

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 30901

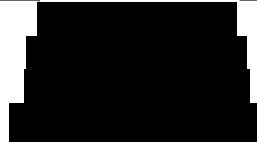
RANDOMIZED PHASE II STUDY OF MAINTENANCE PEMETREXED VERSUS OBSERVATION FOR PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA WITHOUT PROGRESSION AFTER FIRST-LINE CHEMOTHERAPY

Study Chair

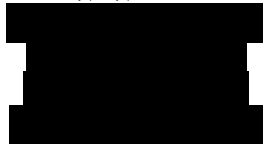
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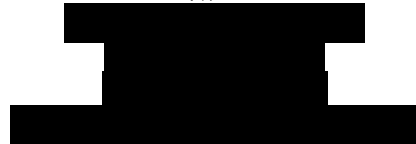
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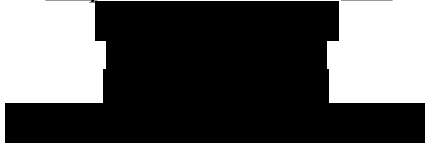
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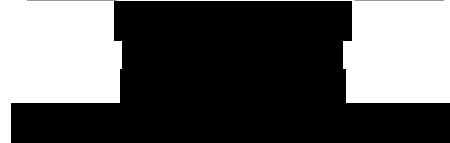
Pathology Co-Chair



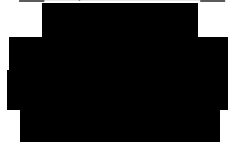
Respiratory Committee Chair



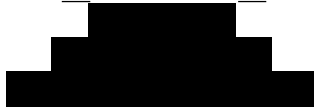
Mesothelioma Subcommittee Chair



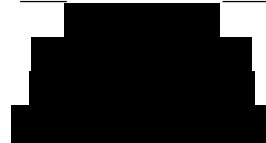
Study Statistician



Data Coordinator



Protocol Coordinator



Participating NCTN Groups: ECOG/ACRIN, Alliance for Clinical Trials in Oncology, NRG, SWOG

Study Resources:

Expedited Adverse Event Reporting http://eapps-ctep.nci.nih.gov/ctepaers/	Medidata Rave® iMedidata portal https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	Biospecimen Management System http://bioms.allianceforclinicaltrialsinoncology.org

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IROC
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Wright Center of Innovation

[Redacted]

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For study data submission:
<p>Regulatory documentation must submitted to the CTSU via the Regulatory Submission Portal:</p> <p>Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [REDACTED] to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at [REDACTED] for regulatory assistance.</p>	<p>Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctscontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The study protocol and all related forms and documents must be downloaded from the protocol-specific page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p>		
<p><u>For clinical questions (i.e., patient eligibility or treatment-related)</u> see the Protocol Contacts, Page 2.</p>		
<p><u>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [REDACTED], or [REDACTED]. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU website is located at https://www.ctsu.org.</p>		

Randomized phase II study of maintenance pemetrexed versus observation for patients with malignant pleural mesothelioma without progression after first-line chemotherapy

Patient Eligibility

Registration Criteria

Histologically documented unresectable malignant pleural mesothelioma
 Prior Treatment : Prior intracavitary cytotoxic or sclerosing therapy, prior surgery and prior radiotherapy are allowed
 Age \geq 18 years

Non-pregnant and non-nursing

Randomization Criteria

CR, PR or SD after 4, 5 or 6 cycles of pemetrexed + cisplatin or carboplatin
 \leq 6 cycles of pemetrexed + cis or carbo
 ECOG Performance Status 0-1

Required Initial Laboratory Values (for Randomization Only)

Granulocytes	\geq 1,500/ul
Platelet count	\geq 100,000/ul
Total Bilirubin	\leq 1.5 x ULN
AST (SGOT)	\leq 2 x ULN
Creat. clearance by Cockcroft/Gault	\geq 45 ml/min

SCHEMA

1 cycle = 3 weeks

REGISTER (no later than the last day of cycle 4 of first-line therapy)

Continue treatment with pemetrexed + platinum

4, 5, or 6 cycles

↓ CR, PR, or SD

RANDOMIZE*

Stratify:

Cisplatin vs. Carboplatin

Epithelioid Histology vs. Other

Number of cycles received: < 6 vs. 6 cycles

↓

Arm A

Observation

↓

Arm B

Continue pemetrexed until progression or intolerable toxicity

* Patients will be randomized following cycle 4, 5 or 6, within 1 week of completing first-line treatment. If randomized to pemetrexed, treatment will begin within 14 days of randomization.

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1.0 INTRODUCTION

1.1 Chemotherapy for Mesothelioma

Malignant pleural mesothelioma (MPM) is an uncommon tumor afflicting up to 3,000 patients annually in the United States. Most patients present with advanced disease, and treatment is limited to palliative chemotherapy. Only recently has the first chemotherapy regimen for mesothelioma, pemetrexed and cisplatin, been approved by the FDA. In a randomized phase III trial, treatment with pemetrexed and cisplatin was better than cisplatin alone with regard to response rates (41 vs. 17%), time to progression (6 vs. 4 months), and overall survival (12 vs. 9 months) (1). The combination of pemetrexed and carboplatin is a reasonable alternative for patients who cannot tolerate cisplatin based on results from large phase II trials and the expanded access experience showing comparable response rates and survival times (2-4).

1.2 Duration of Therapy

The optimal duration of first-line chemotherapy has been a long-standing question in the treatment of many solid tumors. Many investigators have argued that if a patient's cancer is controlled and the toxicities of the treatment are manageable, then discontinuation of the therapy will only result in earlier tumor regrowth. On the other hand, solid tumors ultimately reach a response plateau at which time additional chemotherapy does not result in further tumor shrinkage. Furthermore, continuation of chemotherapy for prolonged periods results in cumulative toxicities.

The experience in non-small cell lung cancer highlights this issue with several clinical trials designed to address the optimal duration of chemotherapy. In one study, patients with advanced NSCLC were randomized to receive paclitaxel and carboplatin for four cycles, or to continue that treatment until disease progression (5). No difference in survival, response rate, or quality of life was observed between the two study arms, yet patients on the continuation arm developed more peripheral neuropathy. Indeed, a meta-analysis presented at the ASCO 2008 Annual Meeting pooling data from 13 randomized trials demonstrated that maintenance chemotherapy significantly improves progression free-survival, but has minimal effect on overall survival (HR 0.94, $p=0.10$) (6). Current treatment guidelines for advanced NSCLC recommend four to six cycles of first-line platinum based chemotherapy and then monitoring for progression.

Another approach involves the use of a non-cross resistant regimen after completion of first-line therapy. The question becomes an issue of timing—does immediate treatment with a second-line regimen improve outcomes, or should patients be allowed to recover from the first regimen and restart chemotherapy at the time of progression? One trial also presented at the ASCO 2008 Meeting brought this issue to the forefront. In that study, 663 patients with advanced NSCLC and at least stable disease after completion of four cycles of platinum-based chemotherapy were randomized to receive pemetrexed or placebo (7). Treatment with pemetrexed not only improved PFS from 2 to 4 months, but also improved median overall survival from 10 to 13 months. These results may be confounded by the study design, however, since only 12% of patients on the placebo arm ultimately received pemetrexed as second-line therapy. For comparison, another phase III study randomized NSCLC patients to treatment with delayed vs. immediate second-line therapy with docetaxel (8). While PFS was markedly improved with immediate docetaxel from 2.8 to 6.5 months ($p<0.0001$), only a trend toward improved survival was observed (9.1 to 11.9 months, $p=0.07$). Nonetheless, when the data from the pemetrexed maintenance trial were added to the meta-analysis described above, the favorable effect of maintenance chemotherapy on overall survival became significant with a HR of 0.92 and $p=0.03$ (6).

1.3 Rationale for Study Design

This study aims to determine if continuing pemetrexed as “maintenance” therapy after treatment with a pemetrexed/platinum regimen will improve outcomes for patients with malignant pleural mesothelioma. This concept is based on several points: 1) Pemetrexed/cisplatin is a standard first-line regimen in MPM; 2) Maintenance pemetrexed improved PFS and OS in NSCLC with a relatively low rate of cumulative toxicity in that study; 3) A phase III trial in advanced MPM confirmed that treatment with pemetrexed as a second-line regimen resulted in improved progression free survival over best supportive care (although that trial was conducted in patients who had not received pemetrexed as part of their first-line therapy) (9); 4) A Dutch single arm study conducted in patients with mesothelioma who had at least stable disease after 6 cycles of pemetrexed-based chemotherapy demonstrated that maintenance therapy with pemetrexed in patients with mesothelioma was well tolerated, resulted in some radiologic responses, and hinted at improved TTP and OS (10).

In this proposed study, patients with MPM who have a response or stable disease after four to six cycles of pemetrexed and cisplatin or carboplatin will be randomized to continued treatment with pemetrexed alone or to observation. At the time of progression, the choice of chemotherapy will be at the discretion of the treating physician. Many patients in the observation arm are likely to receive pemetrexed again which will help address the question regarding immediate vs. delayed therapy.

1.4 Correlative Studies: Background

1.4.1 Serum Markers

The levels of soluble mesothelin related peptide (SMRP) and osteopontin were found to be elevated in patients with mesothelioma and may have a role as tumor markers (11,12). In prior reports, the levels of these markers were compared with those in control patients including those with asbestos related non-malignant pulmonary disease. Data that is available regarding whether these markers can be used as an adjunct to monitoring the disease status (such as response to chemotherapy) or estimating prognosis (such as overall survival) in patients with MPM is limited (13).

1.4.2 Tumor Thymidylate Synthase Expression and Analysis of Genetic Variants

Pemetrexed exerts its activity through inhibition of folic acid metabolism. One of the enzymes critical in this metabolism is thymidylate synthase. It has been hypothesized that tumors over-expressing thymidylate synthase may not respond to pemetrexed as well as tumors having low expression of this enzyme (14).

Expression of thymidylate synthase will be determined by immunohistochemistry using standard light microscope techniques. In addition, DNA will be extracted from whole blood collected for the analysis of genetic variants in the TYMS, DPYD, and MTHFR genes. These variants have been shown to affect the efficacy of therapeutics targeting thymidylate synthase (15).

1.4.3 Novel Radiologic Techniques to Monitor Response

Tumor measurement in patients with malignant pleural mesothelioma has been notoriously challenging. Rather than a rounded tumor mass that can be measured in one or two dimensions (as in lung tumors), mesothelioma spreads as a sheet along the pleura. This has led investigators to measure the pleural thickness as a surrogate. A “modified RECIST” system has been “qualified/validated” in which pleural thickness is measured at reproducible levels and the sum of the thickness measurements is used to assess response to therapy (16). This process remains suboptimal, especially in terms of reproducibility and assessment of tumor burden.

Pass et al. have demonstrated that preoperative tumor volume is representative of T status in MPM and predictive of overall and progression-free survival as well as postoperative stage. Large volumes are associated with nodal spread and post resection residual tumor burden may predict outcome (17). However, lack of automated/semi-automated tools to the identification and measurement of tumor volumes prevents further validation of such critical clinical findings as well as clinical use of the volumetric technique in the diagnosis of mesothelioma and assessment of therapeutic response.

Dr. Lawrence Schwartz and Dr. Binsheng Zhao, radiologists at Memorial Sloan-Kettering Cancer Center, have developed a three-dimensional (3D) computer method to assist in separation of tumor volume of MPM from its surrounding normal organs/tissues on CT images. By employing *a priori* knowledge and modeling relevant normal anatomical structures, they have developed a novel segmentation strategy to sequentially dissect MPM from its surrounding organs/tissues including chest wall, liver, spleen and lung parenchyma. A mathematical modeling method is used to obtain the thoracic volume by introducing a parabolic curve model to interpolate disconnected chest ribs on the coronal images and an arc interpolation algorithm to interpolate disconnected chest ribs on the axial images. An optimal combination of the two thoracic volumes enclosed with the connected chest ribs on the two view images will create a final thoracic volume (18). Internal organs such as the liver and spleen are automatically detected and segmented using a Gradient Vector Flow (GVF) snake technique that was developed for segmentation of the liver volume in a liver CAD project (19). In the thorax and the abdomen where relevant organs are segmented and removed, MPM can be separated using a thresholding method.

To correlate with clinical outcomes, this algorithm was retrospectively applied to two mesothelioma clinical trials in which the patients were treated with induction chemotherapy followed by surgery and radiation. The clinical characteristics and outcome from 30 patients enrolled on these two clinical trials were compiled and the segmentation algorithm applied to assist in calculating tumor volumes on baseline and 2 follow-up scans (cycles 2 and 4 of chemotherapy). Overall survival was measured using a landmark time at three months post treatment start date such that all patients had already received 2 and 4 cycles of chemotherapy. The percent change of tumor volume from baseline to 2 cycles of chemotherapy was significantly associated with overall survival (Hazard Ratio: 1.90 (95% CI: 1.02 – 3.55), $p=0.04$).

1.5 Inclusion of Women and Minorities

Patients who meet the eligibility criteria will be included in this study without regard to gender, race, or ethnicity, which are not expected to influence response or toxicity to the treatment. However, gender, race and ethnicity will be analyzed as important co-variates in reporting the results.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	0	0	2
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	12	43	1	1	57
More Than One Race	0	0	0	0	0
Total	15	46	1	1	63

Accrual Rate: 2 pts/month **Total Expected Accrual:** 60 Min 63 Max

2.0 OBJECTIVES

2.1 Primary Objective

To determine if maintenance therapy with pemetrexed improves progression-free survival in patients with malignant pleural mesothelioma who have at least stable disease after completion of first-line therapy with pemetrexed plus cisplatin or carboplatin.

2.2 Secondary Objectives

2.2.1 To determine if maintenance therapy with pemetrexed improves overall survival.

2.2.2 To evaluate frequency of responses to maintenance therapy with pemetrexed.

2.2.3 To assess toxicity of maintenance therapy with pemetrexed.

2.3 Correlative Objectives

2.3.1 To assess whether serum biomarkers, including but not limited to soluble mesothelin related peptide (SMRP) (in epithelioid histology) and osteopontin, correlate with tumor response, progression free survival and overall survival.

2.3.2 To determine whether high expression of thymidylate synthase correlates with lack of clinical benefit of pemetrexed (response rate, progression free survival, and overall survival).

2.3.3 To determine whether specific polymorphisms in the TYMS, DPYD and MTHFR genes correlate with a lack of clinical benefit of pemetrexed.

2.3.4 To determine the association between volumetric measurement of tumor response and usual methods of modified RECIST criteria.

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following might increase the risk to the patient entering this protocol:

- Patients with medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient should not be enrolled. Such conditions include ongoing or active infection, such as HIV+ patients; inability to take oral medications; or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients with clinically significant pleural or peritoneal effusions that cannot be adequately managed by drainage prior to or during pemetrexed.
- Psychiatric illness which would prevent the patient from giving informed consent.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers and carcinoma in situ of the cervix. Patients are not considered to have a “currently active” second malignancy if they have completed therapy and have no evidence of recurrence for at least 5 years.
- Estimated life expectancy <12 weeks.

4.0 ELIGIBILITY CRITERIA

4.1 Registration Eligibility Criteria

4.1.1 Histologic Documentation: Histologically documented malignant pleural mesothelioma, epithelial, sarcomatoid or mixed type, not amenable to surgical resection.

4.1.2 Prior Treatment

- Currently receiving first-line treatment with pemetrexed + platinum. Patients are to be registered to CALGB 30901 no later than the last day of cycle 4 of first line therapy.
- Prior intracavitary cytotoxic or sclerosing therapy (including bleomycin) are acceptable. Prior intrapleural cytotoxic chemotherapy will not be considered systemic chemotherapy.
- Prior surgical treatment is allowed.
- Prior radiation therapy is allowed.

4.1.3 Age \geq 18 years

4.1.4 Non-pregnant and non-nursing since the effects of pemetrexed on the fetus/infant are unknown. In addition, women of child bearing potential and men must agree to use an appropriate method of birth control throughout their participation in this study. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier methods (diaphragm plus condom).

4.2 Randomization Eligibility Criteria

4.2.1 Patients with complete response, partial response, or stable disease following 4, 5 or 6 cycles of first-line chemotherapy with pemetrexed AND either cisplatin or carboplatin. A maximum of 6 cycles of chemotherapy may have been given.

4.2.2 ECOG performance status of 0-1.

4.2.3 Required Randomization Initial Laboratory Data:

Granulocytes	≥ 1,500/ ul
Platelet count	≥ 100,000/ ul
Total Bilirubin	≤ 1.5 x ULN
AST (SGOT)	≤ 2 x ULN
Calculated Creatinine Clearance *	≥ 45 ml/min

* The calculated creatinine clearance will be estimated by the Cockcroft-Gault formula as follows:

$$\frac{(140-\text{age}) \times \text{wt. in kg.}}{72 \times \text{serum creatinine}} \times \begin{matrix} 0.85 \text{ for females} \\ 1.0 \text{ for males} \end{matrix}$$

5.0 REGISTRATION/RANDOMIZATION AND STRATIFICATION

Patients will be registered no later than the last day of cycle 4 of first-line therapy. Patients with CR, PR or SD following 4, 5 or 6 cycles of first-line therapy will then be randomized within a week of completing first-line treatment. The completion date of therapy is considered day 21 of cycle 4, 5 or 6. Patients will be randomized to maintenance therapy with pemetrexed or to observation. If randomized to pemetrexed, treatment is to begin within 14 days following randomization.

5.1 Registration Requirement

Informed Consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and consent form is required.

5.2 Patient Registration/Randomization

5.2.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iam>). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP’s web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	

Documentation Required	IVR	NPIVR	AP	A
HSP/GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at [REDACTED]

5.2.2 CTSU Registration Procedures

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

IRB Approval:

Each 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 be approved to enroll patients.

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to:

- an active Federal Wide Assurance (FWA) number,
- an active roster affiliation with the Lead Network or a participating organization,
- a valid IRB approval, and
- compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory

Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the CALGB 30901 protocol page located on the CTSU members' website.

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the *Alliance* link to expand, then select trial protocol CALGB 30901
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for CALGB 30901 Site Registration:


- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission Portal

CTSU Regulatory Office

A large black rectangular redaction box covers the contact information for the CTSU Regulatory Office.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen

- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.2.3 Patient Registration through OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website 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.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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 OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at [REDACTED]

5.2.4 Registration to Companion Studies

There are two substudies within CALGB 30901. All patients will be registered to the imaging study (CALGB 580903) at the time of registration to the treatment trial, however, only randomized patients will participate in the imaging study. The correlative science study (CALGB 150912) **must be offered to all patients** registered to CALGB 30901 (although patients may opt to not participate). However, submission of samples is required only for those patients who are randomized.

These substudies do not require separate IRB approval. The substudies included within CALGB 30901 are:

- CALGB 150912 - Correlative studies in pts on CALGB 30901 ([Section 6.2.1](#))
- CALGB 580903 - Imaging study in pts on CALGB 30901 ([Section 6.3](#))

The instructions for submitting specimens for the correlative science companion substudy are in [Section 6.2](#); the imaging study is in [Section 6.3](#).

If a patient answers "yes" to "My specimen(s) may be used for the genetic research described above," question #1 and/or "I agree that my specimen(s) may be used for the research studies described above," question #2 in the model consent, they have consented to participate in the correlative substudy described in [Section 15](#). The patient should be registered to CALGB 150912 at the same time they are registered to the treatment trial (30901). Samples should be submitted per [Section 6.2](#).

5.2.5 Patient Randomization through OPEN

Following cycle 4, 5 or 6 of chemotherapy, patients with responding or stable disease will be randomized. Patients should be randomized within a week of completing first-line

pemetrexed + platinum therapy. If randomized to pemetrexed, treatment is to begin within 14 days following randomization. The CRA will enter the patient ID number obtained at registration into the OPEN registration system. The patient is randomized according to the stratification factors, which must be entered to obtain a treatment assignment. Once the randomization is complete, note the patient’s treatment assignment in your records.

5.2.6 Stratification Factors

First-line chemotherapy regimen: cisplatin/pemetrexed vs. carboplatin/ pemetrexed

Histology: epithelioid vs. other

Number of cycles received: < 6 vs. 6 cycles

6.0 DATA SUBMISSION AND SAMPLE SUBMISSION

6.1 Data Submission

Forms should be submitted to the Alliance Statistics and Data Center at Mayo Clinic, Data Operations, in compliance with the Data Submission schedule below.

- All data forms available online must be submitted electronically using the “Print and/or Submit to CALGB” button located at the bottom of the last page of each form. Forms submitted electronically should not be submitted by FAX or mail.
- Supporting documentation (e.g., scan reports) and amended forms will be mailed to the Alliance Data Center, Attn: CALGB 30901 Data Manager, RO FF-3-24-CC/NW Clinic, 200 First St, SW, Rochester, MN 55906.

Visit the CALGB 30901 study page on the Alliance website for the most up-to-date forms.

Form*		Submission Schedule
After Registration (All Patients)		
C-2123	CALGB 30901 Pre-randomization Form	At time of randomization or decision not to randomize.
After Randomization/Baseline (Randomized Patients Only)*		
C-1938	CALGB 30901 On-Study Form	Within 14 days of registration
Report	CT and Pathology reports	
C-2000	CALGB Solid Tumor Evaluation Form†	
C-2001	CALGB Mesothelioma Measurement Form†	
During Treatment / Observation and Post-treatment Follow-up		
C-1941	CALGB 30901 Adverse Event Form**	At the end of each cycle for patients randomized to the treatment arm.
C-1942	CALGB 30901 Follow-up and Response Form	Every 2 cycles for 6 months, then every 3 cycles for 6 months, then every 4 cycles months for a maximum of 3 years from date of randomization or until disease progression (whichever happens first). For patients who discontinue protocol therapy for reasons other than disease progression (including observation patients receiving non-protocol therapy), post-treatment follow-up
C-2000	CALGB Solid Tumor Evaluation Form†	
C-2001	CALGB Mesothelioma Measurement Form†	
Report	CT reports	

		should continue at the same time points described above. Note: For patients on observation or in post-treatment follow-up, the equivalent of a cycle is 3 weeks.
After Disease Progression		
C-1942	Follow-up and Response Form	After disease progression, every 6 months for a maximum of 3 years from date of randomization to report survival data.
Other		
C-300	Off Treatment Form††	At end of all protocol treatment (and before beginning non-protocol treatment).
C-113	Notification of Death	At time of death.
C-1001	New Malignancy Form	At time of diagnosis of new malignancy.
C-1820	Adverse Events Addendum Form	Complete if additional space is needed to report other adverse events. See form for instructions.

*Use CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed. If patient never starts treatment, only submit on-study data and C-300.

**Submit AE form until all treatment related events have resolved or non-protocol treatment begins.

†For patients randomized to the Observation Arm, the reporting period question should be marked as 'Post treatment' for all measurement forms except at Baseline.

††For patients randomized to the Observation Arm, submit if the patient begins another non-protocol therapy prior to progression, otherwise submit at progression as 'Completed per protocol therapy.'

6.2 Sample Collection and Submission

The following section will provide details about how specimens will be collected, when they will be collected, and where they will be submitted for those randomized patients who consent to CALGB 150912.

Sample Type	Pre-Treatment	Prior to Cycle 3 (Week 6)	At Progression	Ship To
Tissue Block	X			PCO
Whole Blood (lavender top)	1 x 10 mL			PCO
Plasma (lavender top)	1 x 6 mL	1 x 6 mL	1 x 6 mL	PCO
Serum (red/gray SST)	1 x 6 mL	1 x 6 mL	1 x 6 mL	PCO

6.2.1 Correlative Substudy Sample Collection

For the study of genetic variants, one 10 ml tube of blood will be collected prior to treatment. Initial blood samples collected for evaluation of SMRP and Osteopontin levels will be obtained within 7 days prior to beginning the first cycle of therapy with maintenance pemetrexed (or the observation period). The time and day of sample acquisition is not critical as long as it occurs within the week prior to receiving any treatment. A second sample will be collected within 2 days of beginning cycle 3 (week 6 for observation

patients). A third sample will be drawn when the patient's tumor progresses while on pemetrexed therapy or observation. This third sample should be drawn prior to initiation of any additional chemotherapy.

Blood Sample Collection

- For analysis of genetic variants, collect one 10 ml lavender top (EDTA) tube of whole blood. The tube should be inverted 8-10 times to mix the tube additive and then refrigerated until shipped. Samples should be packaged to prevent breakage and shipped on a cold pack for processing. **Samples should be shipped via overnight courier the same day they are collected.**
- For plasma measurement of osteopontin collect one 6 ml lavender top (EDTA) tube of peripheral or central venous blood. Gently invert the tube 8 times to mix the additive and immediately centrifuge at 1300g or 3000 RPM for 10 minutes at room temperature. After centrifugation, aspirate plasma without disturbing cells, then place 1 ml aliquots into 2.0 ml cryogenic vials (see details below)*. Store the vials at -70°C or colder until shipping. Ship samples within 30 days on dry ice.
- For serum measurement of SMRP collect one 6 ml red/gray serum separator tube (tiger top) of peripheral or central venous blood. Gently invert 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot. Centrifuge at 1300g or 3000 RPM for 10 minutes. After centrifugation, place 1 ml aliquots of serum into 2.0 ml cryogenic vials (see details below)*. Store the vials at -70°C or colder until shipping. Ship samples within 30 days on dry ice.

*Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

- Label all samples with patient's initials, (last, first, middle), patient ID number, study number, date drawn and type of specimen collected (e.g., serum, whole blood).

6.2.2 Pathology Specimen

For patients who consent, institutions will submit the pathology report and an adequate sized paraffin block from the core biopsy. The Alliance has instituted special considerations for the small percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, please contact the Alliance Biorepository for alternative instructions.

6.2.3 Specimen Registration, Tracking and Submission Instructions

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: <http://bioms.allianceforclinicaltrialsinoncology.org> using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [REDACTED] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [REDACTED]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

Shipment of samples

- All samples should be labeled with study number, patient ID number, patient initials, sample collection date and time, and be accompanied by the completed specimen submission shipping manifest which will be generated by BioMS.

Note for CRA – The following PHI must be removed or blacked out for all specimens or reports: signature, name, date of birth, other identifying information, except initials and study identification number.

- All samples should be shipped to the Alliance Biorepository at Ohio State.
- Specimens may be sent to the Alliance Biorepository on Monday through Thursday for next day delivery. **The Bank cannot receive specimens on Saturdays, Sundays or holidays. Do not send specimens the day before a holiday.**
- The institution is expected to pay the cost of mailing specimens and will be reimbursed through capitation fees set for each individual study.
- Arrange for express courier pick-up through your usual institutional procedure. Ship specimens to the address below:

Alliance Biorepository at Ohio State
Innovation Centre



On the day that specimens are sent to the specimen bank, please contact the bank by phone or e-mail to notify what is being sent and when the shipment is expected to arrive.

6.3 Required Imaging Substudy (CALGB 580903)

6.3.1 CT Imaging Requirement

Contrast enhanced CT scans will be obtained at the following time points for all patients:

- Baseline: Within one month before patient randomization
- During Treatment/Observation: Every 2 cycles for 6 months, then every 3 cycles for 6 months, then every 4 cycles until disease progression for a maximum of 3 years from the date of randomization.
- Follow-Up (after progression): None

Contrast enhanced CT scans will be performed using 2.5 mm cuts. In the event that a site is unable to obtain a 2.5 mm cut, 5 mm cuts will also be permitted.

Optimal Technique: The requirements listed below are to be used for the chest CT scan whenever possible.

- Scanning mode: Helical
- Patient position: Supine, arms up
- Scan extent: Thoracic inlet through the most inferior extent of the pleural spaces
- Scan time: Single breath-holding period, in full inspiration

- Section thickness: 1.5 mm or less
- Enhancement: Intravenous contrast unless contraindicated by allergy
- Reconstruction: Contiguous or overlapping sections; no gaps

Minimum CT requirements are listed below.

- Scanning mode: Helical
- Patient position: Supine
- Scan extent: Thoracic inlet through the most inferior extent of the pleural spaces
- Scan time: Single breath-holding period, in full inspiration
- Section thickness: 5mm or less
- Enhancement: Preferred but not mandatory
- Reconstruction: Contiguous or overlapping sections; no gaps

6.3.2 CT Data Submission

Images must be submitted to the Alliance Imaging Core Lab within **3 business days** once the image acquisition is completed at the site.

Send de-identified digital CT images in DICOM format on a CD or electronically via Web or FTP to the Alliance Imaging Core Lab at The Ohio State University. BMP files, JPG files or hard copies (films) are not acceptable.

Sites interested in sending images electronically via Web or FTP to the Imaging Core Lab should send an e-mail to [REDACTED] for standard Web or FTP access information.

If the electronic data transfer cannot be achieved at sites, CT scans may be sent on a CD to the Imaging Core Lab at:

Alliance Imaging Core Laboratory
Attn: CALGB30901
Wright Center of Innovation
The Ohio State University



Institutions must complete the CALGB 30901 Radiology Submission Form (C-1958) and fax or mail it to the Imaging Core Laboratory within 24 hours of submitting the baseline scan. The Imaging Laboratory will acknowledge receipt of the submission by e-mail within 24 hours of receipt of the materials, excluding holidays and weekends.

7.0 REQUIRED DATA**Guidelines for Pre-Study Testing**

To be completed within 16 DAYS before randomization:

- All blood work

To be completed within 28 DAYS before randomization:

- Any scan which is utilized for tumor measurement

Tests & Observations	Prior to Randomization	Every 3 weeks (Pemetrexed arm only)	Every 6 weeks (Both arms)
History and Progress Notes	X	X	X
Physical Examination	X	X	X
Pulse, Blood Pressure	X	X	X
Weight	X	X	X
Height	X	X	X
BSA†	X	X	X
Performance Status	X	X	X
Tumor Measurements	X		X
Drug Toxicity Assessment		X	
Laboratory Studies			
CBC, Differential, Platelets*	X	X	X
Serum Creatinine, BUN*	X	X	X
Serum Electrolytes*	X	X	X
SGOT, Alk.Phos., Bilirubin*	X	X	X
Serum or urine HCG**	X		
Correlative Substudy	B		B
Pathology Block	C		
Staging			
Chest and upper abdomen CT scan w/ contrast***	A		A††
Imaging Substudy	D		D††

* Pre-study laboratory tests may be used for the day 1 of Cycle 1 requirements if obtained within 14 days of treatment.

** If female and of childbearing potential.

*** CT Scan requirements for this protocol:

Optimal Technique: The requirements listed below are to be used for the chest CT scan whenever possible.

- Scanning mode: Helical
- Patient position: Supine, arms up
- Scan extent: Thoracic inlet through the most inferior extent of the pleural spaces
- Scan time: Single breath-holding period, in full inspiration
- Section thickness: 1.5 mm or less
- Enhancement: Intravenous contrast unless contraindicated by allergy
- Reconstruction: Contiguous or overlapping sections; no gaps

- † It is not necessary to change the dose of pemetrexed unless the calculated dose changes by $\geq 10\%$.
- †† Every 2 cycles for 6 months, then every 3 cycles for 6 months, then every 4 cycles until disease progression for a maximum of 3 years from the date of randomization.
- A CT chest and any other known site of extrathoracic metastasis: Use intravenous contrast when possible. CT scans should be performed with 2.5 mm cuts for volumetric assessment (See [section 15.4](#)).
- B For patients who consent, blood will be collected according to [Section 6.2.1](#).
- C For patients who consent, a block should be submitted per [Section 6.2.2](#).
- D For more information on the imaging substudy (CALGB 580903) please refer to [Section 6.3](#).

8.0 TREATMENT PLAN

Questions regarding treatment should be directed to Dr. Arkadiusz Dudek.

Patients will be registered no later than the last day of cycle 4 of first-line therapy. Patients with CR, PR or SD following 4, 5 or 6 cycles of first-line therapy will then be randomized within a week of completing first-line treatment. Patients will be randomized to maintenance therapy with pemetrexed or to observation. If randomized to pemetrexed, treatment is to begin within 14 days following randomization.

Patients assigned to the treatment arm will receive pemetrexed 500 mg/m² IV over 10 minutes (or per institutional guidelines) every three weeks. Patients will continue treatment until disease progression or excess toxicity. At the time of disease progression, the choice of therapy is left to the physician's discretion.

Pemetrexed Premedications:

Folic Acid: Oral folic acid (0.35 - 1 mg/day) starting at least 1 week before the first pemetrexed dose and continue for 21 days after the last dose of pemetrexed.

Vitamin B₁₂: Vitamin B₁₂ 1000 mcg IM injection. A vitamin B₁₂ injection must be administered at least 1 week before the initial pemetrexed dose and repeated every 9 weeks while on pemetrexed until 21 days after last dose of pemetrexed.

Dexamethasone: Dexamethasone (4 mg orally or equivalent) BID the day before, the day of, and the day after each dose of pemetrexed, for a total of 6 doses per cycle.

8.1 Drug Interactions

Patients should avoid taking NSAIDs for a period of 5 days before, the day of, and 2 days after pemetrexed administration. If patients must be on NSAIDs, they are to be monitored closely for toxicities.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

The starting dose of pemetrexed is 500mg/m², even if the patient required a pemetrexed dose reduction during platinum doublet therapy.

If multiple toxicities are evident and more than one of the dose modifications applies, use the most stringent dose reduction (i.e., the greatest dose reduction). Dose may not be re-escalated once it has been reduced.

9.1 Dose Levels for Pemetrexed

Treatment should be discontinued in patients requiring a dose level reduction beyond level -2. Dose levels for pemetrexed are below.

Dose Level	Pemetrexed
0	500 mg/m ²
-1	375 mg/m ²
-2	250 mg/m ²

9.2 Pemetrexed Guidelines for Dose Modification and Management of Toxicity

9.2.1 GI Toxicity

Grade 3 or 4 diarrhea despite antidiarrheal medication and prophylactic vitamin supplementation at any time during a cycle: Delay pemetrexed until diarrhea resolves to \leq grade 2. Resume pemetrexed when diarrhea resolves to \leq grade 2 at one dose level lower than the previous dose for all subsequent cycles. If diarrhea has not improved to \leq grade 2 within 3 weeks, discontinue pemetrexed.

Grade 3 or 4 oral mucositis despite prophylactic vitamin supplementation at any time during a cycle: Delay pemetrexed and resume when mucositis resolves to \leq grade 2 at one dose level lower than the previous dose for all subsequent cycles. If oral mucositis has not improved to \leq grade 2 within 3 weeks, discontinue pemetrexed therapy.

9.2.2 Hematologic Toxicity

For ANC <1,500 or platelets <100,000 on day 1, delay treatment with pemetrexed until ANC \geq 1,500 and platelets \geq 100,000, then resume pemetrexed at one dose level lower for all subsequent doses. If treatment is delayed for \geq 3 weeks, discontinue all protocol treatment.

For febrile neutropenia occurring at any time during a cycle, decrease pemetrexed by one dose level for all subsequent doses.

9.2.3 Calculated CrCl < 45 ml/min

If creatinine clearance is < 45 ml/min, delay pemetrexed until CrCl \geq 45 ml/min. When CrCl improves to \geq 45 ml/min, resume pemetrexed at the previous doses. If CrCl remains < 45 ml/min at 3 weeks, discontinue pemetrexed therapy.

9.2.4 Clinically Significant Effusions

For patients who develop clinically significant pleural or pericardial effusions (on the basis of symptoms of physical examination) during therapy, consideration should be given to draining the effusion prior to the next dose of pemetrexed. However, in the opinion of the treating physician, if the effusion represents progression of disease, the patient should discontinue protocol therapy.

9.2.5 Skin Toxicity

Grade 3 or 4: For grade 4 skin toxicity, discontinue pemetrexed. For Grade 3, hold pemetrexed until toxicity improves to \leq grade 1, then resume pemetrexed at the previous dose level. For recurrent grade 3 skin toxicity, hold pemetrexed until toxicity improves to \leq grade 1, then resume pemetrexed with one dose level reduction. If pemetrexed is held for skin toxicity for 3 weeks, discontinue pemetrexed.

9.2.6 Hypersensitivity Reactions

For grade 3 or 4 allergic reactions or anaphylaxis thought to be due to pemetrexed, discontinue pemetrexed.

9.2.7 Other Non-Hematologic Grade 3 Toxicity

Excluding fatigue and anorexia: Hold pemetrexed until toxicity improves to \leq grade 2, then resume pemetrexed with one dose level reduction. If pemetrexed is held for 3 weeks, discontinue therapy with pemetrexed.

For recurrent other non-hematologic grade 3 toxicity: Discontinue all protocol therapy.

9.2.8 Other Non-Hematologic grade 4 toxicity (not described above):

Discontinue pemetrexed therapy.

9.3 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol.** This will minimize the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on Alliance protocols.

10.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

- Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.
- Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.
- The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.
- It is not necessary to change the doses of any of the agents used in this trial unless the calculated dose changes by $\geq 10\%$.

10.1 Pemetrexed (Alimta®)

Please refer to the FDA approved package insert for additional information

Availability

Pemetrexed is available commercially as a lyophilized powder for reconstitution in single-use vials containing 500 mg pemetrexed.

Storage and Stability

Intact vials of pemetrexed should be stored at room temperature. The reconstituted and further diluted solutions for infusions are stable for up to 24 hours when refrigerated or stored at room temperature.

Preparation

Each 500 mg of pemetrexed is reconstituted with 20 mL of 0.9% sodium chloride for injection, resulting in a concentration of 25 mg/mL. The desired dose should be withdrawn and further diluted in 100 mL of 0.9% sodium chloride for injection, for IV infusion.

Administration

Pemetrexed will be administered as a 10 minute IV infusion every 21 days

Toxicities

The most common toxicities reported with pemetrexed to date include myelosuppression, GI toxicities, rash and fatigue. Neutropenia is more common than thrombocytopenia, and it is minimized with vitamin supplementation. Specifically, folic acid and Vitamin B12 starting before pemetrexed and continuing throughout pemetrexed therapy are recommended. It is thought that severe pemetrexed toxicity is due to a subclinical folate deficiency, as may be documented by an elevated plasma homocysteine. Similarly, diarrhea and mucositis are also minimized with the use of folic acid and B12. Single agent pemetrexed was associated with nausea and vomiting in approximately 30% of patients. In the majority of patients, nausea and vomiting were \leq grade 2 severity. The incidence and severity of pemetrexed-induced rash appears to be decreased with the administration of dexamethasone, beginning the day before pemetrexed. Fatigue, grade 1-3 severity, is also common.

Drug Interactions

As is the case with methotrexate, the potential exists for various drugs (e.g., NSAIDs, probenecid, salicylates, sulfonamides) to delay pemetrexed renal clearance and increase toxicity.

11.0 ANCILLARY THERAPY

- Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on form C-260.
- Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic or as premedication for pemetrexed.
- Palliative radiation therapy may not be administered during protocol therapy. Any patients requiring palliative radiation therapy will be removed from protocol therapy.
- Therapy for severe diarrhea (grade 3 or 4) may require supportive measures such as hydration, octreotide, electrolyte repletion and antidiarrheals as clinically appropriate. If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia, physicians should give consideration to prescribing broad-spectrum antibiotics.

11.1 Alliance Policy Concerning the Use of Growth Factors

11.1.1 Epoetin (EPO)

Use of epoetin or darbepoetin is **permitted** at the discretion of the treating physician. When used, the administration of erythropoiesis-stimulating agents should be consistent with the approved indication for patients receiving chemotherapy as described in current product literature.

11.1.2 Filgrastim (G-CSF), Sargramostim (GM-CSF) and Pegfilgrastim

1. Filgrastim (G-CSF), sargramostim (GM-CSF), or pegfilgrastim may be used according to ASCO guidelines.
2. If filgrastim, sargramostim or pegfilgrastim are used, they must be obtained from commercial sources.

12.0 CRITERIA FOR RESPONSE, PROGRESSION

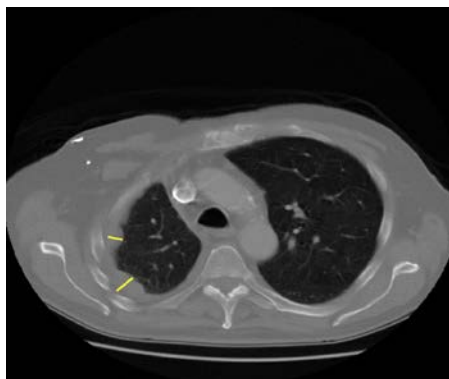
For the purposes of this study, patients should be reevaluated every six weeks (2 cycles) for 6 months, then every 9 weeks (3 cycles) for 6 months and then every 12 weeks (4 cycles) until disease progression for a maximum of 3 years from date of registration. In addition to a baseline scan, confirmatory scans should also be obtained at least four weeks following initial documentation of objective response.

12.1 Target Lesions

All measurable lesions up to a maximum of 5 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Measurable lesions are defined as those that can be accurately measured in at least one dimension as ≥ 10 mm with CT scan. A lymph node must be ≥ 15 mm in short axis by CT scan in order to be considered pathologically enlarged and measureable. All measurements must be recorded in millimeters. A sum of the diameters (long diameter (LD) for all non nodal target lesions and short axis for nodal lesions) will be calculated and reported as the baseline sum LD. The baseline sum of all diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

In patients with pleural mesothelioma the typical mesothelial “rind” should be measured on 3 separate levels at least 2 cm apart, **perpendicularly** from the chest wall on a given cut. Each level should be measured in two different places (please see fig 1). The three rind thicknesses should be recorded for a given level and compared on subsequent scans. Clear anatomic landmarks should be recorded carefully to ensure consistency from scan to scan. At least one level should have a measurement ≥ 1.5 cm. Pleural areas where the initial thickness is less than 1 cm should not be used as evaluation measurement.

Figure 1. Measurement of mesothelioma rind. The typical mesothelioma rind should be measured in 2 different places (yellow/white lines) **perpendicularly** from the chest wall. These measurements should be performed at 3 anatomic levels at least 2 cm apart.



A sum of the measurements of the pleural rind obtained at 3 different levels should be calculated and reported as the baseline sum LD.

These modified RECIST criteria have been previously validated in patients with mesothelioma (16). Response assessment using these methods has been found to be a greater clinical predictor

for survival in patients with mesothelioma than a method of longest diameter to assess pleural thickness.

- 12.1.1 Complete Response:** Disappearance of all target lesions. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.
- 12.1.2 Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum LD. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.
- 12.1.3 Progression (PD):** At least a 20% increase in the sum of the diameters of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- 12.1.4 Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of the diameters since the treatment started. Patients having a documented response with no reconfirmation of the response will be listed with stable disease.

12.2 Non-target Lesions

All other lesions (or sites of disease) not included in the “target disease” definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent.”

- 12.2.1 Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- 12.2.2 Non-complete response (non-CR)/Non-progression (non-PD):** Persistence of one or more non-target lesion and/or maintenance of tumor marker level above the upper limits of normal.
- 12.2.3 Progression (PD):** Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

12.3 Evaluation of Best Overall Response

The best overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria (see [Section 12.5](#)).

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD
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Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration” on the Off-treatment Form (C-300) under “other.” Every effort should be made to document the objective progression even after discontinuation of treatment.
- Conditions that may define early death include patients that have died without documentation of disease progression and before it was time to conduct the first tumor reassessment. Inevaluable patients are defined as not having received protocol treatment (regardless of how much was received) and no follow-up assessment completed before initiation of alternative treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.4 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

12.4.2 Chest X-ray: Lesions on chest X-ray are not acceptable as measurable lesions. A CT scan of the chest (with abdomen and pelvis if needed) must be used to evaluate measurable disease in this trial. For pelvic and/or abdominal lesions an MRI may be used to evaluate measurable disease. The imaging modality used to determine the initial measurement should continue to be used consistently for subsequent measurement evaluations.

12.4.3 Conventional CT of the chest should be performed with contrast if possible and with cuts of 2.5 mm in slice thickness contiguously (see [section 6.3](#)). Spiral CT is preferred. CT scans of the abdomen, and pelvis may also be performed using standard slice thickness (5 mm).

12.4.4 Endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

12.5 Confirmation Measurement/Duration of Response

12.5.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than four weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of six to eight weeks.

12.5.2 Duration of Overall Response

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

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

12.5.3 Duration of Stable Disease

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

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Duration of Treatment

13.1.1 CR, PR, or SD: Continue treatment until the appearance of disease progression.

13.1.2 Disease Progression: Give a minimum of two cycles of therapy. Remove from protocol therapy any patient with rapid disease progression. Document details, including tumor measurements, on C-2000.

13.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on Form C-260.
- Follow the patient for survival, secondary malignancy, and new primaries.

14.0 STATISTICAL CONSIDERATIONS

14.1 Background and Rationale for Update #4

CALGB 30901 was activated on 4/15/2010. In the original protocol design (30901-01, 30901-02 and 30901-03), we assumed that arm A (observation) would produce a median PFS of 3 months during the maintenance phase. Arm B (experimental) would have a 67% improvement in median PFS to 5 months. Under constant hazards, this corresponds to a hazard ratio $\lambda_A/\lambda_B=1.67$. With 90 eligible patients (45 per arm) randomized to Arm A and Arm B with a 1:1 allocation and an accrual rate of 4 randomized patients per month and an additional follow-up of 12 months after the enrollment of the last patient, the study had approximately 86% to reject the null hypothesis $\lambda_A/\lambda_B = 1$ when the true $\lambda_A/\lambda_B=1.67$ using a log rank test at a 1-sided

significance level of 0.10. With an allowance of 5% ineligibility/cancellation rate, a maximum of 96 (90 eligible) patients, or 48 (45 eligible) per arm, were to be accrued.

As of November 18, 2014, 38 out of 55 registered patients were randomized. In the last 12 months, the registration rate has been approximately 1.5 patients per month and the randomization rate is approximately 1 patient per month. The accrual rate is lower than we wish due to rarity of malignant pleural mesothelioma and existing, although unproven, clinical care patterns of offering maintenance therapy. The purpose of this amendment is to reduce the number of randomized patients by targeting a bigger effect size while maintaining the same level of Type I error in the original design. Instead of targeting a 2-month increase in median PFS, the amendment is looking for a 3-month increase in median PFS, which corresponds to a hazard ratio $\lambda_A/\lambda_B = 2$. We believe that a 3-month increase relative to observation in median PFS is justifiable for malignant mesothelioma patients who have achieved stable disease after the first line therapy. The interim analysis plan has been changed accordingly to have a futility test conducted after half of the total events have been observed. As a result, a maximum of 63 patients (60 eligible) after achieving stable disease from the first line chemotherapy will be randomized. The valuable data collected from this randomized phase II trial will help us to decide if a randomized phase III trial is worthy to pursue in the future.

14.2 Overview of Study Design

This will be a randomized phase II study with a primary endpoint of progression free survival. All patients will be treated initially with pemetrexed plus either cisplatin or carboplatin at the discretion of the treating physician. Patients documented to have a complete or partial radiologic response, or stable disease after completion of 4, 5 or 6 cycles will be eligible for enrollment. Patients will be stratified by first-line regimen (cisplatin vs. carboplatin) and histologic subtype (epithelioid vs. other) and randomly assigned to Arm A or Arm B with 1:1 allocation using a permuted block scheme (20). Arm A will be monitored for progression. Arm B will continue on chemotherapy with pemetrexed until disease progression. All patients will be followed for a maximum of 3 years from the date of randomization. The primary endpoint will be progression free survival, which is the time from patient randomization to disease progression or death from any cause, whichever comes first. An interim analysis is planned when accrual reaches 28 events (or 50% of information). Secondary objectives include (1) to determine if maintenance therapy with pemetrexed improves overall survival; (2) to evaluate frequency of responses to maintenance therapy with pemetrexed; (3) to assess toxicity of maintenance therapy with pemetrexed; (4) to assess whether biomarkers correlate with disease status; and (5) to determine the association between volumetric measurement of tumor response and usual methods of modified RECIST criteria.

CT scans will be performed in both arms every 6 weeks for 6 months, then every 9 weeks for 6 months and then every 12 weeks until disease progression for a maximum of 3 years from the date of randomization. The choice of chemotherapy regimen at the time of progression is at the discretion of the physician. Specifically, patients in Arm A would be allowed to receive treatment with pemetrexed at that time.

14.3 Sample Size Determination

In a recent phase III trial, treatment with pemetrexed and cisplatin had a median progression free survival (PFS) of 6 months and median overall survival (OS) of 12 months (1). For the purpose of sample size determination, we assume that (i) arm A will produce a median PFS of 3 months during the maintenance phase. Arm B will have a 67% improvement in median PFS to 5 months. Under constant hazards, this corresponds to a 3 month PFS of 50% for Arm A and 66% for the experimental arm (Arm B) and a hazard ratio $\lambda_A/\lambda_B = 1.67$; (ii) 90 eligible patients (45 per arm)

will be randomized to Arm A and Arm B with 1:1 allocation; (iii) an accrual rate of 4 randomized patients per month and an additional follow-up of 12 months after the enrollment of the last patient; (iv) a planned look at 50% information. Using a log rank test at a 1-sided significance level of 0.10, the study has approximately 86% power to reject the null hypothesis $\lambda_A/\lambda_B = 1$ and accept the alternative hypothesis $\lambda_A/\lambda_B > 1$ when the true $\lambda_A/\lambda_B = 1.67$. We will closely monitor the first 12 randomized patients on Arm B for treatment related adverse events. If 4 or more out of the 12 patients develop grade 3 or higher drug related adverse events, the study team will either recommend a reduction in the starting dose or permanently terminate the study.

14.3.1 Amended Sample Size Determination (Effective 01/15/15)

In a recent phase III trial, treatment with pemetrexed and cisplatin had a median progression free survival (PFS) of 6 months and median overall survival (OS) of 12 months (1). For the purpose of sample size determination, we assume that (i) arm A will produce a median PFS of 3 months during the maintenance phase. Arm B will have a 100% improvement in median PFS to 6 months. Under constant hazards, this corresponds to a 3 month PFS of 50% for Arm A and 70.7% for the experimental arm (Arm B) and a hazard ratio $\lambda_A/\lambda_B = 2$; (ii) 60 eligible patients (30 per arm) will be randomized to Arm A and Arm B with 1:1 allocation; (iii) an accrual rate of 2 patients per month and an additional follow-up of 6 months after the enrollment of the last patient; (iv) a planned look at 50% information. Using a log rank test at a 1-sided significance level of 0.10, the study has approximately 91% power to reject the null hypothesis $\lambda_A/\lambda_B = 1$ and accept the alternative hypothesis $\lambda_A/\lambda_B > 1$ when the true $\lambda_A/\lambda_B = 2$.

14.4 Logistics & Patient Accrual

With allowance of 5% ineligibility and an expected 70% initially registered patients remaining progression free after 4, 5, or 6 cycles of combination therapy, we expect to register 137 patients and to randomize 96 patients. Once 96 patients (90 eligible) have been accrued, a notice suspending accrual will be issued to the Group via an e-mail broadcast announcing termination of accrual effective within 10-14 days. On average, CALGB has accrued approximately 3-8 patients per month in mesothelioma trials. The three most recent mesothelioma trials (CALGB 30101, 30107 and 30307) accrued 5-8 patients per month. Assuming an accrual rate of 4 randomized patients per month, we expect target accrual will be met after approximately 3 years.

14.4.1 Amended Logistic and Patient Accrual (Effective 01/15/15)

With allowance of 5% ineligibility and an expected 67% initially registered patients remaining progression free after 4, 5, or 6 cycles of combination therapy, we expect to register 94 patients and to randomize 63 patients. Once 63 patients (60 eligible) have been randomized, a notice suspending accrual will be issued to the Group via an e-mail broadcast announcing termination of accrual effective within 10-14 days. On average, CALGB has accrued approximately 3-8 patients per month in mesothelioma trials. The three most recent mesothelioma trials (CALGB 30101, 30107 and 30307) accrued 5-8 patients per month. CALGB 30901 was activated on 4/15/2010. As of November 18, 2014, a total of 55 patients were registered and 38 patients were randomized after achieving stable disease of the first line chemotherapy. Assuming that 2 patients are registered per month, we expect approximately an additional 20 months after Update #4 is issued to reach the target accrual.

14.5 Analytic Methods Including Plans for Interim Analysis

Interim analysis for futility will be conducted when we have 28 cumulative events (50% information) on both arms. As of November 18, a total of 23 events have been observed. Since this is a relatively small randomized phase II trial, interim analysis will focus on testing futility.

At the futility analysis, we will compare the distribution of the PFS of the experimental with the standard arm. If the observed hazard ratio (experimental/standard) is greater than or equal to 1.0, then trial will be terminated early at the interim analysis for futility (i.e., the experimental arm will be considered ineffective in this disease population) and the results will be reported. If the observed hazard ratio of the experimental arm relative to the standard arm is less than 1.0, then the trial will continue to the full target accrual. Early stopping for futility using this rule is found to result in minimal loss of power (less than 2%) for the primary hypothesis test (21).

The primary analysis will include all randomized patients but exclude ineligible patients or patients who are canceled from the study before receiving any protocol treatment.

Progression free survival (PFS) is defined as the time from registration to disease progression or death of any cause, whichever comes first. Overall survival (OS) is defined as the time from registration to death of any cause. The primary analysis of comparing the patients continued on chemotherapy with pemetrexed (Arm B) relative to the patients discontinued from chemotherapy (Arm A) will be conducted using one-sided stratified log rank test with a significance level of approximately 0.10 corresponding to standardized Z statistics boundary of 1.316.

The product limit estimator developed by Kaplan and Meier will be used to graphically describe PFS and OS (22). From these product limit estimates, median PFS, median OS, 3-month PFS, 12-month OS rate and their 95% confidence intervals will be estimated for patients randomized to each arm. Cox proportional hazards model (23) will be used to estimate the hazard ratios and their 95% confidence intervals of the experimental regimen relative to the control group with and without adjusting for baseline prognostic factors. As an exploratory analysis, survival endpoints of the two arms will be compared using log rank test (24). The frequency of best response (CR+PR) to each arm will be tabulated and its 95% exact binomial confidence intervals will be computed. Response rates (including complete and partial response) will be tested using Fisher's exact test (25). Gender, race and ethnicity will be analyzed as covariates and these results will be reported. Frequencies of toxicities will be tabulated for patients on maintenance therapy with pemetrexed.

14.6 Statistical Consideration for Correlative Sciences

The correlation of PFS and OS with serum biomarkers, soluble mesothelin related peptide (SMRP) and osteopontin, and their changes with treatment will be examined using a log rank test for categorical variables and using Cox's proportional hazard model for continuous variables after adjusting for other prognostic factors. The optimal threshold for these biomarkers will be determined univariately using maximally selected log rank test with adjusted p-values. The correlation of PFS, OS, RR with thymidylate synthase expression will be examined similarly. The Mann-Whitney U test or Fisher's exact test will be applied as appropriate to assess differences or proportions of genetic data for TYMS, DPYD and MTHFR genes. Tumor response classification using volumetric measurement will be compared to usual methods of modified RECIST criteria and the level of agreement will be obtained using the kappa statistic.

15.0 CORRELATIVE AND IMAGING SUBSTUDIES

15.1 SMRP and Osteopontin Levels

Patients who receive all 4 cycles of pemetrexed with cisplatin or carboplatin and then are randomized to either the treatment or observation arm will have blood samples obtained at 3 distinct times during the course of the study: Baseline, prior to cycle 3 (week 6), and at the time of progression. Procedures for collecting and shipping the specimens are detailed in [Section 6.2](#).

Two specific studies will be carried out on the samples obtained. The first will be to determine the circulating levels of osteopontin in plasma and SMRP in serum of patients prior to treatment and following therapy. The circulating levels of osteopontin and SMRP will be determined using commercially available ELISA kits (R and D Systems; Mesomark). These will be carried out in the laboratory of [REDACTED] (University of Minnesota) as his laboratory has previously carried out on the serum of lung cancer patients.

15.2 Tumor Tissue Expression of Thymidylate Synthase (TS)

TS expression in tumor tissue will be assessed by semiquantitative immunohistochemistry (IHC) using commercially available monoclonal antibodies (TS (2D8.D11) from Santa Cruz Biotechnology, Inc.) and automated IHC instrumentation. Determination of TS overexpression will be performed on unstained tumor tissue sections that have been placed onto glass slides. The Alliance Biorepository at Ohio State will provide five slides containing unstained sections for each case, which will be evaluated for TS expression and IHC control reactions.

Paraffin embedded tissue sections are cut at 4 microns, deparaffinized with xylene and hydrated through graded alcohols and then rinsed in distilled water. The Biogenex Antigen Retrieval procedure is carried out in a steamer under pressure. The tissues are rinsed with distilled water and are subsequently rinsed with PBS after each step. They are treated with Peroxide block, Power block, Avidin, Biotin and are incubated with the primary antibody specific for the antigen to be demonstrated for 30-60 minutes. Sections are then incubated with MultiLink antibody (a biotinylated anti-immunoglobulin in PBS) and followed by incubation with the Label (Peroxidase-conjugated streptavidin). The antibody complex is then made visible by addition of a chromogen substrate until adequate color development is seen. Slides are washed in water to stop the reaction, counterstained, dehydrated, cleared and mounted with an aqueous mountant. This procedure is performed using an automated staining protocol on the BioGenex I6000 autostainer with Biogenex reagents.

15.3 Analysis of Genetic Variants in the TYMS, DPYD and MTHFR Genes

DNA will be extracted from 10 mL of whole blood collected into an EDTA- anticoagulated vacutainer. This DNA will be used for the analysis of constitutional genetic variants in the TYMS, DPYD, and MTHFR genes. Real time PCR will be used to assess the genetic status of each study patient with respect to the markers mentioned as these have been shown to affect the efficacy of therapeutics targeting thymidylate synthase.

15.4 Volumetric Tumor Measurements

In this study, in addition to CT response evaluation by modified RECIST criteria (15), novel methods of radiologic assessment for mesothelioma will be used. These include specialized assessments of CT scans developed by [REDACTED] (MSKCC) and [REDACTED] (U. of Chicago). At the University of Chicago, this involves semi-automated measurements of the pleural rind (26). At MSKCC, computerized modeling that extracts pleural disease from surrounding chest wall and mediastinal structures is used to subsequently allow calculations of tumor volume (18). Mesothelioma tumor volumes have been associated with outcomes in one surgical study (17). In order to facilitate these studies, contrast enhanced CT scans at baseline, and subsequent 6, 9, and 12-week intervals will be performed using 2.5 mm cuts. This CT data in digital format will be submitted to the Imaging Core Lab at Ohio State which will collate and make available for analysis to [REDACTED]

Response status, as determined by modified RECIST will be used as the overall response in this trial. However, the semi-automated methods and the changes in tumor volumetrics described

above will also be calculated and compared as an exploratory endpoint to the modified RECIST in terms of time to response, time to progression and reproducibility.

16.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by federal regulations to report serious adverse events as defined below. Investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

All reactions determined to be reportable in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (CTEP-AERS).

16.1 CALGB 30901 Reporting Requirements

CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of Treatment

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)				
NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)				
An adverse event is considered serious if it results in ANY of the following outcomes:				
<ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	
<p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report. ○ “10 Calendar Days” - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE. 				
<p>¹ Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p>Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p>				

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
 - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
 - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

16.2 Additional Instructions or Exclusions from CTEP-AERS Expedited Reporting Requirements for CALGB 30901:

- Grade 3/4 myelosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 3/4 diarrhea or mucositis and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study form C-1001.
- CTEP-AERS reports are to be submitted electronically using CTEP-AERS <http://eapps-ctep.nci.nih.gov/ctepaers/>.
- The reporting of adverse events described above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms.
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Death due to progressive disease should be reported as Grade 5 “Disease progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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