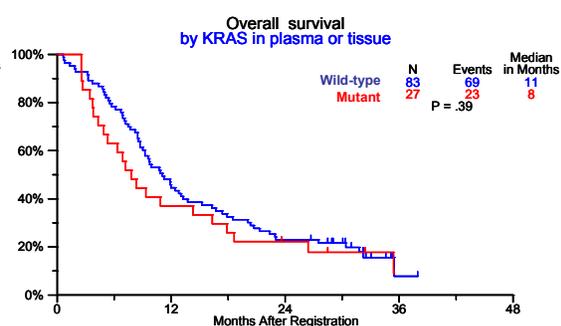


As shown below, while OS is somewhat higher in KRAS wild type tumor patients in the **S0342** analysis, in the absence of a higher response rate or PFS, this difference in OS may reflect only the *prognostic* effects of KRAS.

**S0342 Analysis for OS: Tissue Alone**



**S0342 Analysis for OS: Tissue + Plasma**



It is our understanding that KRAS analysis from FLEX and BMS 099 have recently been completed, and that the results mimic those described above for [S0342](#). In summary, the limited KRAS data in NSCLC patients treated with cetuximab do not present a compelling argument to exclude KRAS mutant tumor patients from the proposed [S0819](#) trial. While the major correlative science goal of the proposed [S0819](#) trial is to define the role of EGFR FISH in optimizing outcomes from cetuximab-based chemotherapy, this Phase III study will also provide a unique patient and specimen resource for prospective testing of KRAS mutations. As discussed below, the statistical design has been altered to accommodate real time testing for KRAS mutations, so that results can be considered at time of interim analysis.

## Significance

The importance of the [S0819](#) proposal is emphasized by the results of four previously published Phase III trials of chemotherapy with or without the EGFR TKIs gefitinib and erlotinib (INTACT I and II, TRIBUTE, TALENT) and two recent Phase III trials testing chemotherapy with or without cetuximab in advanced stage NSCLC. None of the four EGFR TKI trials showed benefit for the combination in any outcome parameter: response, PFS, or OS. Instead, for some parameters, numerically higher results were observed in placebo arms. For example, in INTACT I, median OS was 9.9 months in each gefitinib arm versus 10.9 months in the placebo arm. In an analysis by Hirsch, et al., of limited tumor specimens available from TRIBUTE, patients who were EGFR FISH-positive seemed to do particularly poorly with chemotherapy plus erlotinib, when compared to chemotherapy plus placebo (response rate 29.8% in the placebo arm, 11.6% in the erlotinib arm). [\(25\)](#) These data may conceivably reflect a negative interaction between concurrent chemotherapy and EGFR TKIs, as hypothesized by Gandara, et al. [\(17\)](#) Results of the two cetuximab-chemotherapy trials appear more favorable. The first, BMS 099, a trial of 676 patients, demonstrated no statistical improvement in the primary endpoint of radiology review-determined PFS between carboplatin-paclitaxel with or without cetuximab in unselected NSCLC patients (4.4 versus 4.2 months, HR=0.9, 95% CI 0.76-1.06, p=0.23). [\(18\)](#) Investigator-determined PFS was more positive. BMS 099 was designed with a 90% power at the 5% level to reject the null hypothesis of no PFS difference between treatment arms, given a true hazard ratio of 0.75. Response rate was higher in the cetuximab arm: 25.7% versus 17.2%, p=0.0066. Survival data in BMS 099 have been recently presented. The modest overall survival differences, 9.7 months for chemotherapy-cetuximab and 8.4 months for chemotherapy alone, are similar in magnitude to the FLEX data, and were not significantly different.

In the preliminary report of the FLEX trial at ASCO 2008, a larger randomized study of 1,400 patients comparing cisplatin-vinorelbine with or without cetuximab as first line therapy, the primary endpoint of a 25% improvement in survival was not achieved. However, given the large sample size the trial did demonstrate a statistically significant survival advantage (HR=.87, p=0.04) with the combination. Subset analysis showed benefit across most major subgroups, with the exception of race, where Asians did not benefit from the combination. Response rate and time to progression were in favor of the combination, while there was no difference in PFS between the two study arms. Thus, while FLEX can be considered a positive study, the results leave many questions open regarding the exact role of cetuximab-chemotherapy in NSCLC. Of note, FLEX patients were selected based on EGFR protein expression (IHC), whereas there was no selection process in BMS 099. [\(19\)](#)

Taken together, we believe the clinical trials summarized above suggest fundamental differences in how chemotherapy interacts with EGFR TKIs versus the monoclonal antibody cetuximab in NSCLC, which can be further exploited by biomarker selection of patients most likely to benefit. EGFR FISH has considerable potential to change practice and impact patient care for patients receiving cetuximab plus chemotherapy. While the FLEX study results can be considered a positive lead, selection was based on IHC positivity only (1 EGFR positive cell), an EGFR biomarker of questionable significance. EGFR FISH offers a potentially better way to select patients for this combination therapy (given the data presented in the background), and is highly

applicable to clinical practice. Routine use of FISH technology is widespread. HER 2 FISH is performed on paraffin embedded material routinely for selection of breast cancer patients for trastuzumab therapy, and adoption of EGFR FISH could similarly become practice changing. The current proposed Phase III trial is statistically designed to address both the clinical role of cetuximab using an "all comer" design, and the biologic role of EGFR FISH in maximizing efficacy. Further data from **S0536** provide the basis for inclusion of bevacizumab in "bevacizumab-appropriate" patients. Considering the current state of therapy for advanced NSCLC, it is likely that the results of **S0819** will significantly alter clinical practice.

**Inclusion of Women and Minorities:**

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below, however all institutions will be encouraged to make every effort to increase accrual in minority populations.

Ethnic Category	Females	Males	Total
	Hispanic or Latino	19	22
Not Hispanic or Latino	773	732	1505
<b>Ethnic Category: Total of all subjects</b>	792	753	1546
<b>Racial Category</b>			
American Indian or Alaskan Native	1	1	2
Asian	15	19	34
Black or African American	80	83	163
Native Hawaiian or other Pacific Islander	2	2	4
White	694	649	1343
<b>Racial Category: Total of all subjects</b>	792	753	1546

**3.0 DRUG INFORMATION**

**3.1 Bevacizumab (rhuMAb VEGF) (Avastin®) (NSC #704865)**

**a. DESCRIPTION**

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, induction of proteinases leading to remodeling of the extracellular matrix, increased vascular permeability, maintenance of survival for newly formed blood vessels, and, possibly, suppression of dendritic cell antigen presentation. The biologic effects of VEGF are mediated through binding and stimulation of two receptors on the surface of endothelial cells: Flt-1 (fms-like tyrosine kinase)/VEGFR-1 and KDR (kinase domain region)/VEGFR-2.

Increased levels of VEGF expression have been found in most human tumors examined to date, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, and cervix, angiosarcomas, glioblastomas, as well as multiple myeloma, lymphoma, and AML. Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice. The human cancers represented by these cell lines that are growth-inhibited by anti-VEGF antibody include non-small cell lung cancer (Calu-6), colorectal cancer (LS174T, HM-7, LSLiM6), breast cancer (MCF-7), prostate cancer (D-145), head and neck cancer (KB), ovarian cancer (SK-OV-3), and others.

b. TOXICOLOGY

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with **bold** and **italicized** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/adverse\\_events.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) for further clarification.

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, May 23, 2016<sup>1</sup>

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<b>Anemia (Gr 3)</b>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<b>Febrile neutropenia (Gr 3)</b>

CARDIAC DISORDERS			
		Acute coronary syndrome <sup>2</sup>	
	Cardiac disorders - Other (supraventricular arrhythmias) <sup>3</sup>		<b>Cardiac disorders - Other (supraventricular arrhythmias)<sup>3</sup> (Gr 3)</b>
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction <sup>2</sup>	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<b>Abdominal pain (Gr 3)</b>
	Colitis		<b>Colitis (Gr 3)</b>
	Constipation		<b>Constipation (Gr 3)</b>
	Diarrhea		<b>Diarrhea (Gr 3)</b>
	Dyspepsia		<b>Dyspepsia (Gr 2)</b>
		Gastrointestinal fistula <sup>4</sup>	
	Gastrointestinal hemorrhage <sup>5</sup>		<b>Gastrointestinal hemorrhage<sup>5</sup> (Gr 2)</b>
	Gastrointestinal obstruction <sup>6</sup>		
		Gastrointestinal perforation <sup>7</sup>	
		Gastrointestinal ulcer <sup>8</sup>	
	Ileus		
	Mucositis oral		<b>Mucositis oral (Gr 3)</b>
	Nausea		<b>Nausea (Gr 3)</b>
	Vomiting		<b>Vomiting (Gr 3)</b>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		<b>Fatigue (Gr 3)</b>
	Infusion related reaction		<b>Infusion related reaction (Gr 2)</b>
	Non-cardiac chest pain		<b>Non-cardiac chest pain (Gr 3)</b>
	Pain		<b>Pain (Gr 3)</b>
HEPATOBIILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		<b>Allergic reaction (Gr 2)</b>
		Anaphylaxis	

INFECTIONS AND INFESTATIONS			
	Infection <sup>9</sup>		<b>Infection<sup>9</sup> (Gr 3)</b>
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications - Other (anastomotic leak) <sup>10</sup>	
	Wound complication		<b>Wound complication (Gr 2)</b>
	Wound dehiscence		<b>Wound dehiscence (Gr 2)</b>
INVESTIGATIONS			
	Alanine aminotransferase increased		<b>Alanine aminotransferase increased (Gr 3)</b>
	Alkaline phosphatase increased		<b>Alkaline phosphatase increased (Gr 3)</b>
	Aspartate aminotransferase increased		<b>Aspartate aminotransferase increased (Gr 3)</b>
	Blood bilirubin increased		<b>Blood bilirubin increased (Gr 2)</b>
	Creatinine increased		
Neutrophil count decreased			<b>Neutrophil count decreased (Gr 3)</b>
	Platelet count decreased		<b>Platelet count decreased (Gr 4)</b>
	Weight loss		<b>Weight loss (Gr 3)</b>
	White blood cell decreased		<b>White blood cell decreased (Gr 3)</b>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<b>Anorexia (Gr 3)</b>
	Dehydration		<b>Dehydration (Gr 3)</b>
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<b>Arthralgia (Gr 3)</b>
		Avascular necrosis <sup>11</sup>	
	Generalized muscle weakness		

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS (contd.)			
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) <sup>12</sup>		
	Myalgia		<b>Myalgia (Gr 3)</b>
	Osteonecrosis of jaw <sup>13</sup>		
NERVOUS SYSTEM DISORDERS			
	Dizziness		<b>Dizziness (Gr 2)</b>
	Headache		<b>Headache (Gr 3)</b>
		Intracranial hemorrhage	
		Ischemia cerebrovascular <sup>2</sup>	
	Peripheral sensory neuropathy <sup>14</sup>		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		<b>Hematuria (Gr 3)</b>
	Proteinuria		<b>Proteinuria (Gr 2)</b>
		Renal and urinary disorders - Other (nephrotic syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Reproductive system and breast disorders - Other (ovarian failure) <sup>15</sup>		
		Vaginal fistula	
	Vaginal hemorrhage		<b>Vaginal hemorrhage (Gr 3)</b>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		<b>Allergic rhinitis (Gr 3)</b>
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		<b>Cough (Gr 3)</b>
	Dyspnea		<b>Dyspnea (Gr 2)</b>
	Epistaxis		<b>Epistaxis (Gr 3)</b>

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (contd.)			
	Hoarseness		<b>Hoarseness (Gr 3)</b>
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		<b>Pruritus (Gr 2)</b>
	Rash maculo-papular		<b>Rash maculo-papular (Gr 2)</b>
	Urticaria		<b>Urticaria (Gr 2)</b>
VASCULAR DISORDERS			
	Hypertension		<b>Hypertension (Gr 3)</b>
	Thromboembolic event		<b>Thromboembolic event (Gr 3)</b>
		Vascular disorders - Other (arterial thromboembolic event) <sup>2,16</sup>	

<sup>1</sup> This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup> The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

<sup>3</sup>Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

<sup>4</sup> Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>5</sup> Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>6</sup> Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

- 7 Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.
- 8 Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.
- 9 Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
- 10 Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.
- 11 There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.
- 12 Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.
- 13 Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.
- 14 Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.
- 15 Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation ( $\geq 30$  mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level  $< 30$  mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.
- 16 Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

**Adverse events reported on bevacizumab (rhuMab VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMab VEGF) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis

**CARDIAC DISORDERS** - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction

**EAR AND LABYRINTH DISORDERS** - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo

**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism

**EYE DISORDERS** - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP  $>$  or  $= 30$  mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes

**GASTROINTESTINAL DISORDERS** - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain

**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyponatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb

**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain

**NERVOUS SYSTEM DISORDERS** - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction

**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis

**RENAL AND URINARY DISORDERS** - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome

**VASCULAR DISORDERS** - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

**Note:** Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common Grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. Reference may also be made to the Investigator's Brochure for bevacizumab. The Package Insert (or Full Prescribing Information) was prepared for commercial Avastin but not the investigational bevacizumab being used in this protocol. The Package Insert should therefore only be used in combination with the Investigator's Brochure.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a

common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE Grade 3 proteinuria (> 3.5 gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the Phase II randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and Grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a Phase II study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal (Novotny et al., 2001). In the pivotal Phase III trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; Grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs. 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Schilling et al., ASCO 2005). In patients  $\geq$  65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal Phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the IFL/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In a Phase III controlled clinical trial in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal Phase III trial of IFL  $\pm$  bevacizumab (given at 5 mg/kg q2w), the overall incidences of Grade 3-4 venous thromboembolic events were comparable in the two arms (15.1 vs. 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Neutropenia: When combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a Phase III trial with IFL ± bevacizumab in colorectal cancer, Grade 3-4 neutropenia was 21% in the bevacizumab + IFL arm vs. 14% in the IFL arm (Grade 4 neutropenia was 3 vs. 2%). In the Phase III trial with carboplatin and paclitaxel ± bevacizumab in metastatic NSCLC, the bevacizumab-containing arm was associated with increased rates of Grade 4 neutropenia (26% vs. 17%), febrile neutropenia (5.4% vs. 1.8%) and an increased rate of infection with neutropenia (4.5 vs. 1.8%) with 3 cases with fatal outcome in the bevacizumab + chemotherapy arm vs. 0 in the chemotherapy only control.

Tracheoesophageal (TE) fistula: In a Phase II trial of concurrent chemoradiation and bevacizumab in limited SCLC (concurrent irinotecan, carboplatin, radiotherapy, and bevacizumab, followed by maintenance bevacizumab), among the first 25 patients enrolled, there have been two confirmed cases of tracheoesophageal (TE) fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of concurrent bevacizumab and chemoradiation). The TE fistula rate in this trial was higher than expected with chemoradiation alone. While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without radiation), the incidence was extremely low (<< 1%), and the relationships to treatment vs. tumor in those cases were unclear. Experience is limited for bevacizumab administered sequentially after chemoradiation for either NSCLC or SCLC; in a study for chemoradiation followed by bevacizumab in SCLC, one of the 60 patients enrolled developed TE fistula.

c. PHARMACOLOGY

Kinetics: In study AVF0737g, the pharmacokinetics of bevacizumab appeared to be linear for doses of  $\geq 1$  mg/kg, with a half-life of ~15 days. A consistent profile was seen in study AVF0761g. Co-administration of bevacizumab with cytotoxic chemotherapy did not appear to result in a change in the systemic concentrations of the cytotoxic agents.

How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For bevacizumab, each 400 mg (16 mL) and 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

Preparation: Vials contain no preservative and are intended for single use only. **Place the calculated dose in 100 mL of 0.9% Sodium Chloride for Injection.** Once the bevacizumab has been added to the bag with 0.9% Sodium Chloride for Injection, the solution must be administered within 8 hours. When the bevacizumab IV bag is empty, an additional 50 ml of 0.9% Sodium Chloride for Injection should be added to the IV bag and the infusion continued for a volume equal to that of the tubing to insure complete delivery of the bevacizumab. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% Sodium Chloride for Injection and infuse a volume equal to that of the tubing to insure complete delivery of the bevacizumab. Note that this flush is not included in the infusion times.

Storage and Stability: Bevacizumab is only shipped Monday through Thursday. It is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2° to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified of any dating extensions, when lots have expired, and how to handle disposition of the agent. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once diluted in 0.9% Sodium Chloride for Injection, solution of bevacizumab must be administered within 8 hours.

Administration: The route of administration is intravenous as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

d. SUPPLIER

Bevacizumab is commercially available and should be purchased by a third party. Bevacizumab will not be supplied by the NCI.

Avastin Access Solutions provides coverage and reimbursement support, patient assistance and informational resources. Please call 888/249-4918 (M - F 6:00 am - 5:00 pm PST) for assistance.

Examples of how Avastin Access Solutions can help include the following:

- Conducting benefits investigations
- Obtaining prior authorizations for the use of Avastin when necessary
- Helping with appeals when prior authorization or reimbursement is denied
- Referring patients to independent, non-profit organizations for co-pay assistance
- Referring uninsured or rendered uninsured patients to the Genentech Access to Care
- Please refer to the Physician Desk Reference and package insert for complete information.

3.2 Carboplatin (CBDCA) (NSC-241240)

a. DESCRIPTION

Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross-links.

b. TOXICOLOGY

Human Toxicology: Side effects of carboplatin (CBDCA) include myelosuppression, nausea, vomiting, abdominal pain, diarrhea and constipation. Other toxicities include allergic reaction (including hypersensitivity, i.e., rash, urticaria, erythema, pruritus, bronchospasm and hypotension), peripheral neuropathy, paresthesia, loss of hair, hearing loss, visual disturbances and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain, asthenia, cardiovascular, respiratory, genitourinary and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported rarely. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Carboplatin may cause fetal harm, therefore women of childbearing potential should be advised to avoid becoming pregnant.

c. PHARMACOLOGY

Kinetics: The differences in potencies of carboplatin and cisplatin are due to differences in aquation rates. The initial half-life is 1.1 - 2.0 hours and the post-distributional half-life is 2.6 - 5.9 hours. Sixty-five percent of the dose is excreted in the urine within twelve hours. Carboplatin is not bound to plasma proteins.

Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of carboplatin and mannitol. 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, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride Injection, USP (NS).

**Storage and Stability:** Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at controlled room temperature 15° - 30°C, and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for 8 hours at room temperature (25°C). Like cisplatin, this drug should not be given through aluminum needles.  
**CAUTION:** The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

**Administration:** Intravenous.

**Supplier:** Carboplatin is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

#### REFERENCE - PDR 1993

### 3.3 Cetuximab (IMC-C225) (Erbix<sup>®</sup>) (NSC-714692)

#### a. DESCRIPTION

Cetuximab, a chimerized antibody of the IgG<sub>1</sub> subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGF $\alpha$ ) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

#### b. TOXICOLOGY

Pre-clinical toxicology of this drug was performed. A dose-response was demonstrated in sera after a single 15 minute intravenous infusion of cetuximab. Pharmacokinetic studies revealed a dose-response in sera after twice weekly infusions up to 28 days. No evidence of accumulation of antibody was observed. Acute and subacute toxicity studies of single and repeated doses revealed no evidence of treatment-related effects in body weight, food consumption, clinical pathology or gross necropsy data were observed.

A total of 606 subjects treated with cetuximab through February 2002 were tested for the presence of anti-cetuximab antibodies by analyzing pre- and post-treatment sera using a double antigen radiometric assay. The incidence of an anti-cetuximab immune response in these subjects was 4.1%. When it occurred, the anti-cetuximab response was generally found to be weak (upper limit of normal is 10 ng/ml cetuximab binding). The anti-cetuximab antibodies from two subjects with the highest reactivity (4670 and 6516 ng/ml) did not interfere with the ability of cetuximab to inhibit proliferation in a cetuximab sensitive cell line, suggesting that the antibodies in these sera were non-neutralizing. Levels of reactivity in sera from other subjects were not high enough to perform this type of

analysis. In order to determine the specificity of the antibody response, sera from 15 subjects who had a positive anti-cetuximab response were further studied in the double antigen radiometric assay using unlabeled cetuximab as a competitor. This analysis demonstrated that sera from 14 of the 15 subjects contained cetuximab-specific antibodies.

Comprehensive Adverse Events and Potential Risks List (CAEPR) for Cetuximab (NSC #714692)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/adverse\\_events.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) for further clarification. *Frequency is provided based on 2282 patients.* Below is the CAEPR for Cetuximab.

Version 2.1, March 31, 2010<sup>1</sup>

Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	<i>Expected</i>
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
EAR AND LABYRINTH DISORDERS			
	External ear inflammation		
EYE DISORDERS			
	Conjunctivitis		<b><i>Conjunctivitis</i></b>
	Dry eye		<b><i>Dry eye</i></b>
	Uveitis		<b><i>Uveitis</i></b>
	Watering eyes		<b><i>Watering eyes</i></b>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<b><i>Abdominal pain</i></b>
	Cheilitis		<b><i>Cheilitis</i></b>
	Constipation		<b><i>Constipation</i></b>
Diarrhea			<b><i>Diarrhea</i></b>
	Dry mouth		<b><i>Dry mouth</i></b>
	Dyspepsia		<b><i>Dyspepsia</i></b>
	Mucositis oral		<b><i>Mucositis oral</i></b>
			<b><i>Nausea</i></b>
	Vomiting		<b><i>Vomiting</i></b>

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		<b>Chills</b>
	Edema limbs		
			<b>Fatigue</b>
			<b>Fever</b>
	Flu like symptoms		<b>Flu like symptoms</b>
	Infusion related reaction		<b>Infusion related reaction</b>
	Non-cardiac chest pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		<b>Allergic reaction</b>
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection <sup>2</sup>		
		Infections and infestations – Other (aseptic meningitis)	
INVESTIGATIONS			
	Neutrophil count decreased		
	Weight loss		<b>Weight loss</b>
	White blood cell decrease		<b>White blood cell decreased</b>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<b>Anorexia</b>
	Dehydration		<b>Dehydration</b>
	Hypocalcemia		
	Hypomagnesemia		<b>Hypomagnesemia</b>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<b>Arthralgia</b>
	Back pain		<b>Back pain</b>
	Myalgia		<b>Myalgia</b>
NERVOUS SYSTEM DISORDERS			
Headache			<b>Headache</b>
	Syncope		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		<b>Allergic rhinitis</b>
	Bronchospasm		
	Cough		<b>Cough</b>
	Dyspnea		<b>Dyspnea</b>
	Hoarseness		<b>Hoarseness</b>
		Pneumonitis	
		Respiratory, thoracic, and mediastinal disorders - Other (non-cardiogenic pulmonary edema)	

SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		<i><b>Alopecia</b></i>
		<i><b>Dry skin</b></i>
	Nail loss	<i><b>Nail loss</b></i>
		Palmar-plantar erythrodysesthesia syndrome
	Photosensitivity	<i><b>Photosensitivity</b></i>
	Pruritus	<i><b>Pruritus</b></i>
	Purpura	
Rash acneiform		<i><b>Rash acneiform</b></i>
Rash maculo-papular		<i><b>Rash maculo-papular</b></i>
	Skin ulceration	
	Urticaria	<i><b>Urticaria</b></i>
VASCULAR DISORDERS		
	Hypotension	<i><b>Hypotension</b></i>
	Thromboembolic event	<i><b>Thromboembolic event</b></i>

- 1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
- 2 Infection could include all 75 sites of infections under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on cetuximab trials but with the relationship to cetuximab still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Disseminated intravascular coagulation; Hemolysis

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Paroxysmal atrial tachycardia; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**EYE DISORDERS** - Blurred vision; Extraocular muscle paresis; Eyelid function disorder; Keratitis; Photophobia; Vitreous hemorrhage

**GASTROINTESTINAL DISORDERS** - Colitis; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal hemorrhage (including Colonic or Gastric hemorrhage or hemorrhage in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal perforation (Colonic perforation, Duodenal perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal ulcer (ulcer includes Duodenal ulcer, Rectal ulcer, or ulcer in other sites under the GASTROINTESTINAL DISORDERS SOC); Ileus; Pancreatitis; Rectal fistula

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Cholecystitis; Hepatic failure

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Wound dehiscence

**INVESTIGATIONS** - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Serum amylase increased

**METABOLISM AND NUTRITION DISORDERS** - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (myasthenia); Musculoskeletal and connective tissue disorder - Other (Sudeck's Atrophy)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Dizziness; Dysgeusia; Extrapyramidal disorder; Intracranial hemorrhage; Nervous system disorders - Other (cholinergic syndrome); Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

**PSYCHIATRIC DISORDERS** - Agitation; Depression

**RENAL AND URINARY DISORDERS** - Hematuria; Renal and urinary disorders - Other (acute renal failure)

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Reproductive system and breast disorders - Other (balanitis); Vaginal inflammation

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans-organized pneumonia [BOOP])

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hirsutism; Skin hypopigmentation; Skin and subcutaneous tissue disorders - Other (skin fissures)

**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Vasculitis

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

**Additional risks in older patients with NSCLC:** Based on a recent pooled analysis of randomized trials in patients with advanced NSCLC treated with platinum-based chemotherapy with or without cetuximab, cetuximab-chemotherapy was associated with an increase in life-threatening events, some of which were fatal, in patients who were  $\geq 65$  years old, especially in those with a pre-existing cardiac history.

**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 loading 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 1,000). 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. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

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 clinical studies of cetuximab, dermatologic toxicities, including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g. blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneiform 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 acneiform 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. Acneiform 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 (e.g. blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneiform 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 paronychia 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.

#### Hypomagnesemia

The occurrence of hypomagnesemia has been reported.

### c. PHARMACOLOGY

Pharmacokinetic modeling has been employed during cetuximab clinical studies with the objective of determining the dosing regimen(s) of cetuximab that maintains drug concentrations within a range associated with zero-order elimination (saturation of clearance). The analyses suggest that complete saturation of the mechanism(s) governing drug elimination occur in the range of 200 to 500 mg/m<sup>2</sup>, while doses of cetuximab below 200 mg/m<sup>2</sup> are not associated with saturation of clearance. Doses of  $\geq 400$  mg/m<sup>2</sup> demonstrated zero-order elimination for at least 96 hours following drug infusion with increasing amounts of trough level drug accumulation. Since this drug accumulation is an expected result when operating under saturating conditions, the model was

examined to identify cetuximab dose levels that maintained trough concentrations from initial dosing through all subsequent dosing at or just above  $K_m$ . The dosing regimen ultimately selected to satisfy these requirements was one that utilized a loading dose of 400 mg/m<sup>2</sup> followed by subsequent maintenance doses of 250 mg/m<sup>2</sup>.

Formulation: 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.

How Supplied: 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.

Handling and Dispensing of Cetuximab: Cetuximab should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that cetuximab is only dispensed to study subjects. The cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations.

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°C to 8°C. Discard any unused portion of the vial.

Preparation and Administration: 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 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 can be administered via infusion pump or syringe pump.

Infusion Pump:

- 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).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g. Baxter IntraVia), ethylene vinyl acetate bags (e.g. Baxter Clintec), DEHP plasticized PVC bags (e.g. Abbott Lifecare), or PVC bags.

- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- 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).
- Connect up the infusion line and start the infusion after priming the line with cetuximab.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- 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.

**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. For questions regarding cetuximab destruction please contact BMS at GMB-DC-ALL-ClinicalShipment@catalent.com.

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.

**Administration of Cetuximab:** 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 similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m<sup>2</sup> intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m<sup>2</sup> 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.

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.

d. SUPPLIER

Cetuximab is distributed free of charge through an alliance between ImClone Systems, Inc. and Bristol-Myers Squibb (BMS). Quantities must be ordered in multiples of 20 (keeping in mind that 7 - 9 vials will be needed for an initial dose and 4 - 6 for a maintenance dose, depending on patient's BSA). A suggested initial shipment is 20 vials. Institutions should reorder when supply is low based on site needs.

Following collection of all regulatory documents and patient registration, a supply of cetuximab may be ordered from BMS. Investigators must **email** a completed Cetuximab Drug Request Form for **S0819** to the BMS Clinical Supply Manager at GMB-DC-ALL-ClinicalShipment@catalent.com. The form can be downloaded from the SWOG web site for utilization.

Both initial and re-supply drug requests will require approximately **5 business days** from receipt of the Cetuximab Drug Request Form to shipment of product. All product will be shipped via Federal Express in a temperature controlled container to ensure adequate refrigeration of the product. To help segregate product for this study from other investigational or marketed product, stickers bearing the BMS protocol number will be provided and may be affixed to the outer carton so as not to obscure any marking. The SWOG protocol number **S0819** may be added at the site to the same sticker if desired. 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 S0819 be utilized for this study. Cetuximab must be stored under refrigeration at +2° to +8° (+36° to +46°F). **DO NOT FREEZE CETUXIMAB.** Each shipment of cetuximab will contain an internal temperature gauge to ensure the product has remained at the appropriate temperature during shipping. This information should be recorded on the appropriate drug accountability form. For questions regarding cetuximab shipment please contact BMS at GMB-DC-ALL-ClinicalShipment@catalent.com.

Destruction: At the completion of each patient's infusion, destroy any open vials according to institution guidelines. At the completion of the study, all unused drug will be destroyed at the site, in accordance with all applicable regulations, guidelines and institution's procedures. Please maintain appropriate records of the disposal, including dates, quantities and method of destruction.

3.4 Paclitaxel, Taxol® (NSC-673089)

a. DESCRIPTION

Chemistry: Paclitaxel is a diterpene plant product found in the needles and bark of the western yew, Taxus brevifolia. The marketed formulation is prepared in a semi-synthetic process.

Molecular Weight: 853.9

Empirical Formula: C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub>

Description: Clear viscous fluid



b. TOXICOLOGY

Human Toxicity:

Dose-limiting toxicity is myelosuppression with reversible granulocytopenia, anemia, and thrombocytopenia. Allergic reactions occur in up to 8% of patients receiving paclitaxel as an intravenous infusion over 6 to 24 hours. These can be acute anaphylactoid reactions to include flushing, hypotension, and bronchospasm; dermatitis and pruritus are also observed. Hypertension has also been seen, and may be related to concomitant medication with dexamethasone. Premedication with diphenhydramine, cimetidine, and dexamethasone appears to diminish the incidence of these reactions. Neurotoxicity can include distal painful paresthesias. Rarely, this toxicity has required discontinuation of drug due to pain, impairment of fine motor skills, or difficulty ambulating. Experience to date suggests that this neuropathy is reversible. Rarely, associated forms of neurotoxicity have included taste perversion, seizures, and mood changes. Some patients have reported vision abnormalities such as blurred vision, "flashing lights" and scintillating scotomata. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has also been seen. Patients reporting abdominal discomfort should be monitored closely. These events generally occurred while the patients were severely neutropenic. They may be most consistent with neutropenic enterocolitis (typhlitis). Although increased SGOT, SGPT, bilirubin and alkaline phosphatase, as well as hepatic failure and hepatic necrosis have been seen, one patient receiving this drug has also experienced hepatic encephalopathy, and two incidences of pancreatitis have been noted. Neuroencephalopathy has also been reported. Pulmonary toxicities that have occurred are pneumonitis and radiation pneumonitis (following concomitant paclitaxel and radiation).

Other non-hematologic reactions include: diarrhea, alopecia, myalgias and arthralgias, nausea or vomiting, mucositis (stomatitis and pharyngitis), light-headedness, myopathy and fatigue. Less commonly, cardiotoxicity has been associated with paclitaxel administration, to include arrhythmias (sinus bradycardia, ventricular tachycardia, atrial arrhythmia, and heart block), and myocardial infarction. Skin reactions including erythema, induration, tenderness, ulceration, radiation recall, rash and nail changes have occurred including discoloration of fingernails and separation from nail bed.

Pregnancy and Lactation: Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorption and embryo-fetal deaths. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Formulation: Sterile solution containing 6 mg/ml in a 5 ml vial (30 mg per vial) in polyoxyethylated castor oil (Cremaphor EL) 50% and dehydrated alcohol, USP, 50%. There are also vial sizes of 100 mg and 300 mg.

Solution Preparation: Paclitaxel is reconstituted by diluting the total dose in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (D5W) to maintain a paclitaxel concentration between 0.3 and 1.2 mg/ml. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexylphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremaphor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtrations should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II or IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

Administration of Paclitaxel: Paclitaxel, at the appropriate dose, will be given as an intravenous infusion as specified in the protocol, diluted in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered.

Storage and stability: The intact vials of paclitaxel should be stored between 2-25°C. Based on stability data for Taxol® made from either natural or semi-synthetic paclitaxel, stored for up to 12 months at 40°C, potency losses were within the range of 2.0 to 2.4 percent per year. Samples stored for up to 3 months at 60°C lost potency at rates corresponding to 20 to 40% per year. Accordingly, vials left out in a warm place for a few days should still be satisfactory for use. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. Vials will be labeled with a firm expiration date.

Supplier: Paclitaxel is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

#### 4.0 STAGING CRITERIA

Patients must have Stage IV disease as outlined below (AJCC Cancer Staging Manual, 7th Edition, 2009):

##### Stage IV:

- Any T
- Any N
- M1<sub>a</sub> - Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion.\*
- M1<sub>b</sub> – Distant metastases

- \* Most pleural (or pericardial) effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural or pericardial fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

NOTE: Any disease that is recurrent after surgery or radiation is classified as Stage IV.

## 5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0819** Prestudy Form and submit to the Data Operations Center in Seattle (see [Section 14.0](#)). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

**SWOG Patient No.** \_\_\_\_\_

**Patient's Initials (L, F, M)** \_\_\_\_\_

### 5.1 Disease Related Criteria

- \_\_\_\_\_ a. Patients must have histologically or cytologically proven primary non-small cell lung cancer (adenocarcinoma, large cell carcinoma, squamous or unspecified). Disease must be Stage IV, as defined in [Section 4.0](#). Disease may be either newly diagnosed or recurrent after previous surgery and/or irradiation. Patients with additional lesions in an ipsilateral non-primary lobe without M1<sub>a</sub> or M1<sub>b</sub> disease will not be considered to have Stage IV disease and are not eligible.
- \_\_\_\_\_ b. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to registration. Patient must not have brain metastases unless: (1) metastases have been treated and have remained controlled for at least two weeks following treatment, AND (2) patient has no residual neurological dysfunction off corticosteroids for at least 1 day.
- \_\_\_\_\_ c. Patients may have measurable or non-measurable disease (see [Section 10.1](#)) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in [Section 10.1a](#). Measurable disease must be assessed within 28 days prior to registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. See [Sections 15.4](#) and [18.6](#) for guidelines and submission instructions for required central radiology review.
- \_\_\_\_\_ d. **Translational Medicine Studies:** Patients must have tumor tissue available for submission that is sufficient for EGFR FISH testing and must agree to submission of these specimens as defined in [Section 15.0](#). Patients must also agree to submission of specimens for other translational medicine studies as outlined in [Section 15.0](#). Patient must be offered participation in banking for future research.

SWOG Patient No. \_\_\_\_\_

Patient's Initials (L, F, M) \_\_\_\_\_

- \_\_\_\_\_ e. Patients must not have received prior chemotherapy for any stage non-small cell lung cancer. Patients must not have received prior platinum-based chemotherapy for any purpose. Patients must not have received any cetuximab, gefitinib, erlotinib or other investigational agents that target the EGFR pathway. Patients must not have received for any purpose prior bevacizumab or other VEGF-related agents. Patients must not have received for any purpose prior chimerized or murine monoclonal antibody therapy or have documented presence of human anti-mouse antibodies (HAMA).
  
- \_\_\_\_\_ f. Prior radiation is permitted; however, patients must have recovered from all associated toxicities at time of registration. In order to qualify as measurable per [Section 10.1a](#), measurable disease must be outside the previous radiation field or must have progressed.
  
- \_\_\_\_\_ g. Time from surgical or biopsy procedures is dependent on whether it is planned for the patient to receive bevacizumab.
  - 1. For patients who are bevacizumab-appropriate AND bevacizumab is planned: At least 28 days must have elapsed since major surgery (i.e. thoracotomy or VATS resection of lung cancer, open pleural biopsy or another major surgical procedure such as abdominal surgery) or significant traumatic injury. Patients must have recovered from all associated toxicities at the time of registration. There must be no anticipation of need for major surgical procedures during protocol treatment. Patients must not have had a core biopsy, mediastinoscopy, pleurodesis, VATS pleural biopsy or VATS pericardial window within 14 days prior to registration. Patients must not have had a percutaneous fine needle aspiration (FNA), thoracentesis or central venous access device implanted within 7 days prior to registration. **For other surgical procedures not listed here, please contact the study coordinators.**
  
  - 2. For patients who are bevacizumab-inappropriate or bevacizumab is not planned: At least 28 days must have elapsed since major surgery (i.e. thoracotomy or VATS resection of lung cancer, open pleural biopsy or another major surgical procedure such as abdominal surgery) or significant traumatic injury. Patients must have recovered from all associated toxicities at the time of registration. There must be no anticipation of need for major surgical procedures during protocol treatment. Patients must not have had a core biopsy, mediastinoscopy, pleurodesis, VATS pleural biopsy or VATS pericardial window within 7 days prior to registration. Patients must not have had a percutaneous fine needle aspiration (FNA), or thoracentesis within 1 day prior to registration. Patients may have had a central venous access device placed at any time prior to registration. **For other surgical procedures not listed here, please contact the study coordinators.**

SWOG Patient No. \_\_\_\_\_

Patient's Initials (L, F, M) \_\_\_\_\_

5.2 Clinical/Laboratory Criteria

- \_\_\_\_\_ a. Patients must have an ANC  $\geq$  1,500/mcl, platelet count  $\geq$  100,000/mcl, and hemoglobin  $\geq$  9 g/dL obtained within 14 days prior to registration.
- \_\_\_\_\_ b. Patients must have a serum creatinine  $\leq$  institutional upper limit of normal (IULN) AND calculated or measured creatinine clearance  $\geq$  50 cc/min using the following Cockcroft-Gault Formula:

$$\text{Estimated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{actual body weight in kg})}{72 \times \text{serum creatinine}}$$

Multiply this number by 0.85 if the patient is a female.

These tests must have been performed within 14 days prior to registration.

- \_\_\_\_\_ c. For patients who will be receiving bevacizumab, urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio  $>$  0.5, 24-hour urine protein must be obtained and the level must be  $<$  1,000 mg for patient enrollment. The urine protein used to calculate the UPC ratio must be obtained within 14 days prior to registration. UPC or 24-hour protein is not required for patients who will not receive bevacizumab.

Note: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

[urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL  
[(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

- \_\_\_\_\_ d. Patients must have adequate hepatic function documented by serum bilirubin  $\leq$  2 X IULN and either SGOT or SGPT  $\leq$  2 x IULN within 14 days prior to registration (if both SGOT and SGPT are done, both must be  $\leq$  2 x IULN). For patients with liver metastases, bilirubin and either SGOT or SGPT must be  $\leq$  5 x IULN.
- \_\_\_\_\_ e. All patients must have a Zubrod Performance Status of 0 - 1 (see [Section 10.4](#)).
- \_\_\_\_\_ f. Patients must not have  $\geq$  Grade 2 symptomatic neuropathy-sensory (NCI Common Terminology Criteria Version 3.0).
- \_\_\_\_\_ g. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.
- \_\_\_\_\_ h. Patients must not have the following: history (within past 6 months) of CVA, myocardial infarction or unstable angina; or at the time of registration, uncontrolled hypertension, New York Heart Association Grade 2 or greater congestive heart failure (see [Appendix 18.3](#)), serious cardiac arrhythmia requiring medication, or clinically significant peripheral vascular disease.
- \_\_\_\_\_ i. Patients must have no known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies [examples include trastuzumab (Herceptin) and epoetin alpha].

**SWOG Patient No.** \_\_\_\_\_

**Patient's Initials (L, F, M)** \_\_\_\_\_

- \_\_\_\_\_ j. Patients must be willing to provide prior smoking history as required on the **S0819** Prestudy Form.
- \_\_\_\_\_ k. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- \_\_\_\_\_ l. Patients must not be pregnant or nursing because of the increased risk of fetal harm including fetal death from the chemotherapeutic agents. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

### 5.3 Regulatory Criteria

- \_\_\_\_\_ a. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- \_\_\_\_\_ b. As a part of the OPEN registration process (see [Section 13.2](#) for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

## 6.0 STRATIFICATION FACTORS

Patients will be randomized between Arm 1 (chemotherapy without cetuximab) and Arm 2 (chemotherapy with cetuximab) using a dynamic balancing algorithm. (22) Stratification is based on:

### 6.1 Bevacizumab–APPROPRIATE Status: Yes versus No.

Patients are “bevacizumab-INAPPROPRIATE” if ANY ONE of the following apply (Patients with a recent history of these conditions should be registered on the study only if the condition has resolved or adequately stabilized.):

- $\geq 50\%$  squamous-cell cancer;
- history of hemoptysis (1/2 tsp or more per event within the past year);
- cavitary pulmonary lesion;
- history of documented hemorrhagic diathesis or coagulopathy; patients who have an INR  $> 1.5$ ;
- non-healing wound, ulcer or bone fracture, abdominal fistula, GI perforation or intra-abdominal abscess;
- patients receiving therapeutic anticoagulation; regular use of aspirin ( $> 325$  mg per day), nonsteroidal anti-inflammatory agents that are known to inhibit platelet function, or other agents known to inhibit platelet function;
- patients may be placed in the "bevacizumab-INAPPROPRIATE" stratum at their request or at the discretion of their treating physician.

If NONE of the above apply, the patient will be stratified into the "bevacizumab-APPROPRIATE" cohort.

### 6.2 Smoking Status

Smoking status: current or former (no smoking for 1 year or more) versus never (less than 100 cigarettes lifetime).

### 6.3 Stage

Stage: M1<sub>a</sub> versus M1<sub>b</sub> (see [Section 4.0](#)).

## 7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact any of the following Study Coordinators: Dr. Herbst at 203/785-6879 or roy.herbst@yale.edu, Dr. Kim at 980/442-3105 or edward.kim@carolinashealthcare.org or Dr. Semrad at 916/734-3771 or thomas.semrad@ucdmc.ucdavis.edu. For dosing principles or questions, please refer to the SWOG Investigator Letter distributed with Revision #9 or if you have further questions please contact the Study Coordinators listed above.

### 7.1 Good Medical Practice

The following tests (and/or assessments) are recommended within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. **If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registration.**

- a. Albumin
- b. Serum Sodium, Calcium and Magnesium
- c. LDH
- d. EKG
- e. Alkaline Phosphatase
- f. Bone scan to document bone metastasis, if clinically indicated.
- g. Patients should not have uncontrolled diabetes mellitus.
- h. Patients should not have psychological, familial, sociological or geographical conditions that do not permit weekly medical follow-up and compliance with the study protocol.
- i. Patients should not have dementia or significantly altered mental status that would prohibit the understanding and giving of informed consent.
- j. Patients should not have any immediate life-threatening complications of their malignancies.
- k. Patients should not have a history of allergic reactions to drugs utilizing the vehicle Cremaphor (some anesthetics and muscle relaxants).

## 7.2 Pre-medication

### a. Cetuximab

All patients who will receive cetuximab will be premedicated with:

Agent	Dose	Route	Duration
Diphenhydramine hydrochloride	50 mg	IV	prior to the first dose of cetuximab

Diphenhydramine must be given prior to the first dose of cetuximab in an effort to prevent a hypersensitivity reaction. Premedication is recommended prior to subsequent doses, but at the treating physician's discretion, the dose of diphenhydramine may be reduced.

b. Paclitaxel

All patients should be premedicated with:

Agent	Dose	Route	Duration
Dexamethasone	20 mg*	PO/IV	12 and 6 hours prior to paclitaxel**
Diphenhydramine***	50 mg	IV	30 minutes prior to paclitaxel
<b>plus one of the following</b>			
Ranitidine	50 mg	IV	30 minutes prior to paclitaxel
or			
Cimetidine	300 mg	IV	
Famotidine	20 mg	PO/IV	30 minutes prior to paclitaxel

\* 20 mg is the dose for each administration.

\*\* Alternatively, a single intravenous dose of 20 mg may be given 30 minutes prior to paclitaxel injection.

\*\*\* If patients received diphenhydramine prior to cetuximab, it does not need to be repeated prior to paclitaxel injection.

Dexamethasone (oral)

The investigator should prescribe dexamethasone 4 mg orally every 12 hours for 6 doses beginning in p.m. on Day 1 of each cycle.

DAY	AM DOSE	PM DOSE
Day 1	--	4 mg
Day 2	4 mg	4 mg
Day 3	4 mg	4 mg
Day 4	4 mg	--

c. Carboplatin

Patients should receive antiemetics of the treating physician's choice prior to carboplatin administration. Dose modifications in the antiemetic regimen may be made at the discretion of the treating physician as clinically indicated.

7.3 Treatment

Patients who are bevacizumab-APPROPRIATE will receive bevacizumab (per Arms 1a and 2a). Patients who are bevacizumab-INAPPROPRIATE will not receive bevacizumab (per Arms 1b and 2b). Patients may be placed in the bevacizumab-INAPPROPRIATE stratum at their request or at the discretion of their treating physician.

a. Arm 1-Chemotherapy Without Cetuximab

Based on the criteria outlined in [Section 6.1](#), patients will be treated as "bevacizumab-APPROPRIATE " or "bevacizumab-INAPPROPRIATE".

1. Arm 1a-Bevacizumab-APPROPRIATE (see [Section 6.1](#) for definitions)

**Treatment consists of up to SIX CYCLES of paclitaxel, carboplatin and bevacizumab. If six cycles are completed and none of the criteria in [Section 7.8](#) is met, treatment with bevacizumab will continue until one of the criteria in [Section 7.8](#) is met. ONE CYCLE = 21 DAYS.**

DRUG	DOSE	ROUTE	SCHEDULE
Paclitaxel	200 mg/m <sup>2</sup>	3 hour IV infusion	q 21 days x 6 cycles
Carboplatin	AUC=6 <sup>a</sup>	30 minute IV infusion immediately following paclitaxel	q 21 days x 6 cycles
Bevacizumab	15 mg/kg	IV infusion over 90 ± 15 minutes <sup>b</sup> 1 hour following carboplatin	q 21 days (bevacizumab continues beyond 6 cycles until one of the criteria in <a href="#">Section 7.8</a> is met)

<sup>a</sup> AUC=6 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed (see [Section 7.5](#) for Guidelines for Carboplatin Administration). Serum creatinine must be repeated and creatinine clearance calculated within 3 days prior to each carboplatin dose. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 900 mg. (Please see [Section 18.2](#)).

<sup>b</sup> If no adverse reactions occur, the second dose of bevacizumab should be given over a minimum of 60 minutes. If no adverse event occurs, third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in a volumetric infusion device. Infusions should be run over the shortest period that is well-tolerated. Also, if the patient tolerates bevacizumab treatment after the first cycle, the length of time between the carboplatin and bevacizumab treatment may be shortened at the discretion of the treating investigator.

2. Arm 1b-Bevacizumab-INAPPROPRIATE (see [Section 6.1](#) for definitions)

**Treatment consists of up to SIX CYCLES of paclitaxel and carboplatin if none of the criteria in [Section 7.8](#) is met. ONE CYCLE = 21 DAYS.**

<b>DRUG</b>	<b>DOSE</b>	<b>ROUTE</b>	<b>SCHEDULE</b>
Paclitaxel	200 mg/m <sup>2</sup>	3 hour IV infusion	q 21 days X 6 cycles
Carboplatin	AUC=6 <sup>a</sup>	30 minute IV infusion immediately following paclitaxel	q 21 days x 6 cycles

<sup>a</sup> AUC=6 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed (see [Section 7.5](#) for Guidelines for Carboplatin Administration). Serum creatinine must be repeated and creatinine clearance calculated within 3 days prior to carboplatin dose. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 900 mg. (Please see [Section 18.2](#)).

b. Arm 2-Chemotherapy with Cetuximab

Based on stratification, patients will be treated as "bevacizumab-APPROPRIATE" or "bevacizumab-INAPPROPRIATE".

1. Arm 2a-Bevacizumab-APPROPRIATE (see [Section 6.1](#) for definitions)

Treatment consists of up to SIX CYCLES of paclitaxel, carboplatin, cetuximab and bevacizumab. If six cycles are completed and none of the criteria in [Section 7.8](#) is met, treatment with cetuximab and bevacizumab will continue until one of the criteria in [Section 7.8](#) is met. ONE CYCLE = 21 DAYS.

DRUG	DOSE	ROUTE	SCHEDULE
Cetuximab <sup>a</sup>	400 mg/m <sup>2</sup> (Loading dose)	2 hour IV infusion	Cycle 1, Week 1 only
	250 mg/m <sup>2</sup> (Maintenance dose)	1 hour IV infusion	Weekly starting at Week 2 (cetuximab continues beyond 6 cycles until one of the criteria in <a href="#">Section 7.8</a> is met)
Paclitaxel	200 mg/m <sup>2</sup>	3 hour IV infusion 1 hour following cetuximab	q 21 days starting at Week 1 x 6 cycles
Carboplatin	AUC=6 <sup>b</sup>	30 minute IV infusion immediately following paclitaxel	q 21 days starting at Week 1 x 6 cycles
Bevacizumab	15 mg/kg	IV infusion over 90 ± 15 minutes <sup>c</sup> 1 hour following carboplatin	q 21 days starting at Week 1 (bevacizumab continues beyond 6 cycles until one of the criteria in <a href="#">Section 7.8</a> is met)

<sup>a</sup> An initial dose of cetuximab 400 mg/m<sup>2</sup> infused over 2 hours will be given at Week 1 only. Beginning at Week 2, cetuximab will be administered weekly at a dose of 250 mg/m<sup>2</sup> infused over 1 hour. Cetuximab may be administered on Day 1 or Day 2 each cycle when given with chemotherapy, depending on the preference of the treating physician. Despite this option, the order in which paclitaxel, carboplatin and bevacizumab are given must remain as stated above. Subsequent doses of weekly cetuximab given without chemotherapy should be administered as closely to a weekly schedule as possible. During Cycle 1, cetuximab must be given prior to paclitaxel, carboplatin and bevacizumab.

- b AUC=6 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed (see [Section 7.5](#) for Guidelines for Carboplatin Administration). Serum creatinine must be repeated and creatinine clearance calculated within 3 days prior to each carboplatin dose. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 900 mg. (Please see [Section 18.2](#)).
- c If no adverse reactions occur, the second dose of bevacizumab should be given over a minimum of 60 minutes. If no adverse event occurs, third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in a volumetric infusion device. Infusions should be run over the shortest period that is well-tolerated. Also, if the patient tolerates bevacizumab treatment after the first cycle, the length of time between the carboplatin and bevacizumab treatment may be shortened at the discretion of the treating investigation.

2. Arm 2b-Bevacizumab-INAPPROPRIATE (see [Section 6.1](#) for definitions)

**Treatment consists of up to SIX CYCLES of paclitaxel, carboplatin, and cetuximab. If six cycles are completed and none of the criteria in [Section 7.8](#) is met, treatment with cetuximab will continue until one of the criteria in [Section 7.8](#) is met. ONE CYCLE = 21 DAYS.**

	DOSE	ROUTE	SCHEDULE
Cetuximab <sup>a</sup>	400 mg/m <sup>2</sup> (Loading dose)	2 hour IV infusion	Cycle 1, Week 1 only
	250 mg/m <sup>2</sup> (Maintenance dose)	1 hour IV infusion	Weekly starting at Week 2 (cetuximab continues beyond 6 cycles until one of the criteria in <a href="#">Section 7.8</a> is met)
Paclitaxel	200 mg/m <sup>2</sup>	3 hour IV infusion 1 hour following cetuximab	q 21 days starting at Week 1 x 6 cycles
Carboplatin	AUC=6 <sup>b</sup>	30 minute IV infusion immediately following paclitaxel	q 21 days starting at Week 1 x 6 cycles

<sup>a</sup> An initial dose of cetuximab 400 mg/m<sup>2</sup> infused over 2 hours will be given at Week 1 only. Beginning at Week 2, cetuximab will be administered weekly at a dose of 250 mg/m<sup>2</sup> infused over 1 hour. Cetuximab may be administered on Day 1 or Day 2 each cycle when given with chemotherapy, depending on the preference of the treating physician. Despite this option, the order in which paclitaxel and carboplatin are given must remain as stated above. Subsequent doses of weekly cetuximab given without chemotherapy should be administered as closely to weekly as possible. During Cycle 1, cetuximab must be given prior to paclitaxel and carboplatin.

- <sup>b</sup> AUC=6 by modified Calvert formula. Carboplatin is given after paclitaxel infusion is completed (see [Section 7.5](#) for Guidelines for Carboplatin Administration). Serum creatinine must be repeated and creatinine clearance calculated within 3 days prior to each carboplatin dose. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing. This change is an addition to the requirement not to exceed a maximum dose of carboplatin of 900 mg. (Please see [Section 18.2](#)).

#### 7.4 Precautions

**CAUTION:** Allergic reactions may occur during or following cetuximab and paclitaxel administration. As a routine precaution, patients enrolled in this study will be observed closely for any potential adverse events by the medical staff from the start of the cetuximab infusion to one hour after the end of the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. Vital signs (blood pressure, heart rate, respiratory rate and temperature) should be checked prior to the administration, midway through the infusion, at the completion of the infusion and 1 hour post the infusion. Should an allergic or infusion reaction to cetuximab occur, the patient must be treated according to the best available medical practices. The cetuximab infusion rate should never exceed 5 mL/minute. The patient's blood pressure and heart rate should be monitored during the paclitaxel infusion. (Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.) Epinephrine and diphenhydramine for injection should be readily available during the infusion, for emergency treatment of hypersensitivity reactions.

#### 7.5 Guidelines for Carboplatin Administration

The carboplatin dose (mg) = AUC x (CrCl + 25) where AUC = 6 depending on the dose level. The creatinine clearance will be calculated using a serum creatinine obtained within 3 days prior to each dose. Carboplatin dose will be based on GFR\* (glomerular filtration rate) based on the measurement of creatinine clearance where GFR is calculated using the Cockcroft-Gault Formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{actual body weight (kg)**}}{72 \times \text{serum creatinine***}}$$

Multiply this number by 0.85 if the patient is female.

\* GFR = calculated creatinine clearance determined using the Cockcroft-Gault Formula based on age, weight (actual body weight) and serum creatinine.

\*\* Use current (actual) weight. This should be actual weight but not exceed 140% of IBW.

\*\*\* In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.

Please note that: GFR should not exceed 125 mL/min. Hence, the maximum total carboplatin dose should NOT exceed 900 mg.

See [Appendix 18.2](#) for Carboplatin Dosing Worksheet.

#### 7.6 Hematologic Requirements for Day 1 of Each Cycle

Dose delay based on hematologic counts the day of treatment: The ANC count must be  $\geq$  1,500/mcl and the platelet count  $\geq$  100,000/mcl on the day of planned treatment. If this recovery is not achieved by the day of treatment, the next cycle will be delayed until recovery occurs or a maximum of 2 weeks have passed. If a delay is  $>$  2 weeks based on these parameters, discontinue carboplatin and paclitaxel.

#### 7.7 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, etc., when appropriate. Zoledronic acid is allowed for patients with bone metastases.

#### 7.8 Criteria for Removal from Protocol Treatment

- a. Progression of disease based on the investigator's assessment (and as defined in [Section 10.2d](#)) or symptomatic deterioration (as defined in [Section 10.2e](#)).
- b. Unacceptable toxicity.
- c. Completion of 6 cycles of treatment for bevacizumab-INAPPROPRIATE patients on Arm 1b.
- d. Treatment delay  $>$  4 weeks for any reason for any agent, except as outlined in [Section 7.6](#). If more than one study drug requires permanent discontinuation contact the Study Coordinator.
- e. The patient may withdraw from the study at any time for any reason.

#### 7.9 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented on the Off Treatment Notice.

#### 7.10 Follow Up Period

All patients will be followed for 3 years after registration or until death, whichever comes first.

#### 7.11 Radiology Review

- a. To ensure the highest standards and consistency between different centers, **all** scans for disease assessment (baseline, interim, and end of treatment scans) must be submitted to the Quality Assurance Review Center (QARC) in Providence, RI for centralized review (see [Section 15.4](#)).
- b. **Centralized review will be performed by 3 radiology experts. The scans will be submitted to QARC. QARC will transmit the scans to the reviewers who will transmit the results to the SWOG Statistical Center.**
- c. Details of submission of scans to QARC for centralized review and on the central review process are listed in [Section 15.4](#) and [Appendix 18.6](#).

## 8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

### 8.1 NCI Common Terminology Criteria for Adverse Events (CTCAE)

**Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.**

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

### 8.2 General Dose Modifications

Dose adjustments of carboplatin, paclitaxel, cetuximab and bevacizumab will be made based on the occurrence and extent of toxicity.

**NOTE: ALL DOSE REDUCTIONS ARE PERMANENT. THERE WILL BE NO DOSE RE-ESCALATIONS AFTER A DOSE REDUCTION, except as specifically described in [Section 8.6](#) in conjunction with the use of G-CSF.**

- a. Carboplatin, paclitaxel and bevacizumab therapy will not be held for cetuximab related toxicities.
- b. Cetuximab therapy will not be held for carboplatin, paclitaxel or bevacizumab related toxicities.
- c. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

### 8.3 Dose Modifications for Carboplatin and Paclitaxel

Dose Level	Carboplatin (AUC)	Paclitaxel (mg/m <sup>2</sup> )
(Starting Dose)		
0	6	200
-1	5	175
-2	4	150
-3*	3	125

\* Dose reductions beyond this level are not permitted.

a. Hematologic - Carboplatin and Paclitaxel

1. Neutropenia: The following dose adjustments are based on either Day 1 CBC or interim CBC if done. Repeat dose reduction for each subsequent occurrence:

Absolute Neutrophil Count (/mcl)	Carboplatin (AUC)	Paclitaxel Dose Level
≥ 500	No change	No change
< 500 or febrile neutropenia	No change	Reduce by 1 dose level *

\* Patients with ANC < 500/mcl or febrile neutropenia despite two dose level reductions of paclitaxel, should have one dose level reduction of carboplatin, in addition to a third dose level reduction of paclitaxel.

2. Thrombocytopenia: The following dose adjustments are based on the hematological nadir of the preceding treatment cycle. Repeat dose reduction for each subsequent occurrence:

Platelet Count (/mcl)	Carboplatin (AUC)	Paclitaxel Dose Level
≥ 50,000	No change	No change
< 50,000	Reduce by 1 dose level *	No change

\* For example, if current AUC is 6, reduce dose to AUC 5. Patients with platelets < 50,000/mcl despite two dose level reductions of carboplatin, should have one dose level reduction of paclitaxel, in addition to a third dose level reduction of carboplatin.

b. Hepatic - Paclitaxel

The following paclitaxel dose adjustments are based on SGOT or SGPT and bilirubin serum levels and (after the first cycle of treatment) should be obtained within seven days prior to treatment.

SGOT or SGPT		Bilirubin	Paclitaxel
Grade 0 - 1	and	Grade 0 - 2	No change
Grade 2 - 4	or	Grade 3 - 4	HOLD*

\* If recovery of toxicity exceeds two weeks, discontinue carboplatin and paclitaxel. If recovery of toxicity occurs within two weeks (< Grade 2), resume treatment with one dose level reduction of paclitaxel.

c. Arthralgia/Myalgia - Paclitaxel

The following dose adjustments are based on the worst toxicity grade experience of arthralgia/myalgia of any preceding treatment cycle.

Arthralgia/Myalgia	Paclitaxel
Grade 0 - 2	No Change
Grade 3	- 1 dose level **
Grade 4	- 2 dose levels**

\*\* Reduce if post-medication dexamethasone ([Section 7.2b](#)) was incorporated in regimen. If no post-chemotherapy dexamethasone was administered, then prior to making any dose level reduction, the treating physician must add the regimen described in [Section 7.2b](#) to subsequent courses.

d. Neuropathy: Motor/Sensory - Carboplatin and Paclitaxel

The following dose adjustments are based on the worst toxicity grade experience of neuropathy - motor/sensory of any preceding treatment cycle.

Neuropathy - motor/sensory	Carboplatin and Paclitaxel
Grade 0 - 1	No Change
	Grade 2 - 3 HOLD BOTH DRUGS (until resolution to $\leq$ Grade 1); resume at a one dose level reduction for both drugs
	Grade 4 REMOVE PATIENT FROM PAC-LITAXEL AND CARBOPLATIN TREATMENT

e. Cardiac Toxicity - Carboplatin and Paclitaxel

If a patient develops chest pain or arrhythmia during the infusion, the infusion should be stopped. Manage any arrhythmias according to standard practice. Patients who experience chest pain during paclitaxel infusion should not restart paclitaxel until a cardiac ischemic event has been ruled out. Patients will be removed from paclitaxel and carboplatin treatment in cases of symptomatic arrhythmias or AV block (except first degree) or other heart block. In case of first degree AV block, patient may continue paclitaxel infusion with continuous cardiac monitoring during the infusion, at the discretion of the treating physician.

f. Hypersensitivity Reactions - Paclitaxel

Caution: Patients who have a mild to moderate hypersensitivity reaction should be rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

For moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort), stop the infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. After recovery of symptoms, resume infusion at a low rate, 20 mg/hr for 15 minutes. If no further symptoms, resume at full dose rate until infusion is complete. If symptoms recur, stop infusion. The patient should receive no additional paclitaxel for that cycle, but may be retreated after discussion with the Study Coordinator.

For severe life threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilator therapy, generalized urticaria), stop the infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The patient will be taken off paclitaxel treatment.

g. Hyperglycemia - Carboplatin and Paclitaxel

Diabetic patients will occasionally experience Grade 3 - 4 hyperglycemic reaction to premedication:

Hyperglycemia	Carboplatin and Paclitaxel
Grade 3 (> 250 - 500 mg/dl)	Continue with planned treatment, if possible, and give appropriate dose(s) of insulin during chemotherapy infusion.
Grade 4 (> 500 mg/dl or ketoacidosis)	Hold both drugs until hyperglycemia resolves.*

\* If indicated, subsequent treatment may be continued with insulin or appropriate oral agent to prevent Grade 4 hyperglycemia in subsequent treatment courses.

h. Renal - Carboplatin

There will be no dose modifications of paclitaxel dose based on renal toxicity. If creatinine is greater than IULN, hold carboplatin until  $\geq 50$  cc/minute then recalculate dose based on Calvert Formula ([Section 7.5](#)).

8.4 Dose Modifications for Cetuximab

Dose Level	Cetuximab (mg/m <sup>2</sup> )
(Starting Dose)*	
0	250
-1	200
-2	150

\* The cetuximab dose levels indicated pertain to administration of a maintenance dose. If toxicities occur with the loading dose, cetuximab should be held until resolution (as defined throughout [Section 8.4](#)), then begun at the starting dose of 250 mg/m<sup>2</sup>. **There will be no cetuximab dose level reductions below a weekly dose of 150 mg/m<sup>2</sup>.**

a. Dermatologic Toxicities

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae and appropriate treatment of these symptoms should be initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe acneiform rash (Grade 3).

For the treatment of rash, it is recommended that patients be started on a tetracycline (e.g., tetracycline 500 mg BID; minocycline 100 mg BID; or doxycycline 100 mg BID) and clindamycin topical lotion BID within 5 days after the start of therapy. Treatment will be discontinued or modified following completion of cetuximab therapy or if the treating physician feels it is in the patient's best interest. ([See Appendix 18.4.](#))

Dry skin will be noted in most patients receiving cetuximab. This should be treated with an emollient twice daily.

With prolonged use of cetuximab, some patients may develop paronychia inflammation of the fingers and toes or fissuring of the fingertips. In general, good hygiene with appropriate local measures such as soaks in aluminum acetate (Burow's) solution BID-QID will prevent secondary infection. Symptom relief may be achieved with standard bandages or with the application of liquid bandages (cyanoacrylate preparations such as Band-Aid Liquid Bandage®).

Toxicity and Grade	Dose Modification
Rash: acne/acneiform	<p>No dose modification is required for Grade 1 or 2 rash. Treatment with topical and/or oral antibiotics should be considered at the discretion of the treating physician. Topical corticosteroids are <u>not</u> recommended. For Grade 2 rash that is unacceptable to the patient for symptomatic reasons, cetuximab may be held until resolution to <math>\leq</math> Grade 1 for up to 4 weeks.</p> <p><u>1st Occurrence</u>  Delay cetuximab treatment for 1 to 2 weeks. If toxicity resolves to <math>\leq</math> Grade 2, treatment may resume without change in dose level. If toxicity does not resolve to <math>\leq</math> Grade 2 after 4 weeks, discontinue cetuximab.</p> <p><u>2nd Occurrence</u>  Delay cetuximab treatment for 1 to 2 weeks. If toxicity resolves to <math>\leq</math> Grade 2, treatment should be re-initiated at 200 mg/m<sup>2</sup>. If toxicity does not resolve to <math>\leq</math> Grade 2 after 4 weeks, discontinue cetuximab.</p> <p><u>3rd Occurrence</u>  Delay cetuximab therapy for 1 to 2 weeks. If toxicity resolves to <math>\leq</math> Grade 2, treatment should be re-initiated at 150 mg/m<sup>2</sup>. If toxicity does not resolve to <math>\leq</math> Grade 2 after 4 weeks, discontinue cetuximab.</p> <p><u>4th Occurrence</u>  Discontinue cetuximab.</p>

b. Infusion Reactions

Toxicity and Grade	Dose Modification
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Mild to moderate (Grade 1 or 2) infusion reactions are managed by slowing the infusion rate for cetuximab and by employing prophylactic use of antihistamine medications for subsequent doses. If the patient experiences Grade 1 or 2 infusion reaction, the infusion rate should be permanently reduced by 50%.\* Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in patients.

Severe infusion reactions, characterized by airway obstruction (bronchospasm, stridor, hoarseness), urticaria and/or hypotension require immediate interruption of cetuximab infusion and permanent discontinuation from further cetuximab. 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.

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\* In the event of isolated drug fever, the treating physician must use clinical judgment to determine if the fever is related to cetuximab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (physician discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for subsequent doses.

c. Pulmonary Toxicities

Toxicity and Grade	Dose Modification
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Hold cetuximab. If not resolved within 4 weeks, discontinue protocol treatment. If interstitial lung disease (ILD) is confirmed, cetuximab should be discontinued and patient should be treated appropriately.

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In the event of acute onset (Grade  $\geq$  2) or worsening pulmonary symptoms that are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab re-treatment 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.

d. Hypomagnesemia

In the event of hypomagnesemia, more frequent monitoring and magnesium repletion should be instituted as per routine clinical practice. Cetuximab will be held for Grade 3-4 hypomagnesemia until recovery to Grade 2 or less.

- e. For any other medically concerning event  $\geq$  Grade 2, please contact any of the following Study Coordinators: Dr. Herbst at 203/785-6879 or roy.herbst@yale.edu, Dr. Kim at 980/442-3105 or edward.kim@carolinashealthcare.org or Dr. Semrad at 916/734-3771 or thomas.semrad@ucdmc.ucdavis.edu.

### 8.5 Dose Modifications for Bevacizumab

There are no reductions for bevacizumab dose levels, just dose delays. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Adverse events requiring delays or permanent discontinuation of bevacizumab are outlined below.

Patients who require discontinuation of bevacizumab for toxicity may continue to receive the other treatment agents.

Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE v3.0 Grade	Action to be Taken
<b>Allergic reactions, or Acute infusional reactions/ cytokine release syndrome</b>	Grade 1-3	If infusion-related or allergic reactions occur, premeds should be given with the next dose, and infusion time must not be reduced for the subsequent infusion. <b>For patients with Grade 3 reactions</b> , bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or re-instituted with premeds and at a rate of $90 \pm 15$ min. <b>If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.</b>
	Grade 4	Discontinue bevacizumab
<b>Arterial Thrombosis</b> Cardiac ischemia/ infarction CNS ischemia (TIA, CVA) any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab
	Grade 3-4	Discontinue bevacizumab
<b>Reversible Posterior Leukoencephalopathy Syndrome</b>		Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.
<b>Venous Thrombosis</b>	$\geq$ Grade 3	Discontinue bevacizumab

<b>Hypertension</b>	
The dose of bevacizumab should be held for resting SBP > 150 or resting DBP > 100 at the time of infusion. Dose should also be held for symptomatic hypertension regardless of grade or blood pressure level. Dose may be held for up to 4 weeks.	
No dose modifications for Grade 1-2 events.	
Grade 3	<p>Medications should be used for blood pressure control. Ideal goal for blood pressure is &lt; 140/80. If a new anti-hypertensive is to be added, the choice of drug is at the discretion of treating physician. Prior experience with bevacizumab-associated hypertension among carcinoid patients suggested dihydropyridine calcium channel blockers and alpha adrenergic vasodilators were effective. In general, the dose of agents should be maximized prior to changing or adding new agents. Record any new anti-hypertensive added and whether blood pressure was adequately controlled.</p> <p><u>Recommended anti-hypertensives:</u></p> <ul style="list-style-type: none"> <li>• nifedipine (Procardia XL<sup>®</sup>, Adalat CC<sup>®</sup>) 30 to 90 mg q day</li> <li>• nifedipine (Cardine SR<sup>®</sup>) 30 to 60 mg BID</li> <li>• terazosin (Hytrin<sup>®</sup>) 2 to 10 mg per day</li> <li>• doxazosin (Cardura<sup>®</sup>) 1 to 2 mg q day</li> </ul> <p>If HTN cannot be controlled with medications, remove patient from protocol treatment.</p>
Grade 4	Remove patient from protocol treatment
<b>Proteinuria</b>	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab.]
	UPC ratio < 3.5      Continue bevacizumab
	UPC ratio ≥ 3.5      Hold bevacizumab until UPC recovers to < 3.5. If bevacizumab is held for > 8 weeks due to proteinuria, discontinue bevacizumab.
	Grade 4 or nephrotic syndrome      Discontinue bevacizumab
<b>Wound dehiscence requiring medical or surgical intervention</b>	Discontinue bevacizumab
<b>GI perforation, GI leak or fistula</b>	Discontinue bevacizumab
<b>Hemoptysis</b>	≥ Grade 2      Discontinue bevacizumab

<b>Hemorrhage</b>	Grade 3	<ul style="list-style-type: none"> <li>• Patients receiving full-dose anticoagulation should discontinue bevacizumab.</li> <li>• For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> <li>- the bleeding has resolved and Hb is stable</li> <li>- there is no bleeding diathesis that would increase the risk of therapy</li> <li>- there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.</li> </ul> </li> <li>• Patients who experience recurrence of Grade 3 hemorrhage should discontinue bevacizumab.</li> </ul>
	Grade 4	Discontinue bevacizumab
<b>Other clinically significant AEs attributable to bevacizumab</b> (except controlled nausea/vomiting)	Grade 3	Hold bevacizumab for up to 4 weeks until symptoms resolve to ≤ Grade 1
	Grade 4	<ul style="list-style-type: none"> <li>• Discontinue bevacizumab</li> <li>• <b>Upon consultation with the Study Coordinator</b>, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤ Grade 1 within 4 weeks and is unlikely to recur with retreatment.</li> </ul>

## 8.6 G-CSF Usage

G-CSF (Amgen) has been licensed by the Food and Drug Administration for the prevention of chemotherapy induced neutropenia and may be used according to clinical practice guidelines. It may be used for patients who develop Grade 3 - 4 neutropenia. For patients who experience Grade 3 or 4 neutropenia or develop neutropenic fever between cycles of chemotherapy, G-CSF may be added to all subsequent cycles of chemotherapy. G-CSF is commercially available and should be purchased through third party mechanisms. The NCI will not provide G-CSF for this study.

If G-CSF is used, it is recommended that it be used in the following manner:

If a patient develops neutropenia following chemotherapy, all dose modifications outlined in the protocol will be followed according to the original protocol. However, G-CSF will be added to all subsequent cycles of chemotherapy, unless there is clinical suspicion that the neutropenia was due to an unrelated medical condition and not due to the chemotherapy.

If the patient maintains an ANC of  $\geq 1,000/\text{mm}^3$  throughout the initial cycle of G-CSF supported chemotherapy, then the next cycle of chemotherapy may be increased back to the original dose level with the continued support of the G-CSF. **No dose escalations above the original dose level should be performed on patients taking G-CSF.**

G-CSF will be given at a dose of 5 mcg/kg/d subcutaneously beginning 24 hours after completion of chemotherapy and continuing until the ANC exceeds 1,000/mcl on two successive determinations. Doses may be rounded off to the nearest vial size (300 mcg and 480 mcg vials). G-CSF should be discontinued at least 24 hours before the next chemotherapy dose. While the patient is receiving G-CSF, the CBC should be monitored at least twice a week (more frequently if clinically indicated).

NOTE: Neulasta™ (pegfilgrastim) is allowed in the place of G-CSF. The dose is 6 mg given once, 24 hours after chemotherapy. While the patient is receiving Neulasta™, the CBC should be monitored weekly.

The use of G-CSF or pegfilgrastim must be documented on the **S0819** Treatment Form.

#### 8.7 G-CSF Dose Modifications

Dose adjustments for toxicities associated with G-CSF (bone pain, splenomegaly, abnormalities in uric acid concentrations, LDH and alkaline phosphatase, transient elevations of serum creatinine and aminotransferase activity)

Dose modifications for G-CSF toxicity should only be initiated if symptomatic control of the toxicity fails (i.e., analgesics such as acetaminophen or acetaminophen with codeine for myalgias or bone pain, etc.).

Toxicity Grade	Dose Adjustment
Grade 0 - 1	No change
Grade 2	Decrease G-CSF to 3 mcg/kg/d
Grade 3 - 4	Discontinue G-CSF

#### 8.8 Dose Modifications for Non-Hematologic Toxicity

In the event of any other (except nausea and vomiting) Grade 3 or 4 non-hematologic toxicity not discussed above, **hold all protocol treatment and discuss** with one of the Study Coordinators listed in [Section 8.9](#).

#### 8.9 Dose Modification Contacts

For treatment or dose modification related questions, please contact any of the following Study Coordinators: Dr. Herbst at 203/785-6879 or roy.herbst@yale.edu, Dr. Kim at 980/442-3105 or edward.kim@carolinashealthcare.org or Dr. Semrad at 916/734-3771 or thomas.semrad@ucdmc.ucdavis.edu.

#### 8.10 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in [Section 16.0](#) of the protocol must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

## 9.0 STUDY CALENDAR

9.1 Study Calendar - ARM 1a - Chemotherapy plus Bevacizumab without Cetuximab

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Cont'd TX √ ≠			Off TX F/U Prior to Prog f ††	Off TX F/U After Prog f	
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W			
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
<b>PHYSICAL</b>																									
H&P	X				X β			X β			X β			X β			X β			X β				X	X
Wt & PS	X				X β			X β			X β			X β			X β			X β				X	X
Disease Assessment ††	X							X β						X β						X β				X	
Toxicity Notation					X			X			X			X			X			X				X	X
<b>LABORATORY</b>																									
CBC/Diff/Platelets £	X				X			X			X			X			X			X				X	X
Serum Creatinine □	X				X			X			X			X			X			X				X	X
Calc or Meas CrCL □	X				X			X			X			X			X							X	X
UPC (Urine Protein Creatinine) Ratio π	X				X						X						X							X	
Total Bilirubin §	X				X			X			X			X			X			X				X	X
SGOT or SGPT §	X				X			X			X			X			X			X				X	X
Alk Phos ∞	X				X			X			X			X			X			X				X	X
INR	X																								
Albumin ∞	X				X			X			X			X			X			X				X	X
LDH ∞	X				X			X			X			X			X			X				X	X
Serum Sodium, Calcium & Magnesium † ∞	X				X			X			X			X			X			X				X	X
<b>SPECIMEN/IMAGE SUBMISSION</b>																									
Plasma Submission *	X							X																X	X
Tissue Submission *	X																								
Image Submission &	X							X						X						X				X	

Calendar continued on next page. Click here for [footnotes](#).

9.1 (contd.)	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Cont'd TX √ ≠			Off TX F/U Prior to Prog f ¶	Off TX F/U After Prog f		
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W			
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
<b>SCANS</b>																									
CT or MRI for Disease Assessment ¶	X							X β						X β											X
Brain CT/MRI	X																								
Bone Scan Ω	X																								
EKG ¥	X																								
<b>TREATMENT Δ</b>																									
Carboplatin		X			X			X			X			X			X								
Paclitaxel		X			X			X			X			X			X								
Bevacizumab √ %		X			X			X			X			X			X						X √		

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in [Section 14.0](#).

- ∞ Results of these tests do not determine eligibility but are recommended prior to registration, during treatment and throughout follow-up in accordance with Good Medical Practice (see [Section 7.1](#)).
- † In the event of hypomagnesemia, more frequent monitoring and magnesium repletion should be instituted as per routine clinical practice.
- ¶ CT or MRI (the same method used at prestudy to meet the eligibility criteria in [Section 5.1b](#) must be repeated every 6 weeks until disease progression. After 9 months from registration, the frequency of this scan may be reduced to every 3 months until disease progression.
- ⊠ Calculated CrCl based on creatinine level obtained within 3 days prior to each dose is required to determine carboplatin dose.
- \* See [Section 15.0](#).
- & Submit scans to QARC as outlined in [Sections 15.4](#) and [Appendix 18.6](#).
- § SGOT or SGPT and bilirubin is required within 7 days prior to each dose of paclitaxel/carboplatin.
- Ω This test is required prestudy for Good Medical Practice only if clinically indicated. It is recommended to be performed during treatment if clinically indicated.
- £ CBC should be obtained more frequently if patient is on G-CSF, per [Section 8.6](#).
- √ After completion of Cycle 6 and if the patient has not met criteria outlined in [Section 7.8](#), bevacizumab will be continued until one of the criteria in [Section 7.8](#) is met. Patients who are bevacizumab inappropriate are removed from protocol treatment at this time.
- f After off treatment, patients should be followed by repeating indicated laboratory tests every 3 months for the first year, then every 6 months for up to 3 years from the date of registration.
- Δ See [Sections 7.2](#) and [7.3](#).
- % Bevacizumab will be given only if patient is determined to be bevacizumab-appropriate.
- π After beginning treatment, UPC ratio required with alternate cycles only for patients who are receiving bevacizumab.
- β To be performed within 7 days prior to starting cycle.
- ¥ This test is required prestudy for Good Medical Practice (see [Section 7.1](#) for guidance on timing and interpretation of these test results).
- ≠ During continued treatment, items marked under physical and laboratory should be performed at every subsequent bevacizumab treatment (every 3 weeks). Disease assessments and image submission are to take place every 6 weeks.

9.2 ARM 1b - Chemotherapy without Cetuximab

REQUIRED STUDIES	PRE STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Off TX F/U Prior to Prog f ¶	Off TX F/U After Prog f
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
<b>PHYSICAL</b>																					
H&P	X				X β			X β			X β			X β			X β			X	X
Wt & PS	X				X β			X β			X β			X β			X β			X	X
Disease Assessment ¶	X							X β						X β						X	
Toxicity Notation					X			X			X			X			X			X	X
<b>LABORATORY</b>																					
CBC/Diff/Platelets £	X				X			X			X			X			X			X	X
Serum Creatinine □	X				X			X			X			X			X			X	X
Calc or Meas CrCL □	X				X			X			X			X			X			X	X
Total Bilirubin §	X				X			X			X			X			X			X	X
SGOT or SGPT §	X				X			X			X			X			X			X	X
Alk Phos ∞	X				X			X			X			X			X			X	X
INR	X																				
Albumin ∞	X				X			X			X			X			X			X	X
LDH ∞	X				X			X			X			X			X			X	X
Serum Sodium, Calcium & Magnesium † ∞	X				X			X			X			X			X			X	X
<b>SPECIMEN/IMAGE SUBMISSION</b>																					
Plasma Submission *	X							X												X	X
Tissue Submission *	X																				
Image Submission &	X							X						X						X	

Calendar continued on next page. Click here for [footnotes](#)

9.2 (contd.)		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 <sup>√</sup>			Off TX F/U Prior to Prog <i>f</i> ¶	Off TX F/U After Prog <i>f</i>
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
<b>SCANS</b>																					
CT or MRI for Disease Assessment ¶	X							X <sup>β</sup>						X <sup>β</sup>						X	
Brain CT/MRI	X																				
Bone Scan Ω	X																				
EKG ¥	X																				
<b>TREATMENT Δ</b>																					
Carboplatin		X			X			X			X			X			X				
Paclitaxel		X			X			X			X			X			X				

Note: Forms are found on the protocol abstract page of the SWOG website ([www.swog.org](http://www.swog.org)). Forms submission guidelines are found in [Section 14.0](#).

- ∞ Results of these tests do not determine eligibility but are recommended prior to registration, during treatment and throughout follow-up in accordance with Good Medical Practice (see [Section 7.1](#)).
- † In the event of hypomagnesemia, more frequent monitoring and magnesium repletion should be instituted as per routine clinical practice.
- ¶ CT or MRI (the same method used at prestudy to meet the eligibility criteria in [Section 5.1b](#) must be repeated every 6 weeks until disease progression. After 9 months from registration, the frequency of this scan may be reduced to every 3 months until disease progression.
- ⊠ Calculated CrCl based on creatinine level obtained within 3 days prior to each dose is required to determine carboplatin dose.
- \* See [Section 15.0](#).
- & Submit scans to QARC as outlined in [Sections 15.4](#) and [Appendix 18.6](#).
- § SGOT or SGPT and bilirubin are required within 7 days prior to each dose of paclitaxel/carboplatin.
- Ω This test is required prestudy for Good Medical Practice only if clinically indicated. It is recommended to be performed during treatment if clinically indicated.
- £ CBC should be obtained more frequently if patient is on G-CSF, per [Section 8.6](#).
- f* After off treatment, patients should be followed by repeating indicated laboratory tests every 3 months for the first year, then every 6 months for up to 3 years from the date of registration.
- Δ See [Sections 7.2](#) and [7.3](#).
- β To be performed within 7 days prior to starting cycle.
- ¥ This test is required prestudy for Good Medical Practice (see [Section 7.1](#) for guidance on timing and interpretation of these test results).

9.3 ARM 2a - Chemotherapy plus Bevacizumab with Cetuximab

REQUIRED STUDIES	PRE STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Cont'd TX √ ≠			Off TX F/U Prior to Prog f	Off TX F/U After Prog f
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
<b>PHYSICAL</b>																								
H&P	X				X β			X β			X β			X β			X β			X β			X	X
Vital Signs Only \$		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Wt & PS	X				X β			X β			X β			X β			X β			X β			X	X
Disease Assessment ¶	X							X β						X β						X β			X	
Toxicity Notation §					X			X			X			X			X			X			X	X
<b>LABORATORY</b>																								
CBC/Diff/Platelets £	X				X			X			X			X			X			X			X	X
Serum Creatinine □	X				X			X			X			X			X			X			X	X
Calc or Meas CrCL ▯	X				X			X			X			X			X			X			X	X
UPC (Urine Protein Creatinine) Ratio π	X				X						X						X						X	
Total Bilirubin §	X				X			X			X			X			X			X			X	X
SGOT or SGPT §	X				X			X			X			X			X			X			X	X
Alk Phos ∞	X				X			X			X			X			X			X			X	X
INR	X																							
Albumin ∞	X				X			X			X			X			X			X			X	X
LDH ∞	X				X			X			X			X			X			X			X	X
Serum Sodium, Calcium & Magnesium † ∞	X				X			X			X			X			X			X			X	X
<b>SPECIMEN/IMAGE SUBMISSION</b>																								
Plasma Submission *	X							X															X	X
Tissue Submission *	X																							
Image Submission &	X							X						X						X			X	

Calendar continued on next page. Click here for [footnotes](#).

9.3 (contd.)		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Cont'd TX √ ≠			Off TX F/U Prior to Prog f ¶		Off TX F/U After Prog f		
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21					
<b>SCANS</b>																											
CT or MRI for Disease Assessment ¶	X							X	β					X	β					X	β						X
Brain CT/MRI	X																										
Bone Scan Ω	X																										
EKG ¥	X																										
<b>TREATMENT Δ</b>																											
Carboplatin		X			X			X			X			X			X										
Paclitaxel		X			X			X			X			X			X										
Cetuximab √		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	√	X	X	X	X		
Bevacizumab √ %		X			X			X			X			X			X			X	√						

**NOTE:** Forms are found on the protocol abstract page of the SWOG website ([www.swog.org](http://www.swog.org)). Forms submission guidelines are found in [Section 14.0](#).

Click here for [footnotes](#).

### Calendar 9.3 Footnotes

- ∞ Results of these tests do not determine eligibility but are recommended prior to registration, during treatment and throughout follow-up in accordance with Good Medical Practice (see [Section 7.1](#)).
- † In the event of hypomagnesemia, more frequent monitoring and magnesium repletion should be instituted as per routine clinical practice.
- ¶ CT or MRI (the same method used at prestudy to meet the eligibility criteria in [Section 5.1b](#) must be repeated every 6 weeks until disease progression. After 9 months from registration, the frequency of this scan may be reduced to every 3 months until disease progression.
- α Calculated CrCl based on creatinine level obtained within 3 days prior to each dose is required to determine carboplatin dose.
- \* See [Section 15.0](#).
- & Submit scans to QARC as outlined in [Sections 15.4](#) and [Appendix 18.6](#).
- § SGOT or SGPT and bilirubin are required within 7 days prior to each dose of paclitaxel/carboplatin.
- Ω This test is required prestudy for Good Medical Practice only if clinically indicated. It is recommended to be performed during treatment if clinically indicated.
- £ CBC should be obtained more frequently if patient is on G-CSF, per [Section 8.6](#).
- √ After completion of Cycle 6 and if the patient has not met criteria outlined in [Section 7.8](#), bevacizumab and cetuximab will be continued until one of the criteria in [Section 7.8](#) is met.
- f After off treatment, patients should be followed by repeating indicated laboratory tests every 3 months for the first year, then every 6 months for up to 3 years from the date of registration.
- Δ See [Sections 7.2](#) and [7.3](#).
- \$ Patients will have vital signs taken (before, during and after treatment) and will be evaluated for toxicities at each visit during cetuximab treatment (see [Section 3.3c](#) – “Administration of Cetuximab”).
- % Bevacizumab will be given only if patient is determined to be bevacizumab-appropriate.
- π After beginning treatment, UPC ratio required with alternate cycles only for patients who are receiving bevacizumab.
- β To be performed within 7 days prior to starting cycle.
- ¥ This test is required prestudy for Good Medical Practice (see [Section 7.1](#) for guidance on timing and interpretation of these test results).
- ≠ During continued treatment, items marked under physical and laboratory should be performed at every subsequent bevacizumab treatment (every 3 weeks). Vital signs and toxicity notation should still be continued on a weekly basis according to the footnote labeled “\$”. Disease assessments and image submission are to take place every 6 weeks.

9.4 ARM 2b - Chemotherapy with Cetuximab

REQUIRED STUDIES	PRE STUDY	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Continued Tx √			Off Tx F/U Prior To Prog <i>f</i>	Off Tx F/U After Prog <i>f</i>
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
<b>PHYSICAL</b>																								
History and Physical	X				Xβ			Xβ			X	X												
Vital Signs Only §		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and Performance Status	X				Xβ			Xβ			X	X												
Disease Assessment ¶	X							X						X					X				X	
Toxicity Notation §		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>LABORATORY</b>																								
CBC/Differential/ Platelets £	X				X			X			X			X			X			X			X	X
Serum Creatinine ☐	X				X			X			X			X			X			X			X	X
Calc or Meas CrCL ☐	X				X			X			X			X			X			X			X	X
Total Bilirubin §	X				X			X			X			X			X			X			X	X
SGOT or SGPT §	X				X			X			X			X			X			X			X	X
Alkaline Phosphatase ∞	X				X			X			X			X			X			X			X	X
INR	X																							
Albumin ∞	X				X			X			X			X			X			X			X	X
LDH ∞	X				X			X			X			X			X			X			X	X
Serum Sodium , Calcium and Magnesium †∞	X				X			X			X			X			X			X			X	X

Calendar continued on next page. Click here for [footnotes](#).

9.4 (contd.)

REQUIRED STUDIES	PRE	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 √			Continued Tx √			Off Tx F/U Prior To Prog <i>f</i>	Off Tx F/U After Prog <i>f</i>
		W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
STUDY		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
<b>SPECIMEN/ IMAGE SUBMISSION</b>																								
Plasma Submission *	X							X															X	X
Tissue Submission *	X																							
Image Submission &	X							X						X						X			X	
<b>SCANS</b>																								
CT or MRI for disease assessment ¶	X							Xβ						Xβ						Xβ			X	
Brain CT/MRI	X																							
Bone Scan Ω	X																							
EKG ¥	X																							
<b>TREATMENT Δ</b>																								
Carboplatin		X			X			X			X			X			X							
Paclitaxel		X			X			X			X			X			X							
Cetuximab √		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X√	X	X		

**NOTE:** All forms for this study can be found on the protocol abstract page of the SWOG website ([www.swog.org](http://www.swog.org)). Form Submission Guidelines can be found in [Section 14.0](#).

Click here for [footnotes](#).

**Calendar 9.4 footnotes.**

- ∞ Results of these tests do not determine eligibility but are recommended prior to registration, during treatment and throughout follow-up in accordance with Good Medical Practice ([see Section 7.1](#)).
- † In the event of hypomagnesemia, more frequent monitoring and magnesium repletion should be instituted as per routine clinical practice.
- ‡ CT or MRI (the same method used at prestudy to meet the eligibility criteria in [Section 5.1c](#)) must be repeated every 6 weeks until disease progression. After 9 months from registration, the frequency of this scan may be reduced to every 3 months until disease progression.
- ⌘ Calculated CrCL based on creatinine level obtained within 3 days prior to each dose is required to determine carboplatin dose.
- \* See [Section 15.0](#).
- & Submit scans to QARC as outlined [in Sections 15.4](#) and [Appendix 18.6](#).
- § SGOT or SGPT and bilirubin is required within 7 days prior to each dose of paclitaxel/carboplatin.
- Ω This test is required prestudy for Good Medical Practice only if clinically indicated. It is recommended to be performed during treatment if clinically indicated.
- £ CBC should be obtained more frequently if patient is on G-CSF, per [Section 8.6](#).
- √ After completion of Cycle 6 and if the patient has not met criteria outlined in [Section 7.8](#), cetuximab will be continued until one of the criteria in [Section 7.8](#) is met.
- f After off treatment, patients should be followed by repeating indicated laboratory tests every 3 months for the first year, then every 6 months for up to 3 years from the date of registration.
- Δ See [Sections 7.2](#) and [7.3](#).
- \$ Patients will have vital signs taken (before, during and after treatment) and will be evaluated for toxicities at each visit during cetuximab treatment (see [Section 3.3c](#) - "Administration of Cetuximab").
- Ⓑ To be performed within 7 days prior to starting cycle.
- ¥ This test is required prestudy for Good Medical Practice (see [Section 7.1](#) for guidance on timing and interpretation of these test results).

## 10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

### 10.1 Measurability of Lesions

- a. **Measurable disease:** Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Conventional CT and MRI 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.

- b. **Non-measurable disease:** All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

### 10.2 Objective Status

**Objective status at each evaluation:** Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

- a. **Complete Response (CR):** Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.
- b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.
- c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.
- d. **Progression:** One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see [Section 10.2e](#)).

- e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.
- f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.
- g. Objective status notes:
  - 1. Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
  - 2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
  - 3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
  - 4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
  - 5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.
  - 6. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.
  - 7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

### 10.3 Best Response

This is calculated from the sequence of objective statuses.

- a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.
- b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

- c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.
- d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.
- e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.
- f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.
- g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.
- h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

#### 10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

<b><u>POINT</u></b>	<b><u>DESCRIPTION</u></b>
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

#### 10.5 Progression-Free Survival (Central-Review Based)

From date of randomization (which is the date of registration) to date of first documentation of progression based on Central Radiological Review of the appropriate CT or MRI scans, or symptomatic deterioration (as defined in [Section 10.2.e](#)), or development of new lesions or progression (as defined in [Section 10.2d](#)) documented by methods other than on CT or MRI, or death due to any cause. Patients who have a local assessment of progression based on CT/MRI imaging, but for whom central review does not concur, will be censored at the last imaging date, unless documentation by subsequent reviewed CT/MRI scans, methods other than CR or MRI, or symptomatic deterioration provides evidence of progression. Patients last known to be alive and progression-free are censored at the date of last contact.

## 10.6 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined in [Sections 10.2d](#) and [10.2e](#)), or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

## 10.7 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

# 11.0 STATISTICAL CONSIDERATIONS

## 11.1 Primary Endpoint

**Entire study population:** The primary objective in the entire study population is to compare overall survival (OS) in advanced NSCLC patients treated with cetuximab chemotherapy plus bevacizumab (if appropriate) versus chemotherapy and bevacizumab (if appropriate). The addition of cetuximab will be judged to be superior if the true increase in median OS is 20%.

**EGFR FISH-positive cohort:** The primary objective for this cohort is to compare progression-free survival (PFS) by institutional review in EGFR FISH-positive patients with advanced NSCLC treated with cetuximab-chemotherapy plus bevacizumab (if appropriate) versus chemotherapy and bevacizumab (if appropriate). The addition of cetuximab will be judged to be superior if the true increase in median PFS is 33%.

## 11.2 Secondary Endpoints

Secondary objectives include the comparison of OS and PFS by centralized review in the EGFR FISH-positive cohort, PFS (by centralized review and institutional review) in the entire cohort, and response and toxicity in both study populations (entire cohort and EGFR FISH-positive cohort) treated with cetuximab and chemotherapy and bevacizumab (if appropriate) versus chemotherapy and bevacizumab (if appropriate), as well as to compare other purported EGFR-related biomarkers to EGFR IHC and EGFR FISH and to patient outcomes. K-ras mutational testing will be performed and correlated to response and outcome. Analysis for EGFR FISH and KRAS mutational status will be evaluated at each interim analysis.

## 11.3 H-Score

Based on the FLEX trial, we assume that among patients with an IHC result, 26% will be determined to have a score > 200. Assuming 95% of patients with an EGFR FISH result will have sufficient tissue for IHC, then 20% of patients will be classified as H-score positive (>200), 1174 patients will have an IHC result, and 306 patients will be available for the analysis of the efficacy of cetuximab (as measured by OS and PFS) among patients with an IHC >200. Further, based on the FLEX trial we assume that IHC score is not prognostic for either outcome. It follows that this design has 82% power to detect a 40% improvement in median PFS using a 1-sided 0.025 level stratified log-rank test. This design also has 80% power to detect a 43% improvement in median OS using a 1-sided 0.025 level stratified log-rank test. If approximately 35% of patients positive for EGFR FISH also have an H-score > 200 (or equivalently 67% of H-score positive are EGFR FISH positive), then the expected numbers of patients in each biomarker category are as below:

	No FISH result	EGFR FISH -	EGFR FISH +	Total
No IHC result	310	31	31	372 (24%)
IHC H-score < 200	--	486	382	868 (56%)
IHC H-score > 200	--	101	205	306 (20%)
Total	310 (20%)	618 (40%)	618 (40%)	1546

#### 11.4 Sample Size With Power Justification

This design employs co-primary objectives with OS within the entire study population and PFS by institutional review as the primary outcome in the EGFR FISH-positive group. Interim testing for efficacy is based on both PFS by institutional review and OS in the EGFR FISH-positive group. As the hypothesis within the EGFR FISH-positive group is partially nested (since PFS and OS are correlated) within the entire study hypothesis, (1-sided) testing of the EGFR FISH-positive hypothesis at the 0.02 level and the entire study hypothesis at the 0.015 level results in an overall level of 0.025 (determined via simulation).

Based on published and unpublished data (Fred Hirsch, personal communication), we expect at least 81% of patients will have adequate specimen for testing. The assay failure rate is estimated to be approximately 2% (98% success rate). Finally we assume that the proportion among those with a EGFR FISH assay result determined positive is 50%. Therefore, the assumed rate of EGFR FISH-positive patients among all patients enrolled is 40% (= 81% \* 98% \* 50%).

We assume for 50% of patients it will be inappropriate to receive bevacizumab, and that the median PFS in this group is less than that in the bevacizumab-appropriate group. The null median PFS is assumed to be 6 months for the bevacizumab-appropriate group, based on data from **E4599**. The null median PFS is assumed to be 4 months, for the bevacizumab-inappropriate group based on data from **S0003**.

**EGFR FISH-positive cohort:** A design with 92% power, 4 years accrual, 1 year of follow-up, requires 618 patients to detect a 33% improvement in median PFS, using a 0.02 1-sided logrank test. This would require ~1,546 patients to be enrolled on study.

**Entire study population:** Assuming 50% of patients are bevacizumab inappropriate, a median OS of 10 months in the bevacizumab-inappropriate stratum, and median OS of 12 months in the bevacizumab-appropriate stratum this design has 86% power to detect a 20% improvement in the entire cohort of 1,546 patients in median OS, using a 0.015 1-sided level stratified logrank test.

**In summary:** Entire study: 1,546 patients, EGFR FISH-positive: 618.

#### 11.5 Analysis Plan Including Plans for Formal Interim Analysis

Primary analyses will be performed on an intent-to-treat basis. A (stratified) log-rank test at the 0.02 level will be used to test the primary hypothesis in the EGFR FISH-positive cohort and at the 0.015 level in the entire study to achieve an overall type I error rate of 0.025.

A formal interim analysis will be done after 30% of the expected progression events in the control arm (87 progression events) in the EGFR FISH-positive cohort, approximately 21 months after the study opens, by which time about 266 EGFR FISH-positive patients and overall 665 patients will have entered into the study. Evidence suggesting early termination of the trial for superiority will only be formally assessed in the EGFR FISH

positive cohort and will be based on PFS and OS. Data on PFS and OS in the entire study population will be provided to the SWOG Data and Safety Monitoring Committee (DSMC). As such, in the EGFR FISH-positive cohort, the conclusion that the experimental arm is better than the control arm would be if the hypothesis of no difference in PFS were rejected at the one-sided 0.002 level and OS were rejected at the 0.004 level, or OS alone were rejected at 0.002 level. The level for OS is adjusted upward as the primary hypothesis within the FISH-positive cohort is PFS, but it is desired to establish a benefit in OS should the trial stop early for efficacy. The following table summarizes the conditions that are to be met for early stopping for superiority.

**Table 1** Conditions for stopping for superiority

<u>Reject null hypothesis:</u>	<u>PFS</u>		<u>OS</u>
EGFR FISH-positive cohort	(P< 0.002	and	P< 0.004)
		or	P< 0.002
Entire study cohort	N/A		N/A

If the conditions in Table 1 are met then the recommendation will be to stop the EGFR FISH-positive group for efficacy. If at this time futility is not reached in the overall group and the EGFR FISH-positive group has been stopped, then the SWOG DSMC will consider all the evidence to determine if the study should continue in the EGFR FISH non-positive group.

Evidence suggesting early termination of the trial for futility will be formally assessed in the EGFR FISH-positive cohort and the entire study population. This assessment will be based on PFS in the EGFR FISH-positive cohort and based on PFS and OS in the entire study population. For futility testing, the alternative hypothesis of at least 33% improvement in PFS for the experimental arm in the EGFR FISH-positive cohort will be tested at one-sided level 0.002, using an extension of the logrank test that allows for testing a relative risk not equal to 1. Additionally, the alternative hypothesis of at least 20% improvement in PFS and OS for the experimental arm in the entire study population will be tested at one-sided level 0.0015, also using the test that allows for testing a relative risk not equal to 1. Evidence suggesting early termination of the trial for futility will be that the alternative hypotheses are rejected for PFS in the EGFR FISH-positive cohort and PFS and OS in the entire study population. If the alternative hypotheses are rejected as specified above (PFS in EGFR FISH-positive, PFS and OS in the entire study), this will be considered evidence suggesting early termination of the trial for futility. The following table summarizing the conditions that are to be met for early stopping for futility.

**Table 2** Conditions for stopping for futility

<u>Reject alternative hypothesis:</u>	<u>PFS</u>		<u>OS</u>
EGFR FISH-positive cohort	P < 0.002	and	N/A
Entire study cohort	(P < 0.0015	or	P < 0.0015)

Evidence suggesting early termination of the study in the non-EGFR FISH positive cohort will be assessed in the entire study population and the non-positive cohort and will be based on PFS and OS. For futility testing, the alternative hypothesis of at least 20% improvement in PFS and OS for the experimental arm in the entire study population will be tested at one-sided level 0.0025, using a test that allows for testing a relative risk not equal to 1. Also, for futility testing, the alternative hypothesis of at least 10% improvement in PFS and OS for the experimental arm in the EGFR FISH non-positive will be tested at one-sided level 0.0025, using a test that allows for testing a relative risk not equal to 1. Evidence suggesting early termination of the trial for futility will be that the alternative hypothesis is rejected for either PFS or OS in the EGFR FISH-positive cohort or the entire study population.

**Table 3** Conditions for stopping EGFR FISH non-positive cohort for futility

<u>Reject alternative hypothesis:</u>	<u>PFS</u>		<u>OS</u>
EGFR FISH non-positive cohort	P < 0.0025	or	P < 0.0025
Entire study cohort	P < 0.025	or	P < 0.0025

The actual decision to terminate accrual early will be made by the DSMC, and will consider K-ras mutations, response, toxicities and other factors in addition to PFS and OS.

A second interim analysis is planned when 2/3 of the expected events in the control arm have occurred, which will be at approximately 39 months after the study opens, with roughly 199 events and an expected 500 accrued in the EGFR FISH-positive cohort and 1,250 overall. Testing of the null and alternative hypotheses will proceed as described for the first interim analysis. A third interim analysis is planned when 85% of the expected events in the control arm have occurred, which will be approximately 48 months after the study opens, with roughly 252 events and accrual to the study completed. Testing of the null and the alternative hypotheses will proceed as described for the first interim analysis. Should a study cohort be stopped at a previous interim analysis, the recommendation will be based on the rules associated with the current study population. If the decision is to continue the study, the final analysis will take place when at least 297 events in EGFR FISH-positive cohort have occurred, approximately 60 months after the study opens. The final analysis in the EGFR FISH-positive cohort will be at level 0.014 (one-sided test) to allow for the effects of interim testing. A modified Haybittle-Peto approach is used to determine alpha spending. The following table summarizes the expected number

**Table 4** Description of planned interim and final analyses based on events in control arm

Time (mo)	EGFR FISH-positive		Overall Population		Percent of:		
	# Prog	# Deaths	# Prog	# Deaths	Prog	Deaths	Accrual
21	89	59	223	148	30%	23%	43%
39	199	153	498	383	67%	59%	81%
48	252	207	630	518	85%	80%	100%
60	297	259	43	648	100%	100%	100%

In addition to the EGFR FISH assay, K-ras will be assessed on the patient specimens for each interim analysis and as a planned subgroup analysis upon study completion. Planned analyses to assess the safety of cetuximab in patients with K-ras mutations are a comparison of OS and PFS by treatment arm using a stratified log-rank test. Analyses following the specifications for the entire study cohort will also be performed within the bevacizumab and non-bevacizumab treated patients to assess safety and efficacy/futility at each interim analysis and as a planned subgroup analysis upon study completion. These analyses will be provided to the SWOG DSMC.

At each analysis, the design assumptions regarding proportions of EGFR FISH-positive patients, numbers of adequate specimens, and assay performance will be evaluated. The number of enrolled patients may be adjusted if the proportion of enrolled patients determined to be EGFR FISH-positive is different than expected to accrue 618 EGFR FISH-positive patients.

Secondary analyses will also be done regarding OS in the EGFR FISH-positive cohort and PFS in the entire study (using a stratified log-rank test), and response and toxicity (using stratified chi-square tests). This design has 87% power to detect a 33% improvement in OS in the EGFR FISH-positive group using a 1-sided 0.02 level log-rank test. Additionally, this design has 91% power to detect a 20% improvement in PFS in the entire study population using a 1-sided 0.015 level log-rank test. With 309 patients per arm in the EGFR FISH-positive group, response and toxicity rates can be estimated to within at worst  $\pm 6\%$  (95% confidence interval). With 773 patients per arm in the entire study, response and toxicity rates can be estimated to within at worst  $\pm 4\%$  (95% confidence interval).

The predictive effect of EGFR FISH will be assessed by testing an interaction between EGFR FISH status and treatment in the respective regression model among the 1,236 patients with a FISH result (80% of 1,546). Assuming EGFR FISH is not prognostic, this design has 58% power to detect a difference in hazard ratios for PFS (1.1 versus 1.33) using a 1-sided 0.05 level log-rank test. Analyses will also be performed within the stratification factor grouping to assess treatment effects within each group. Supportive analyses of the effect of baseline characteristics on survival and progression free survival will be performed using Cox proportional hazards regression modeling. Similarly, the effect of baseline characteristics on response rate will be explored with logistic regression analysis. In addition to the stratification factors, other clinical covariates will include (but may not be limited to) age, gender, race and prior weight loss.

#### 11.6 Amendment to design

**S0819** was placed in temporary closure to further accrual on June 1, 2014. As of this date, 400 eligible EGFR FISH positive patients had been accrued to the study. Following review of the pre-specified second interim analysis, further accrual to the EGFR FISH non-positive cohort was terminated upon the recommendation of the DSMC. Prior to this analysis and independent of the study data, the study team had planned to modify the

study design with the EGFR FISH positive cohort due to a lower than anticipated percentage of patients defined to be EGFR FISH positive and lower than anticipated total accrual rate. The study design within the EGFR FISH positive cohort has been modified to a design with 80% power to detect a 33% improvement in median PFS. As result of the closure of the EGFR FISH non-positive cohort, the hypothesis within the overall population will not be tested and no type I error will be spent on that hypothesis. An additional specification is to change the overall type I error to 0.025 from 0.02 in the EGFR FISH positive cohort. The final level of testing will be performed at the 0.021 to account for the effects of interim testing (a change from 0.014). Testing will still be performed using a 1-sided log-rank test. Given the modified design assumptions, 386 progression events are needed to detect a 33% improvement in median PFS with 80% power at the 1-sided 0.025 level. Due to logistical considerations, the study team determined it would be preferable to extend follow-up among the EGFR FISH positive patients instead of re-opening the study to further accrual in this population. The third interim analysis at 85% information has been dropped, as well. In order to achieve 386 events, the follow-up duration has been extended from 1 year to 2 years. The final analysis will occur upon the observation of 386 progression events in the EGFR FISH positive cohort or by June 2016, whichever comes first. All other analyses will proceed as previously specified. The following table summarizes the changes to the design.

	Original Design	Modified Design
Alternative hypothesis (HR)	1.33	Same
Power	92%	80%
Overall Type I error	0.02	0.025
Number of interim analyses	3	2
Final level of testing	0.014	0.021
Follow-up duration	12 months	24 months
PFS events at analysis	588	386
Sample Size (eligible)	618	400

#### 11.7 Accrual Information

Accrual Rate: 35-40 pts/month. **S0003** accrued approximately 240 patients/year and **SWOG-9509** accrued approximately 300 patients per year in SWOG alone. This study will be available on the CTSU menu. With intergroup participation we anticipate accrual of approximately 400 patients per year.

## 11.8 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG. Group members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

## 12.0 DISCIPLINE REVIEW

This section does not apply to this study.

## 13.0 REGISTRATION GUIDELINES

### 13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than seven working days prior to planned start of treatment).

### 13.2 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

- a. Institution CTEP ID
- b. Protocol Number
- c. Registration Step
- d. Treating Investigator
- e. Cooperative Group Credit
- f. Credit Investigator
- g. Patient Initials
- h. Patient's Date of Birth
- i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- j. Country of Residence

- k. ZIP Code
- l. Gender (select one):
  - Female Gender
  - Male Gender
- m. Ethnicity (select one):
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Unknown
- n. Method of Payment (select one):
  - Private Insurance
  - Medicare
  - Medicare and Private Insurance
  - Medicaid
  - Medicaid and Medicare
  - Military or Veterans Sponsored NOS
  - Military Sponsored (Including Champus & Tricare)
  - Veterans Sponsored
  - Self Pay (No Insurance)
  - No Means of Payment (No Insurance)
  - Other
  - Unknown
- o. Race (select all that apply):
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or other Pacific Islander
  - White
  - Unknown

### 13.3 Registration Procedures

- a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed from the CTSU members' web site OPEN tab, or from the OPEN Patient Registration link on the SWOG CRA Workbench.
- b. Prior to accessing OPEN site staff should verify the following:
  - All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to [Section 5.0](#) to verify eligibility.
  - All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- c. Access requirements for OPEN:
  - Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
  - To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.
2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

- d. Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctscontact@westat.com](mailto:ctscontact@westat.com).

#### 13.4 Registration Exceptions

For either method of registration, exceptions to SWOG registration policies will not be permitted.

- a. Patients must meet all eligibility requirements.
- b. Institutions must be identified as approved for registration.
- c. Registrations may not be cancelled.
- d. Late registrations (after initiation of treatment) will not be accepted.

### 14.0 DATA SUBMISSION SCHEDULE

#### 14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

#### 14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website ([www.swog.org](http://www.swog.org)) and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see [Section 14.3a](#) for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

### 14.3 Data Submission Procedures

- a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (<http://swog.org>) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the [swog.org](http://swog.org) Members logon page). For other difficulties with the CRA Workbench, please email [technicalquestion@crab.org](mailto:technicalquestion@crab.org).

- b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

### 14.4 Data Submission Overview and Timepoints

- a. WITHIN 7 DAYS OF REGISTRATION:

Submit a copy of the following:

**S0819** Prestudy Form

Baseline Tumor Assessment Form

Pathology Report

SWOG **S0819** Pathology Review Form ([Appendix 18.8](#))

Radiology reports from all scans performed to assess disease at baseline

Operative reports from all surgical or biopsy procedures performed within 28 days prior to registration.

- b. WITHIN 14 DAYS AFTER REGISTRATION:

Submit prestudy specimens as outlined in [Section 15.1a](#)

Submit images for central review as outlined in [Appendix 18.6](#).

- c. WITHIN 7 DAYS AFTER EACH CYCLE (1 CYCLE = 21 DAYS) OF TREATMENT:  
Submit a copy of the following:  
**S0819** Treatment Form  
**S0819** Adverse Event Form.
- d. AT WEEK 7:  
Submit blood specimens as outlined in [Section 15.1a](#).
- e. AFTER EVERY TUMOR ASSESSMENT UNTIL DISEASE PROGRESSION (see [Section 9.0](#) for Disease Assessment Schedule):  
Submit a copy of the following:  
Follow-Up Tumor Assessment Form  
Radiology reports from all scans performed to assess disease  
Submit images for central review as outlined in [Appendix 18.6](#).
- f. WITHIN 14 DAYS OF PROGRESSION OR RELAPSE:  
Submit a copy of the following:  
Lung Carcinoma First Site(s) of Progression or Relapse Form  
Follow-Up Tumor Assessment Form  
If the patient is off protocol treatment, submit the Advanced NSCLC Follow Up Form  
Submit images for central review as outlined in [Appendix 18.6](#).
- g. WITHIN 14 DAYS OF DISCONTINUATION OF ALL PROTOCOL TREATMENT:  
Submit a copy of the following:  
Off Treatment Notice documenting the date of completion of protocol treatment, progression/relapse/other reason, and summarizing inclusive dates of treatment and patient status  
Final **S0819** Treatment Form  
Final **S0819** Adverse Event Form  
Submit plasma and buffy coat as outlined in [Section 15.1a](#).
- h. WITHIN 14 DAYS AFTER DIAGNOSIS OF SECOND MALIGNANCY:  
Submit the Advanced NSCLC Follow Up Form.

- i. ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 6 MONTHS FOR UP TO 3 YEARS FROM THE DATE OF REGISTRATION:

Submit the Advanced NSCLC Follow Up Form.

- j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death. If the patient was off protocol treatment at the time of death, submit a Advanced NSCLC Follow Up Form.

## 15.0 SPECIAL INSTRUCTIONS

### 15.1 Required Tissue Specimens for EGFR FISH and KRAS

Specimens for EGFR FISH and KRAS mutation analysis (submitted to the University of Colorado) (Required):

- a. Specimens must be submitted at the timepoints listed below. Collection instructions are outlined in [Section 15.1c](#) and submission instructions are outlined in [Section 15.1e](#).

- b. Specimens must be submitted at the following times (see [Section\(s\) 9.1 – 9.4](#)):

1. Paraffin-embedded tissue/Prestudy

- c. Specimen Collection Instructions

Submit 1-2 paraffin-embedded tissue blocks containing formalin fixed tumor or needle aspirate slides from time of diagnosis (or subsequent, but prior to therapy) must be submitted for evaluation of expression of relevant molecular targets. Paraffin blocks may be processed according to standard institutional protocols. If blocks are unavailable, 10-12 unstained slides are acceptable alternatives. Cytology (i.e. fine-needle aspirations) can be accepted only if they are paraffin embedded as cell blocks. Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. The local pathologist must review and sign off on the **SWOG S0819 Pathology Review Form** ([Appendix 18.8](#)) noting that there are at least 100 tumor cells present in the sample. The number of cells present in the sample must be entered into the Specimen Tracking System along with copies of the **SWOG S0819 Pathology Review Form** and the pathology report when the specimen is submitted to the SWOG Solid Tumor Repository. Please also fax the **SWOG S0819 Pathology Review Form** to the Data Operations Center at 800/892-4007 or 206/342-1680 locally. These samples must be submitted for expression of relevant integral molecular targets ([see Section 15.3](#)).

- d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. Shipping Samples

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (<http://swog.org>) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at <https://gill:crab.org/SpecTrack/>.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to [technicalquestion@crab.org](mailto:technicalquestion@crab.org). For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (<http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf>); or contact the Data Operations Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of paraffin-embedded tissue for EGFR FISH and KRAS mutation analysis is identified as follows:

Lab #78: UCD Biorepository Core Facility  
Department of Pathology  
RC-1 North, Room P18-5404M  
12801 East 17th Avenue  
Aurora, CO 80045

Contact: Adrie van Bokhoven  
Phone: 303/724-3908  
E-mail: [Adrie.vanBokhoven@ucdenver.edu](mailto:Adrie.vanBokhoven@ucdenver.edu)

f. The Federal guidelines for shipment are as follows:

1. The specimen must be wrapped in an absorbable material;
2. The specimen must then be placed in an AIRTIGHT container resealable bag);
3. Pack the resealable bag and specimen in a Styrofoam container;

4. Pack the styrofoam shipping container in a cardboard box.
5. The cardboard box must be marked as "BIOHAZARD."

#### 15.2 Required Plasma and Buffy Coat for Translational Medicine and Optional Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (Required):

- a. Specimens must be collected at the following times and submitted (see [Section\(s\) 9.1 - 9.4](#)):
  1. Draw 10 ml of plasma and buffy coat specimens into two 5 – 10 cc purple top (EDTA) tubes at the following timepoints:
    - a. Prior to treatment (prestudy)
    - b. Week 7
    - c. At time of removal from protocol treatment. It is important that a blood specimen also be obtained from any patient when he/she is removed from protocol treatment or has disease progression. Blood should be processed as soon as possible after venipuncture, preferably within two hours. Samples not processed immediately after blood draw should be refrigerated at 4°C until processing. The **tubes** will be immediately centrifuged at approximately 1,200 rpm for 10 minutes. Buffy coat cells will be removed and placed in labeled cryotubes. Plasma will be separately removed and placed in 4 (2 mL) labeled cryotubes. All tubes are then to be frozen. Store frozen at -80°C until shipped to the SWOG Specimen Repository on **dry ice** as detailed on the specimen submission webpage (see [Section 15.2b](#)). These samples must be submitted for expression of relevant integral molecular targets (see [Section 15.3](#)).
- b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>), or via the link on the **S0819** protocol abstract page on the SWOG website ([www.swog.org](http://www.swog.org)).
- c. Specimen collection kits may be ordered by calling the SWOG Specimen Repository at 614/722-2865.

#### 15.3 Integral Translational Medicine Studies

The study includes embedded integral translational medicine studies (e.g., tests that must be performed in order to conduct the trial): EGFR FISH and KRAS mutation analysis. Thus, both tissue (EGFR FISH) and blood specimens (KRAS mutations) are mandatory for this study in order to perform the integral correlative studies.

**EGFR FISH:** Among enrolled patients, EGFR FISH will be performed on paraffin embedded material and by using the classification system developed by SWOG investigators, in which the results of the EGFR gene copy number will be reported as either EGFR FISH-positive, which includes patients with a tumor having high polysomy ( $\geq 4$  copies of the gene in  $\geq 40\%$  of the cells) or gene amplification

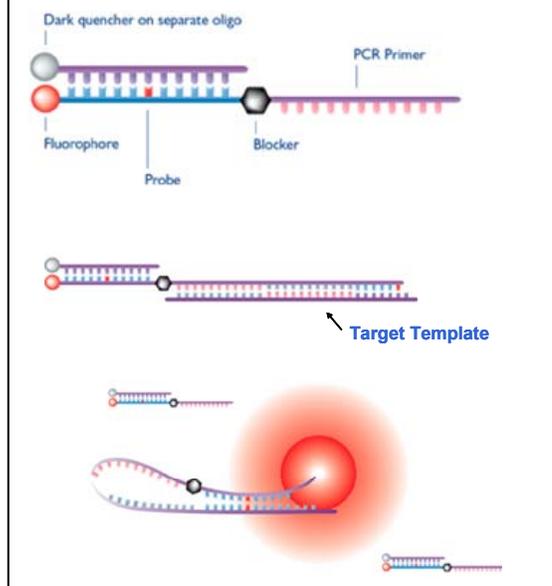
(gene/chromosome ratio > 2, or presence of gene clusters or  $\geq 15$  gene copies in > 10% of the cells) or EGFR FISH-negative, which includes all other patients. This classification has been validated in several previous SWOG studies as well as in several prospective clinical trials. ([8-11](#), [25](#))

The EGFR FISH analysis in this study will be performed in the Dept of Pathology, University of Colorado under the direction of Dr. Marileila Varella-Garcia (CLIA certified laboratorium).

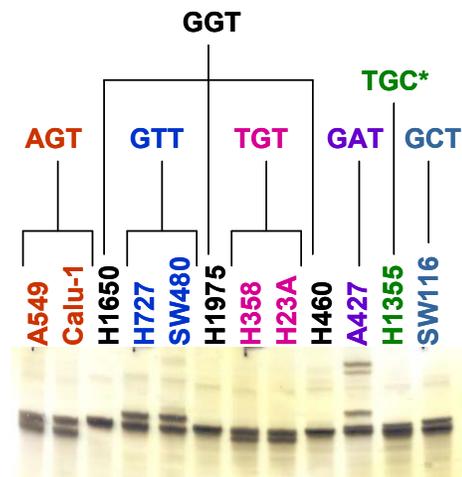
**KRAS mutation analysis:** Retrospective studies, including those by SWOG lung investigators, have found an association between KRAS mutation (codon 12/13) and resistance to EGFR TKIs. Few KRAS data are available for cetuximab in NSCLC, but an association with resistance has been demonstrated in colorectal cancer. KRAS mutations occur in about 30% of lung adenocarcinomas and in 10-15% of non-adenocarcinomas, all together in about 20% of unselected NSCLC patients. We intend to analyze tumor tissue and plasma for KRAS mutation analysis in all patients treated on the **S0819** clinical trial in real time and to incorporate this information into interim analyses, and well as to correlate results with outcomes and with the results of other biomarkers. The KRAS mutation analysis will be performed at UC Davis by Dr. Philip Mack using the DxS Scorpion method as the principle method of analysis and automated SSCP augmented by cold PCR as additional validation. For patients where tissue is not available, or is insufficient for analysis, we will analyze DNA extracted from plasma. These methods are described in the following paragraph.

Allele-specific real-time PCR using scorpion primer and the Amplification Refractory Mutations System (Scorpions-ARMS) will be used to detect the presence of KRAS mutations. ([26-32](#)) Scorpion primers (produced by DxS LTD, Manchester, UK) are multifunctional molecules composed of a PCR primer, a fluorophore and a quencher ([see Figure 1](#)). In the presence of its target sequence (in this case, a WT or mutant KRAS amplicon with a codon 12 or 13 base substitution), the scorpion primer undergoes an internal conformation rearrangement that releases the fluorophore from the quencher, resulting in a detectable light output. Scorpion-ARMS primers recognize the following KRAS point mutations: for codon 12, GGT→GCT (Gly→Ala), GGT→GAT (Gly→Asp), GGT→CGT (Gly→Arg), GGT→TGT (Gly→Cys), GGT→AGT (Gly→Ser), GGT→GTT (Gly→Val), for codon 13, GGC→GAC (Gly→Asp). Sensitivity for Scorpions-ARMS, depending upon the quality/quantity of the available source material (tissue or plasma) approaches 1% mutation detection in a wild-type background. A secondary method, single-stranded conformation polymorphism (SSCP) using cold-PCR for mutation enrichment will be used for validation. Cold PCR is a recently described method for mutation enrichment exploiting differential melting temperatures in heterozygous. ([33,34](#)) Specimens are run on a GenePhor electrophoresis (GE) unit with automated silver staining. We have established primers and conditions that are sufficient to detect (at a threshold of 2-5%) all mutations obtained by Scorpion-ARMS as well as the following additional mutations; for codon 12, GGT→TTT (Gly→Phe), and for codon 13 GGC→TGC (Gly→Asp), with each base substitution resulting in a unique gel migration pattern ([see Figure 2](#)). We have also detected additional rare double base-pair mutations, as well as alterations outside of codon 12 and 13 using this technique.

**Figure 1.** Scorpion-ARMS Strategy



**Figure 2.** KRAS Mutation Detection using cold PCR and SSCP. Cell line controls.



\*codon 13

Definition of KRAS positivity: The cycle threshold (CT) is defined as the fractional cycle number at which the fluorescence passes the fixed threshold, set above baseline, as determined by the software. For each probe set specific to a KRAS codon 12 or 13 base substitution, a cut-off deltaCT, defined as the CT of the mutant minus the CT of the wild type control, has been established by the manufacturer as the point at which a positive signal could be due to background fluorescence of the primer on wild-type DNA. For our purposes, any specimen where the control probe has a CT value of  $\geq 40$  will be repeated and/or disqualified as insufficient material. For a patient specimen to be considered positive for mutation it must have: 1) a mutation CT  $< 45$ , 2) a deltaCT lower than the cut-off for that probe and 3) a smooth amplification curve in the log phase parallel to the control probe. In addition, an independent validation assay will be conducted for each specimen using SSCP. Due to formalin-induced DNA artifacts in archival tumor specimens, mutant positivity will likely be skewed slightly at the lower threshold. (32) As such, all tissue specimens will be compared, based upon sample size and quality of DNA, to determine the appropriate threshold below which any positivity will be determined to result from background artifacts. In addition, differentially migrating bands in the SSCP gel can be isolated, extracted and sequenced to confirm mutations. Divergent results between the DxS Scorpion-ARMS method and SSCP will result in re-analysis from, if at all possible, an additional tumor specimen and repeat of assays. Microdissection and sequencing can be used to resolve any further discrepancies, if required. Plasma analysis is expected to generate cleaner results due to lack of formalin-induced artifact formation, however the quantity of total DNA and mutant DNA extracted may vary tremendously on a patient-to-patient basis. (29, 30) Therefore, while plasma DNA may confirm the presence of a mutation in a tissue specimen, any discrepancy between tissue and plasma will be resolved in favor of the tissue results. Results from plasma analysis will be used as a back-up for patients where tumor tissue is insufficient or not available. If the mutation status remains ambiguous after the rigorous testing outlined above has been completed and no additional specimens are available for analysis, the KRAS status for that patient will be considered undeterminable. Our experience is that this will occur in less than 3% of cases.

In order to compare the results of the FISH assay with other EGFR-related markers, other markers also be assessed in specimens from this trial as integrated translational medicine studies (e.g., tests that are clearly identified as part of the clinical trial from the beginning and intended to identify or validate assays or markers planned for future studies, see [Section 18.5](#)).

#### 15.4 Radiology Review

PET/CT, CT and MRI images will be initially interpreted by the local site radiologist. Imaging exams will then be forwarded to the Quality Assurance Review Center (QARC) for central review.

#### **All CT and/or MRI images must be submitted to QARC for central review.**

All study participants will have a PET/CT, CT or MRI exam prior to study entry. Participants will then undergo additional imaging every 6 weeks until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (i.e., patients with a pre-study PET/CT are to receive follow-up PET/CT scans throughout the trial for assessment of progression; patients with a pre-study CT are to receive follow-up CT scans throughout the trial for assessment of progression; patients with a pre-study MRI are to receive follow-up MRI scans throughout the trial for assessment of progression). Each exam should be performed per [Appendix 18.6](#). QARC will facilitate a central/expert review per RECIST criteria; the central review-

based PFS is the basis for the assessment of objectives (see [Section 1.2a](#) and [1.2b](#)). Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations. Results of the central review will be reported only to the DSMC. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in [Appendix 18.6](#).

## 16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

### Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

### Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

### Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

## 16.1 Adverse Event Reporting Requirements

### a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in [Section 14.0](#).) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also [Appendix 18.1](#) for general and background information about expedited reporting.

### b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/adverse\\_events.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must also be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in [Table 16.1](#). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or [adr@swog.org](mailto:adr@swog.org), before preparing the report.

**Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study. All of the agents used in this study are commercial agents.**

<u>Attribution</u>	<b>Grade 4</b>		<b>Grade 5<sup>a</sup></b>	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			<b>CTEP-AERS</b>	<b>CTEP-AERS</b>
Possible, Probable, Definite	<b>CTEP-AERS</b>		<b>CTEP-AERS</b>	<b>CTEP-AERS</b>
<p><b>CTEP-AERS:</b> Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event<sup>b</sup>.</p> <p><sup>a</sup> This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.</p> <p><sup>b</sup> Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.</p>				

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**18.0 APPENDIX**

- 18.1 Determination of Expedited Adverse Event Reporting Requirements
- 18.2 Carboplatin Dosing Worksheet
- 18.3 New York Heart Association Class
- 18.4 Proposed Rash Management Algorithm
- 18.5 Embedded Translational Medicine Studies
- 18.6 Central Radiology Review
- 18.7 Cancer Trials Support Unit (CTSU) Participation Procedures
- 18.8 SWOG **S0819** Pathology Review Form

## 18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in [Section 14.0](#).) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in [Section 16.1](#).

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

***Steps to determine if an adverse event is to be reported in an expedited manner***  
*(This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.)*

**Step 1:** Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

**An investigational agent** is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

**Commercial agents** are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- **Concurrent administration:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- **Sequential administration:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

**Step 2:** Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

**Step 3:** Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

**Step 4:** Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in [Section 3.0](#) of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEEL (Agent Specific Adverse Event List), or other list of expected toxicities located in [Section 3.0](#) of the protocol, or the drug package insert.
- Exception to Expedited reporting located in [Section 16.1](#) f of the protocol.

An adverse event is considered **unexpected**, for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

**Step 5:** Determine whether the adverse event involved hospitalization or a prolongation of hospitalization ( $\geq 24$  hours).

**Step 6:** Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

**NOTE:** Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in [Section 16.1](#).

18.2 Carboplatin Dosing Worksheet

PATIENT'S INITIALS \_\_\_\_\_ MEDICAL RECORD # \_\_\_\_\_

SWOG PATIENT # \_\_\_\_\_

TO CALCULATE Creatinine Clearance (CrCl) from SERUM CREATININE:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{wt. in kg.}^*}{72 \times \text{serum creatinine}^{**}} \times 0.85 \text{ (if female)}$$

$$\text{CrCl} = \frac{(140 - \quad) \times (\quad)}{72 \times \underline{\hspace{2cm}}} \times 0.85 \text{ (if female)}$$

TO CALCULATE CARBOPLATIN DOSE WITH CALVERT FORMULA:

USE CALCULATED CREATININE CLEARANCE (AS ABOVE) TO SUBSTITUTE FOR GFR.

$$(\text{AUC}) (\text{GFR} + 25) = \text{CARBOPLATIN DOSE PER CYCLE IN mg}$$

$$(6) (\underline{\hspace{2cm}} + 25) = \underline{\hspace{2cm}} \text{ mg of carboplatin}$$

This is the TOTAL DOSE of carboplatin (not mg/m<sup>2</sup>).

Please note that: GFR should NOT exceed 125 ml/min. Hence, the maximum total carboplatin dose should NOT exceed 900 mg for this study.

\* Use current (actual) weight. This should be actual weight but not exceed 140% of IBW.

\*\* Carboplatin dose should be calculated using a serum creatinine value obtained within 3 days prior to each course therapy. In patients whose serum creatinine is < 0.8 mg/dl, 0.8 mg/dl must be substituted in the Cockcroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.

NOTE: PLEASE RETAIN ORIGINAL WORK SHEET as part of patient's PERMANENT RECORD. COPIES MAY BE MADE FOR PHARMACY and/or NURSING RECORDS.

18.3 New York Heart Association Class

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

\* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

\*\* At accustomed occupation or usual tasks.

18.4 Proposed Rash Management Algorithm

	<b><u>Macular Rash</u></b>	<b><u>Pustular/Papular Rash</u></b>	<b><u>Dry Skin</u></b>	<b><u>Pruritis</u></b>	<b><u>Ulcerative Lesions</u></b>
Grade 1	Hydrocortisone cream	Cleocin T Gel for limited single areas	N/A	N/A	N/A
Grade 2	Cutivate Topical BID Medrol dose pack	Minocin OR Bactrim DS	Lotion applied BID	Topical or Benadryl OR Atarax	N/A
Grade 3	Medrol dose pack <u>Consider dermatologic consultation</u>	Minocin OR Bactrim DS <u>Consider dermatologic consultation</u>	Lotion applied TID <u>Consider dermatologic consultation</u>	Benadryl OR Atarax <u>Consider dermatologic consultation</u>	Vaseline or Silvadene <u>Consider dermatologic consultation</u>
Grade 4	Medrol dose pack <u>Consider dermatologic consultation</u>	Minocin OR Bactrim DS <u>Consider dermatologic consultation</u>	Lotion applied TID <u>Consider dermatologic consultation</u>	Benadryl OR Atarax <u>Consider dermatologic consultation</u>	Vaseline or Silvadene <u>Consider dermatologic consultation</u>

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## 18.5 Embedded Translational Medicine Studies-Integrated and Other

In order to compare the results of the FISH and IHC assays outlined in [Section 15.3](#) with other EGFR-related markers, **other** markers also will be assessed in specimens from this trial as **integrated correlative studies**. (e.g., tests that are clearly identified as part of the clinical trial from the beginning and intended to identify or validate assays or markers planned for future studies).

### **Integrated Studies:**

**EGFR Protein Expression by IHC:** Diagnostic specimens will be sent to a central lab (University of Colorado-UCCC-under the direction of Dr. Wilbur Franklin) for assessment of EGFR protein expression by IHC using the DAKO EGFR scoring system (0-3+). EGFR-positive staining is defined as **any** IHC staining of tumor cell membranes above background level: whether it is complete or incomplete circumferential staining. Based on results from a recently completed prospective randomized Phase II study performed by OSI and UCCC in EGFR positive patients we expect similar properties to that of EGFR FISH as specified in [Section 6.0](#).

**EGFR mutation analysis:** EGFR activating mutations, which occur in 10-15% of unselected NSCLC patients in the USA, have proven to be associated with a high objective response rate (about 60%), but no large studies in the western countries have yet demonstrated a survival prolongation in EGFR mutated NSCLC patients (in contrast to Asian populations). EGFR mutation analysis will be performed in all patients included in this study and compared with EGFR FISH and IHC in an exploratory fashion. EGFR mutation analysis will be performed at UC Davis by Dr. Phil Mack using the DxS Scorpion method.

### **Other Studies**

**Proteomic analysis:** Hirsch and collaborators have identified an “8-peak” serum proteomic classifier which is associated with good clinical outcomes after EGFR TKIs, both in 1<sup>st</sup> line therapy and 2<sup>nd</sup> line therapy. (20) In this proposal we will collect blood in all patients for further correlative studies and compare with the tissue-based marker analyses in an exploratory fashion.

**EGFR polymorphism studies:** analysis to be performed by Dr. Alex Adjei with the North Central Cancer Treatment Group (NCCTG) at Roswell Park Cancer Center.

**Angiogenesis-related markers:** analysis will be performed at MD Anderson by Dr. John Heymach.

#### 1.1 Correlative study design (to include methods for obtaining samples, administering forms, or performing radiologic studies):

All registered and eligible patients will have either paraffin embedded blocks or unstained histological or cytological specimen(s) sent to the University of Colorado Cancer Center for EGFR FISH testing, IHC staining, KRAS and assessment of the other proposed EGFR-related biomarkers. These results will not be disclosed to the treatment sites.

Blood (plasma and buffy coat) will be collected at the SWOG specimen bank for future research.

1.2 Specific hypothesis (include relevant background studies):

Based on studies and data reported above, this correlative science proposal has the following hypotheses:

1. Cetuximab plus chemotherapy compared to chemotherapy alone will result in an improvement in progression-free survival (PFS) in EGFR FISH-positive patients.
2. EGFR FISH will identify a cohort of patients deriving the greatest benefit as compared with the unselected population and IHC<sup>+</sup> patients.
3. EGFR FISH will compare favorably in exploratory analyses to other EGFR-related biomarkers in identifying this cohort.

1.3 Statistical design (for each correlative study – include endpoints, sample size and monthly accrual rate): See above.

Based on historical data, we assume that the proportion of IHC-positive patients is 85% and we also assume that there are no EGFR FISH-positive/ IHC-negative patients. Therefore, among 1,236 patients (80% of 1,546) with IHC and FISH results, it is expected that at least 1050 will be IHC positive and 618 will be both FISH positive and IHC positive. The following table states the expected numbers of patients within each grouping:

	FISH/IHC unknown	IHC <sup>-</sup>	IHC <sup>+</sup> /FISH <sup>-</sup>	IHC <sup>+</sup> /FISH <sup>+</sup>
# of patients	310	186	432	618

The assumed median PFS in each of the prognostic/predictive grouping is included in the following table. For the purpose of the following power calculations we have assumed that IHC status and FISH status are not prognostic.

	Control arm	Experimental arm		
		IHC-/FISH -	IHC+/FISH-	FISH+
Median PFS	5.5	6.6	6.6	7.3
HR*	--	1.10	1.10	1.33

\* against control arm

These values correspond to an improvement in median PFS overall of 20%, and an improvement of 22% in the IHC-positive group. The second hypothesis in the unselected population is tested by an interaction test between EGFR FISH and treatment group. Among the 1,236 patients assumed to have an EGFR result for IHC and FISH, this study has 49% power to detect an interaction between treatment arm and FISH status using a 1-sided 0.05 level test under the assumptions in the table above.

The second hypothesis in the IHC<sup>+</sup> population is tested by an interaction test between FISH and treatment group within the IHC<sup>+</sup> population. Among the 1,050 patients assumed to be IHC<sup>+</sup> and have a result for FISH, this study has 43% power to detect an interaction between treatment arm and FISH status using a 1-sided 0.05 level test among IHC<sup>+</sup> patients.

Analysis of the other EGFR-related biomarkers will be exploratory in nature with the goal of augmenting the EGFR FISH analyses.

## 18.6 Central Radiology Review

All participants will undergo serial CT or MRI imaging:

- Baseline/pre-treatment
- Every 6 weeks until progression of disease (as determined by local site assessment)

***The same imaging modality MUST be used throughout the course of the trial. The pre- and post-treatment CT or MRI images must be submitted to QARC for all study participants. Imaging guidelines and image submission instructions are detailed below.***

Since real-time assessment and reporting of the central radiology review is not feasible, clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically appropriate considerations.

**NOTE: If a disease assessment is missed and/or delayed, if a scan is not done during a disease assessment for any reason; QARC must be notified of the missed and/or delayed disease assessment and the reason. The notification must be submitted in writing to SWOG@qarc.org or FAXED to 401/753-7601.**

### 1.0 Image Acquisition

All study participants will undergo serial CT or MRI imaging to be done at baseline and every 6 weeks until progression of disease (as determined by local site assessment).

#### 1.1 CT Imaging

General CT imaging parameters are outlined below. Additional scanning guidelines, per anatomic location, are detailed in the subsequent sections.

- Helical CT scanning is required; axial scanning cannot be used.
- Multi-detector scanning is preferred whenever possible, but single-detector helical scanning can be used.
  - Single detector scanners: Pitch should be 1-1.5; images should be reconstructed at  $\leq 5$ mm intervals in the axial plane.
  - Multi-detector scanners: It is strongly recommended that reconstruction be performed at the highest resolution possible (2 mm or less), but will accept  $\leq 5$ mm intervals.
- Each anatomic area (chest, abdomen, pelvis), scanner settings (kV, mAs) should be per institutional routine procedures.
- Choice of contrast agent should be according to local institutional routine.
- Contrast dose should be 100-150 mL.
- Injection rates should be 2 mL/sec minimum for chest and pelvis imaging and 3-5 mL/sec for abdominal imaging.
- 18G IV is preferred for bolus rates of injection, especially for abdominal imaging.
- Central lines should not be used unless absolutely required due to lack of acceptable peripheral IV access. Central lines should not be used with power injector unless specifically approved for that indication.

#### a. Chest and Abdominal CT

Scanning with IV contrast is preferred, but not required. If IV contrast is used, pre-contrast imaging is not required. Chest CT scanning should be performed per institutional standards, as

long as slice resolution requirements are met ( $\leq 5\text{mm}$ , preferably  $\leq 2\text{mm}$ ). For contrast-enhanced imaging, a scan delay of approximately 20-30 seconds is recommended. If chest imaging is combined with abdominal (and pelvic) imaging, chest imaging should either be performed prior to abdominal imaging (non-contrast chest) or after abdominal (and pelvic) imaging.

Abdominal imaging should be tailored for multi-phase liver imaging techniques. Pre- and post-IV contrast imaging provides optimal evaluation of liver disease; IV contrast should be used whenever possible. In cases when there is a contraindication to IV contrast, MRI is the preferred imaging modality for liver disease (if available).

**Recommended scanning protocol:** Helical non-contrast imaging through the liver prior to contrast-enhanced imaging, followed by dual-phase (arterial and portal) contrast enhanced imaging is recommended. Arterial phase scan delay time 20-30 seconds (or via bolus timing techniques per institutional routine). Portal venous scan delay time approximately 60-75 seconds. Each vascular phase scan of the liver must be obtained in a single helical acquisition.

## 1.2 MRI Imaging

General MRI imaging parameters are outlined below.

- Field strength of 1 tesla or greater.
- Imaging must be performed with a specialized torso array coil or other local coil combinations appropriate for body imaging. Body coil for signal reception is not acceptable.
- Image slice thickness should be  $\leq 7\text{ mm}$ .
- For contrast enhanced scanning, standard gadolinium chelates should be used at a dose of 0.1 mmol/kg to a maximum of 20mL.
- Injection rate should be 2cc/sec, and all injections must be followed by a saline flush of at least 20cc. Peripheral 22-20G IV preferred.

### a. Chest and Abdominal MRI

Axial imaging must be performed. Imaging using T1W and T2W techniques is recommended. Specific imaging sequences are per institutional standards. Breath-held imaging is required. Contrast enhanced imaging is not required, but is recommended for T1W imaging. If chest MRI is performed in combination with abdominal imaging, chest imaging must precede abdominal imaging (i.e., non-contrast) or must be performed after abdominal imaging (i.e., delayed post-contrast).

## 1.3 PET/CT Imaging

General PET/CT imaging parameters are outlined below:

- Only full-ring dedicated PET/CT scanners are acceptable. The CT of the PET/CT is used for attenuation correction of PET data and anatomic localization. CT settings should follow institutional guidelines (usually 120-140kV, at least 60mA).

- A documented daily quality control procedure must be in place and records kept.
- Non-diabetic patients should fast for at least 4 hours prior to the scan. Plain (unflavored water) should be taken during the period of fasting and the uptake period to ensure good hydration.
- Diabetic patients should ideally be given a morning appointment. They should take their usual antidiabetic medication (oral or insulin) and eat a light meal (lighter than they normally would) on that morning. The time interval between that morning meal and PET/CT scan should be approximately 3-4 hours.
- Blood glucose of all patients should be measured on arrival and consideration given to rescheduling when the blood glucose level is higher than 200 mg/dl. Insulin should not be administered to reduce glucose level when the blood glucose is > 200 mg/dl at the time of arrival in the PET clinic.
- Oral diazepam may be given if desired to reduce brown fat uptake one hour prior to tracer injection.
- Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) may be administered, according to institutional guidelines. Intravenous contrast may also be administered, provided this is done in a technique that avoids deterioration of the CT images by streak artifacts from high-concentration iv. contrast bolus.

**a. Scanning**

Administer 260 - 555 MBq (7-15mCi) <sup>18</sup>F- FDG. Emission part of the scan should start no earlier than 60 and no later than 80 minutes after injection. The exact same period of uptake must be used for staging and response scans – within 15 minutes. Perform attenuation corrected 'half-body' PET-CT scan to cover the area from the base of the skull to mid-thigh. This should be done with the arms above the head. Attenuation correction of PET emission data will be based on the low dose CT from the PET/CT.

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed.

**2.0 Image Submission**

Baseline scans and follow-up imaging at every 6 weeks for nine months and then every three months until progression or end of follow-up will be submitted via the AG Mednet service to QARC (the Quality Assurance Review Center).

**Instructions for Electronic Submission of Digital Exams to AG Mednet**

Exams must be submitted electronically via the AG Mednet service provided by SWOG. (Please note that while AG Mednet service is provided by SWOG, SWOG will not be responsible for the cost of the exams). Specific information about the imaging workflow and instructions can be found at <http://www.agmednet.com/doc/TrialUserGuide.pdf>.

## Electronic Submission Set-up

All participating sites will be provided with an AG Mednet Desktop Agent. The Desktop Agent can be ordered by e-mailing a request to [agmednetadmin@swog.org](mailto:agmednetadmin@swog.org). AG Mednet will require the AG Mednet Desktop Agent Order Form to be faxed directly to AG Mednet at 617/674-8125 or submitted online at the link provided. After activating your desktop agent, sites will be able to submit images electronically, directly from a scanner or PACS, and also from a CD or file system.

**Although AG Mednet can accommodate transmission of both DICOM and non-DICOM files, the SWOG image repository can only accept DICOM files. All images must be submitted as DICOM files.**

**NOTE:** The person responsible for activating the desktop agent should be involved in submitting the exams as the desktop agent requires user specific log-in verification. All questions regarding AG Mednet agent use should be directed to 888.9AGMEDNET, and hit 2 for the support option.

**Sites should contact AG Mednet at the time of IRB approval for AG Mednet enrollment to allow time for the Desktop Agent activation prior to patient registration. This contact is needed even if you are using AG Mednet for another SWOG trial. Note that activation of the Desktop Agent may take several weeks.**

## Exam Submission Process

When submitting images, you will be required to follow the **S0819** Image Submission protocol, which includes completing a transmittal form and de-identifying the exam. First import the exam from a CD or file system, PACS, or directly from the scanner. Select the exam in your Desktop Agent worklist, assign it to the **S0819** trial.

To complete the Transmittal Form, select the form under the tasks column. Instructions for the form will be sent to your site at the time you enroll with AG Mednet. The data from that transmittal form will be automatically integrated with the trial databases.

To de-identify the exam, select de-identification in the task list. The Agent will guide you through the proper blind encoding. If sites de-identify exams prior to importing, the AG Mednet Agent de-identification task will ensure the exam has been properly blind encoded.

The final task in your workflow after completing the transmittal form and de-identification is to upload the exam and associated information to SWOG. This can be completed by selecting upload exam in the task list.

Note: All questions regarding AG Mednet Agent use, transmittal forms, de-identification or image submission through AG Mednet should be directed to 888.9AGMEDNET, and hit 2 for the support option.

## 3.0 Central Radiology Review

After registration, SWOG will provide QARC with the registration date and patient number, along with a blinded code indicating which reviewer will be assigned to each case. This ensures that each reader reviews a balanced number of cases from each study arm. An experienced radiologist will review each image for

assessment of progression of disease per RECIST criteria. The same reviewer will read all study images of the study participant. Data from local reviews will not be provided to the central reviewers in order to keep the central reviewers blinded to the results of the local investigator-assessed PFS. The result of this read will constitute the definitive radiographic assessment of progression. If assessment of progression for a participant based on central radiology review is earlier than the local investigator/site assessment progression, the date of central review disease progression will be the date of the exam that documented the progression per the central radiology review. If central radiology review does not verify progression based on local radiographic assessment, QARC will continue to review any subsequent scans (if provided) to determine a later progression.

The actual progression will be determined at the SWOG Statistical Center, using a composite of the QARC assessment, in conjunction with possible data on progression from other sources or symptomatic deterioration (see [Section 10.6](#)). Results of the central review will NOT be communicated to the local site. Decisions regarding clinical management of the patient will be made by the treating physician based on local site assessments/reviews and other clinical considerations.

#### **4.0 Radiology Review Procedures**

Review of CT (or MRI) images will be performed using RECIST criteria.

##### **4.1 Review of pre-treatment CT/MRI exam will be performed as follows:**

The reader will review all anatomic areas (chest, abdomen) imaged and available. The target lesions to be evaluated will be defined/determined by the review of the pre-treatment exam. A maximum of 10 target lesions will be defined with a maximum of 5 in a single organ. The 10 target lesions will be chosen with representation from all organs involved with the tumor. Additional significant non-target lesions and areas of non-measurable disease will be noted. A screen capture of each target lesion, annotated with a pointer and a lesion reference number assigned to the target lesion, will be generated and archived. This will be used on subsequent reads to ensure concordance of lesions on follow-up/post-treatment exams. Measurements will be made from the axial scan (generally the post contrast scan) that best demonstrates the lesion as distinct from background. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at QARC.

**4.2 Review of post-treatment image exam(s) will be performed as follows:** The pre-treatment annotated exam and CRF will be reviewed to ensure lesion concordance. Readers will review all images for the current time point prior to making measurements. When performing lesion measurements on a scan from a given time point for a given target lesion, the previous measurement(s) of the specific target lesion will be reviewed to provide the reader with the previous axis and slice location for measurement. Measurements will be made from the axial post-contrast image that best demonstrates the lesion as distinct from background. Longest axis diameter will be recorded. Unless there is an obvious change in lesion shape, the reader will identify the slice on the current exam that best matches the lesion anatomy of the slice used for the prior measurement(s) and will choose an axis for diameter measurement that best approximates the axis used on the prior

measurement(s). If there is an obvious change in lesion shape, a new axis that corresponds to the longest axis observed in the axial plane will be measured. All measurements will be made by electronic calipers. A screen capture of the actual measurement axis with calipers will be saved and archived with the exam permanently at QARC.

## 18.7 Cancer Trials Support Unit (CTSU) Participation Procedures

### REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at [www.ctsu.org](http://www.ctsu.org)

All forms and documents associated with this study can be downloaded from the **S0819** Web page on the CTSU registered member Web site ([www.ctsu.org](http://www.ctsu.org)). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

#### **Requirements for S0819 site registration:**

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

#### **Pre-study requirements for patient enrollment on S0819**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed (including tumor and plasma samples) within the time period specified in the protocol.

#### CTSU Procedures for Patient Enrollment

All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at [open.ctsu.org](http://open.ctsu.org) or from the CTSU web site OPEN tab at <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the CTSU web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctscontact@westat.com](mailto:ctscontact@westat.com).

#### DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the **S0819** Web page located on the CTSU registered member Web site ([www.ctsu.org](http://www.ctsu.org)). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800-892-4007. Do NOT include a cover sheet for faxed data. Do NOT send study data to the CTSU.
3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data include the query sheet that was originally sent from SWOG.
4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP IAM account contact information current**. This will ensure timely communication between the clinical site and the SWOG data center.

#### Special Materials or Substudies

1. All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol [Section 15.0](#).
2. You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0819** protocol page and click on the link provided under the Case Report Forms header.

#### Specimen Collection ([Section 15.0](#))

- **Collection and shipment kits will be provided by SWOG. Ordering instructions are listed in protocol [Section 15.1](#).**
- **Tumor and plasma specimen submissions are mandatory. Additional information for tumor and plasma specimens submissions are outlined in [Section 15.0](#) of the protocol.**
- Radiology Review ([Section 15.0](#))
- Submission of CT and/or MRI images is mandatory for central review. Please refer to [Section 15.4](#) and [Appendix 18.6](#) for more information.

#### SERIOUS ADVERSE EVENT REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Report System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage ([www.ctsu.org](http://www.ctsu.org)) or by selecting Adverse Event Reporting Forms from the document center drop down list on the protocol number Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of CTEP-AERS. Submit the completed form and supporting documentation as outlined in the protocol.

#### Drug Procurement ([Section 3.0](#))

Commercial agents: Bevacizumab (Avastin®), Carboplatin (CBDCA), Paclitaxel (Taxol®), Cetuximab (Erbix®)
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Bevacizumab, Carboplatin, and Paclitaxel are commercially available and will not be supplied free of charge.

Cetuximab will be provided free of charge by ImClone Systems, Inc/Bristol-Myers Squibb (BMS) and distributed by BMS. Ordering instructions can be found in [Section 3.3.d](#) of the protocol. A copy of the Cetuximab Drug Request Form is available under Pharmacy Forms on the CTSU members' web site.

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in [Section 3.0](#) of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy under the Document folder on the **S0819** Web page.

## **REGULATORY AND MONITORING**

### Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page  
<http://ctep.cancer.gov/monitoring/guidelines.html>.

### Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

### Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.

18.8 SWOG **S0819** Pathology Review Form

SWOG **S0819** Pathology Review Form  
SWOG Solid Tumor Biorepository

SWOG ID # \_\_\_\_\_ Patient Initials: \_\_\_\_\_ (L, FM)  
Protocol of Interest: **S0819f**

Pathology Diagnosis: \_\_\_\_\_

Preliminary Data Specimen Submission:

Resected Tissue       Fine Needle Aspiration (FNA)       Core Biopsy

Specimen Type Submitted:

Block – Surgical Pathology Number\* \_\_\_\_\_

Slides – Surgical Pathology Number\* \_\_\_\_\_

**Specimen Review**

Tumor Cells Available (**PLEASE CHECK ONLY ONE**):

Adequate ( $\geq 100$  cells)       Inadequate ( $< 100$  cells)

\* This is **not** the number given to the specimen from the Specimen Tracking System.

\_\_\_\_\_  
Interpreted by

\_\_\_\_\_  
Date

NOTE: A copy of this form is to be submitted with the pathology report to the SWOG Solid Tumor Specimen Repository as outlined in [Section 15.1](#). This form must also be faxed to the Data Operations Center at 800/892-4007 or 206/342-1680 locally.

**Comments:**