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SWOG

A RANDOMIZED PHASE II TRIAL OF CARBOPLATIN-PACLITAXEL WITH OR WITHOUT RAMUCIRUMAB IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED, RECURRENT, OR METASTATIC THYMIC CARCINOMA.

NCT#03694002

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AGENTS:

Commercially Available Agents:
Carboplatin (CBDCA) (NSC-241240)
Paclitaxel, Taxol® (NSC-673089)

SWOG Held IND Agents:
Ramucirumab (NSC-749128) (IND 139595)

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
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NRG/NRG Oncology
SWOG/SWOG

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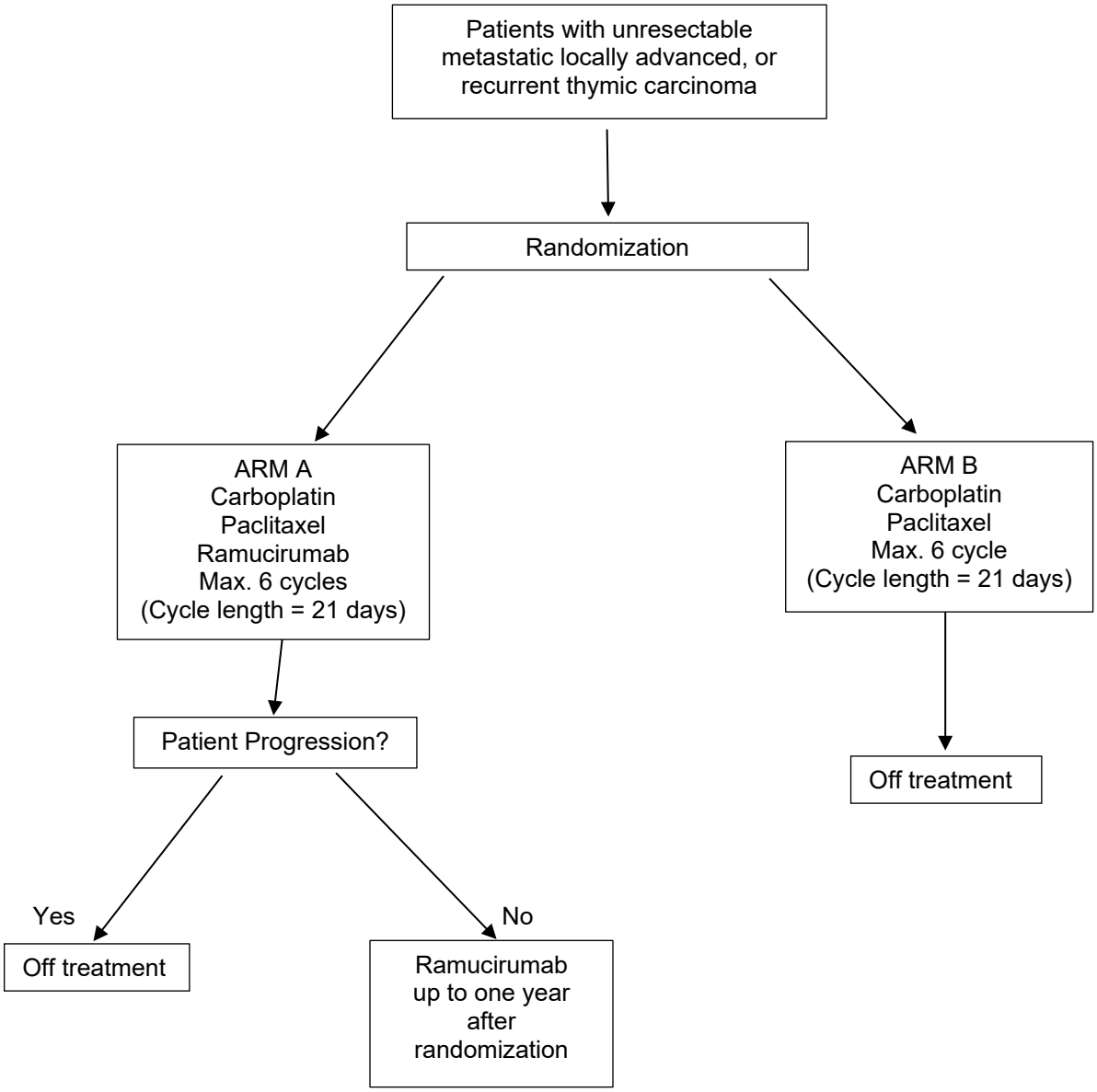
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol 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. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM user ID and password at the following url: www.swog.org.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site 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.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 lungquestion@crab.org **For treatment or toxicity related questions** contact the Study Chairs Anne Tsao, M.D. and Marianna Koczywas, M.D., at S1701Medical@swog.org.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA


Patients with unresectable metastatic locally advanced, or recurrent thymic carcinoma
Randomization
ARM A
Carboplatin
Paclitaxel
Ramucirumab
Max. 6 cycles
(Cycle length = 21 days)
ARM B
Carboplatin
Paclitaxel
Max. 6 cycle
(Cycle length = 21 days)
Patient Progression?
Off treatment
Yes
No
Off treatment
Ramucirumab up to one year after randomization

1.0 OBJECTIVES

1.1 Primary Objective(s)

a. The primary study objective is to compare progression-free survival between patients with incurable unresectable locally advanced, or recurrent, or metastatic thymic carcinoma randomized to carboplatin-paclitaxel with or without ramucirumab

1.2 Secondary Objective(s)

a. To evaluate the frequency and severity of toxicity of carboplatin-paclitaxel with or without ramucirumab in this patient population

b. To compare the response rate (complete response, partial response, confirmed and unconfirmed) between treatment arms in the subset of this patient population with measurable disease

c. To compare disease control rate (complete response, partial response, confirmed or unconfirmed, stable disease) between treatment arms in the subset of this patient population with measurable disease

d. To compare overall survival between treatment arms

1.3 Additional Objective(s)

a. To bank specimens for future research

2.0 BACKGROUND

Thymic carcinoma is a rare malignancy that arises from the thymus. It is histologically classified as WHO type C thymoma and is a distinct entity from thymomas – they are composed of highly atypical cells similar in features to other carcinomas and lack any immature T-cell lymphocytes. Most thymic carcinomas are well-differentiated squamous cell carcinomas but other histologies such as mucoepidermoid carcinoma, basaloid carcinoma, clear cell carcinoma, sarcomatoid carcinoma, small cell carcinoma, and anaplastic/undifferentiated carcinoma can occur. Unlike thymoma (WHO type A, AB, B), development of myasthenia gravis and other paraneoplastic syndromes are rare in thymic carcinoma.

Thymic carcinoma has an incidence of 1.3 per 1000000 persons per year in the USA. *(1)* Patients with this disease are typically between 40 and 60 years old and are more likely to have locally invasive or distant metastasis than patients with thymoma WHO types A-B. *(2,3)* To date, there are few trials that have evaluated frontline chemotherapy regimens for thymic carcinoma. The current literature, based on retrospective analyses and small Phase II non-randomized trials (see Table 1), indicates that carboplatin-paclitaxel is the preferred regimen for thymic carcinoma. *(4,5,6,7,8)* It is the recommended regimen in the NCCN guidelines.

In thymic carcinoma, carboplatin-paclitaxel yields response rates of 21.7% to 37.5%. *(9,10,11,12,13)* The median PFS ranges from 5 to 8.6 months, while median OS ranges from 20 to 49.4 months. Of note, 3 of the listed prospective trials, and the retrospective study are from Japan. *(14,15,16,17)* However, the Lemma et al. *(18)* study was conducted in 4 centers in the United States. It is clear, based on these clinical results, there is a critical need for developing novel therapies in thymic carcinoma.

Table 1: Single-arm clinical trials with carboplatin-paclitaxel in thymic carcinoma patients.

Author	Dose	Thymic Carcinoma (n)	ORR	Median PFS (months)	Median OS (months)
Igawa et al.[3]	Carbo AUC 6 Paclitaxel 200 mg/m^2	11	36%	7.9	22.7
Furugen et al.[4]	Carbo AUC 6 Paclitaxel 200 mg/m^2	16	37.5%	8.6	49.4
Lemma et al.[5]	Carbo AUC 6 Paclitaxel 225 mg/m^2	23	21.7%	5	20
Takeda et al.[6]	Carbo AUC 6 Paclitaxel 200 mg/m^2	40	36%	7.5	NR
Maruyama et al.[7]*	Carbo AUC 6 Paclitaxel 200 mg/m^2	5	100%	11**	32

* retrospective single institution analysis
** reported as median duration of response

Novel targets for thymic carcinoma have been challenging to identify. Several publications have reported anecdotal C-KIT mutations (see Table 2) that have responded to targeted agents, but other case series suggest that the benefit of the angiogenic agents may be independent of KIT mutations. Several biomarkers of the angiogenic pathway, such as VEGF-A, VEGFR-1, and VEGFR-2 are known to be overexpressed in thymic carcinomas, and their immunohistochemical (IHC) expression levels correlate with tumor invasiveness and clinical stage. *(19,20)* In addition, serum VEGF is also highly upregulated in thymic carcinoma patients, suggesting an active pathway in carcinogenesis. *(21)*

Anti-angiogenic agents have been assessed in combined trials enrolling both thymomas and thymic carcinomas in small early phase clinical trials. However, many of these reports were derived from monotherapy agent studies, and none are in combination with chemotherapy, where a synergistic effect with anti-angiogenic agents may be found. However, even as monotherapy, this class of agents does appear to have clinical benefit in both thymoma and thymic carcinomas. For thymoma patients, a Phase I trial of SU14813 (VEGFRs, PDGFRs, KIT, and FLT-3), enrolled 4 thymoma patients with 2 patients achieving a PR with response durations of 15.3 and 9.0 months. *(22)* Motesanib diphosphate (AMG 706), and oral inhibitor of VEGFR-1,2,3, PDGFR and KIT, stabilized a metastatic thymoma patient for 1 year. *(23)* Other thymoma case reports have noted benefit with sorafenib (inhibits VEGFR, PDGFR, Raf family kinases) as monotherapy and in combinations. (24)

Specifically for thymic carcinoma, 5 separate case reports (see Table 2) showing durable partial responses to sorafenib in patients with refractory, previously treated thymic carcinoma.

(25,26,27,28,29) A case series of 4 chemo-refractory thymic carcinoma patients reported significant response durations over 1 year with sunitinib (inhibits all PDGFR, all VEGFR, KIT, CSF1R, FLT3, and glial cell line-derived neurotropic factor receptor). *(30)* A prospective Phase II trial administering sunitinib in platinum-refractory thymoma/thymic carcinoma reported in the thymic carcinoma cohort (n=23 evaluable) a 26% PR and 65% stable disease (SD). *(31)* In this trial, there were no mutations in KIT detected in thirteen of the 25 patients. 4 of the 6 responders were assessed and did not carry actionable mutations; suggesting that the response to sunitinib was independent of a KIT mutation. A Phase II trial of bevacizumab-erlotinib (NCT 00369889) in refractory thymoma and thymic cancers has completed enrollment, but results are still pending.

Table 2: Clinical trials or case reports evaluating anti-angiogenic agents in thymic carcinoma patients.

Author	Agent	Thymic Carcino-ma (n)	ORR	Median PFS (months)	Median OS (months)	KIT Mutations and/or Protein expression
Thomas et al.[20]	Sunitinib	25	26%	7.2	Not reached 1-yr OS 78%	No mutations detected in 13 patients (4 of 6 responders had tumor evaluation)
Strobel et al.[19]	Sunitinib	4	3 PR 1 PR/SD	2 not reported, 18+ months, 14+ months	2 not reported, 40+ months, 4 months	No mutations detected. High expression of C-KIT IHC on all 4 cases.
Pagano et al.	Sorafenib	5	2 PR 2 SD 1 PD	28 weeks	92 weeks	1 C-KIT mutation exon 17 (D820E) in responder.
Li et al.[16]	Sorafenib	1	1 PR	9+ months	Not reported	High expression of C-KIT IHC; mutations not assessed.
Bisagni et al.[14]	Sorafenib	1	1 PR	15+ months	Not reported	C-KIT missense mutation exon 17 (D820E)
Disel et al.[15]	Sorafenib	1	1 PR	6+ months	Not reported	C-KIT deletion mutation exon 11, also amplified
Catania et al.[18]	Sorafenib	1	1 PR	6 months	3 years	C-KIT missense mutation exon 13 (K642E)
Neuhaus et al.[17]	Sorafenib	1	1 PR	18 months	21 months	C-KIT mutations not assessed. C-KIT IHC negative. EGFR gene amplification noted.
Anti-angiogenic Trials that include thymic carcinoma patients						
NCT00369889	Bevacizumab Erlotinib	refractory	-	-	-	-
NCT01621568	Sunitinib alternate dosing	refractory	-	-	-	

Author	Agent	Thymic Carcino-ma (n)	ORR	Median PFS (months)	Median OS (months)	KIT Mutations and/or Protein expression
	with 3-week cycle					
NCT02623127	Sunitinib	refractory	-	-	-	-

Note – several studies included other tumor types, such as thymoma or other solid tumors. Table 2 depicts only the thymic carcinoma patients.

Currently, there is 2 active thymic malignancy trials in the world with anti-angiogenic agents in the chemo-refractory salvage setting. The KOSMIC trial (NCT02623127), a Phase II study of sunitinib, is being conducted in South Korea with the primary endpoint of ORR. A second trial that utilizes an alternative schedule of sunitinib (NCT01621568) is ongoing at Indiana University.

Recently, ramucirumab**,** a fully humanized monoclonal antibody that targets VEGFR-2 has achieved regulatory approval in several tumor types. It has demonstrated activity as single agent and in combination with paclitaxel in 2 large, randomized trials for the treatment of refractory gastroesophageal cancer. *(32)* Also, ramucirumab was FDA approved in the second line setting for NSCLC in combination with docetaxel (REVEL trial). *(33)* The addition of ramucirumab to docetaxel improved response rates (22.9% vs. 12.6%); median PFS (4.5 vs. 3 months); and median OS, the primary study end-point (10.5 vs. 9.1 months). *(34,35)* Based on its positive synergistic activity with chemotherapy and its reasonable preservation of quality of life, ramucirumab would be a potential agent to study in thymic carcinoma in combination with chemotherapy.

The pre-clinical evidence of overexpression of VEGF receptors in thymic carcinoma together with the preliminary results of clinical activity of VEGFR inhibitors in refractory thymic carcinomas, suggest that anti-angiogenic therapy is a rationale therapeutic option and should be further evaluated in thymic carcinoma patients. This benefit appears to be independent of any actionable mutation and should be investigated further.

Given the positive results in gastroesophageal and NSCLC, there is significant rationale to believe that the combination of ramucirumab with chemotherapy will improve clinical outcomes of inoperable, advanced thymic carcinomas. As there is currently no FDA approved targeted agent in thymic carcinoma, there is a significant opportunity for ramucirumab to become utilized in the front-line setting for this orphan disease. We hypothesize that the triplet regimen of carboplatin-paclitaxel-ramucirumab may have efficacy in thymic carcinoma. Of note, the triplet regimen of carboplatin-paclitaxel with VEGF ligand inhibitor bevacizumab, is utilized in NSCLC and is a well-tolerated frontline regimen. We do not anticipate any safety issues or have any concerns with replacing bevacizumab with ramucirumab.

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.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	3	1	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0		0
Black or African American	3	1	0	0	4
White	39	12	5	1	57
More Than One Race	1	0	0	0	1
Total	46	14	5	1	66

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, carboplatin and paclitaxel are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, ramucirumab is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 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. 65% of the dose is excreted in the urine within 12 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).

Carboplatin is also supplied as a solution for injection in vials containing 50 mg, 150 mg, 450 mg, and 600 mg with a concentration of 10 mg/mL.

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 8 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.

3.2 Paclitaxel, Taxol® (NSC-673089)

a. PHARMACOLOGY

Mechanism of Action: 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. Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stabilization results in the inhibition of the normal dynamic reorganization of the microtubule network that is required for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle which interrupt mitosis.

b. PHARMACOKINETICS

1. Absorption: Following intravenous administration of paclitaxel, the drug, plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is a result, in part, of a relatively slow efflux of paclitaxel from the peripheral compartment.

2. Distribution: *In vitro* studies of paclitaxel binding to human serum proteins using concentrations from 0.1 to 50 microgram/mL indicated that between 89%-98% of paclitaxel is protein bound. A Phase III study comparing 3- and 24-hour infusion showed that with a 24-hour infusion of paclitaxel, a 30% increase in dose (135 mg/m^2 vs 175 mg/m^2) increased the maximum plasma concentration (Cmax) by 87%, whereas the area under the plasma concentration-time curve from time 0 to infinity [AUC(0-∞)] remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the Cmax and AUC(0-) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of paclitaxel, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

3. Metabolism: Paclitaxel is metabolized via the cytochrome P450 isoenzyme CYP2C8 to one major inactive metabolite (6-alpha-hydroxypaclitaxel), and via the cytochrome P450 isoenzyme CYP3A4 to 2 minor inactive metabolites (3-para-hydroxypaclitaxel and 6-alpha, 3-para-dihydroxypaclitaxel). There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times upper limit of normal and therefore, caution should be used when administering paclitaxel to patients with liver dysfunction.

4. Elimination: Following the administration paclitaxel, the cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. Using radiolabeled paclitaxel infusion showed that unchanged paclitaxel in the feces accounted for 5% of the administered dose while total recovery of paclitaxel and its metabolites in the feces accounted for 56% to 101% of the administered

dose. The elimination half-life of paclitaxel ranged between 13.1 and 52.7 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Paclitaxel: adverse effects reported in >20% of patients include anemia, infection, diarrhea, nausea, vomiting, mucositis, allergic reaction which may cause rash, hypotension, wheezing, shortness of breath, facial edema and swelling of the throat, asthenia, parathesia, and alopecia.

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.

Post marketing experience with paclitaxel protein-bound particles for injectable suspension (Abraxane®) indicated reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with Abraxane. Most of the affected individuals were previously exposed to

cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.
When paclitaxel protein-bound particles for injectable suspension was administered in combination with gemcitabine, sepsis occurred in patients with or without neutropenia. Risk factors for severe or fatal sepsis included biliary obstruction or presence of biliary stent.

Refer to the current FDA-approved paclitaxel package insert for the most comprehensive and up to date information on adverse reactions.

I. Pregnancy and Lactation: Pregnancy Category D. 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 implanatations 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.

II. Drug Interactions: Paclitaxel metabolism is catalyzed by cytochrome P450 (CYP450) isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is co-administered with substrates, inhibitors, and inducers of CYP3A4 and CYP2C8. In addition, plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and liposomal doxorubicin are used in combination. Although this interaction has not been reported with doxorubicin hydrochloride injection, the potential for the same reaction is possible. In a Phase I trial, sequential infusions of escalating doses of paclitaxel and cisplatin showed that administration of paclitaxel after cisplatin may decrease the clearance of paclitaxel and cause profound myelosuppression.

Due to potential drug interactions, a complete patient medication list, including paclitaxel, should be screened prior to initiation of and during treatment with paclitaxel. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Paclitaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.3 Ramucirumab (Cyramza™, IMC-1121B, LY3009806) (NSC-749128, IND #139595)

a. PHARMACOLOGY

Mechanism of Action: Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2). The binding of ramucirumab to VEGFR2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D) and as a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream intracellular signaling components, including Erk1/Erk2, neutralizing ligand-induced proliferation and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an *in vivo* animal model.

b. PHARMACOKINETICS

1. Absorption: Ramucirumab is given via intravenous infusion.

2. Distribution: In population pharmacokinetic models involving 2,820 patients, the mean volume of distribution (Vd) of ramucirumab at steady state was 4.47 L.

3. Metabolism: As a monoclonal antibody, ramucirumab is largely confined to the extracellular space, and elimination is primarily by catabolism.

4. Elimination: The mean clearance of ramucirumab was 0.0132 L/hour. The mean terminal half-life was 10.2 days.

c. ADVERSE EFFECTS

1. Adverse Effects: The below summary is based on patients receiving single-agent ramucirumab for gastric cancer (N=236). The type and frequency of adverse events observed vary when ramucirumab is administered in combination with other antineoplastic agents. Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Version: April 2022

Adverse Events with Possible Relationship to Ramucirumab		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia* Neutropenia	
CARDIAC DISORDERS		
	Hypertension	Arterial thromboembolic events (myocardial infarction, cardiac arrest, cerebrovascular accidents, and cerebral ischemia)
GASTROINTESTINAL DISORDERS		
Abdominal pain	Diarrhea	Intestinal obstruction Gastrointestinal perforation
METABOLISM AND NUTRITION DISORDERS		
	Hypokalemia* Hyponatremia*	
NERVOUS SYSTEM DISORDERS		
	Headache	

Adverse Events with Possible Relationship to Ramucirumab		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
RENAL AND URINARY DISORDERS		
	Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	

* Serious events reported

Important adverse events, including serious adverse events, observed with ramucirumab across clinical trials and disease states: hemorrhage and gastrointestinal hemorrhage, infusion related reactions, impaired wound healing, Posterior Reversible Encephalopathy Syndrome (PRES), nephrotic syndrome, thyroid dysfunction, and worsening of pre-existing hepatic impairment.

2. Pregnancy and Lactation:

There are no available data on ramucirumab use in pregnant women. Based on its mechanism of action, ramucirumab can cause fetal harm. Avoid the use of ramucirumab in pregnant women and advise a pregnant woman of the potential risk to a fetus. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Contraception should be used during treatment and for at least 3 months after the last dose of ramucirumab. Based on animal models, ramucirumab may potentially impair female fertility.

Studies have not been conducted to assess ramucirumab's impact on milk production, its presence in breast milk, or its effects on the breast-fed child. It is not known whether ramucirumab is secreted in human milk. Women should not breastfeed during treatment with ramucirumab and for 2 months after the last dose.

3. Drug Interactions:
No clinically meaningful changes in the exposure of either ramucirumab or its concomitant drugs in the currently approved combinations, including paclitaxel, docetaxel, irinotecan (or its active metabolite, SN-38), and erlotinib were observed in patients with solid tumors. Studies indicate that it is unlikely for drug-drug interactions with concomitant administration of ramucirumab and durvalumab.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Ramucirumab is administered through a separate infusion line. The use of a protein sparing 0.22 micron in-line filter is recommended. The line should be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion. Do not administer as an intravenous push or bolus.

e. HOW SUPPLIED

1. Ramucirumab will be supplied free of charge by Eli Lilly and distributed by McKesson.

2. Ramucirumab is supplied in single-use, 50-mL glass vials. Each vial contains 500 mg of ramucirumab at a concentration of 10 mg/mL in a sterile, preservative-free solution. Each vial is stoppered with a chlorobutyl elastomer stopper laminated with FluroTec® (West Pharmaceutical Services, Inc., Exton, PA), and secured with an aluminum 2-piece flip-top seal.

   Ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL. The buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80.

   Ramucirumab is a clear to slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is 6.0.

   All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. Ramucirumab molecular weight is 146.8 kDa.

f. STORAGE, PREPARATION & STABILITY

1. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

2. Preparation:

   - Inspect vial contents for particulate matter and discoloration prior to dilution. If particulate matter or discolorations are identified, discard the vial.

   - Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.

   - Gently invert the container to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

   - Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).

   - Discard vial with any unused portion of ramucirumab, as the product contains no preservatives.

3. Compatibility information: Do not mix with dextrose containing solutions or infuse with electrolyte solutions or other medications.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Drug orders must be submitted by faxing the Drug Order Form – SWOG **S1701** to McKesson at the number listed on the order form. This form can be found on the CTSU website (www.CTSU.org).

2. Drug Handling and Accountability: Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

   Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.

3. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

Questions about drug orders, transfers, returns, or accountability should be addressed to protocols@swog.org.

4.0 STAGING CRITERIA

Not applicable for this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the On study Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or lungquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion
(http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm)

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have histologically or cytologically confirmed thymic carcinoma. Thymic carcinoma may be defined as “thymic epithelial malignancy, consistent with thymic carcinoma”, or “WHO Type C thymic epithelial tumor”, or “thymic epithelial malignancy” with radiographic imaging consistent with thymic carcinoma.

c. Patients must have unresectable thymic carcinoma, defined in Section 5.1.b., that is either locally advanced, recurrent, or metastatic.

d. Patients must not be candidates for localized surgery.

e. Patients must have measurable or non-measurable disease (See Section10.1) documented by CT or MRI. Measurable disease must be assessed within 28 days

prior to randomization. Non-measurable disease must be assessed within 42 days prior to randomization. The CT from a combined PET/CT may be used only if it is of diagnostic quality as defined in Section 10.1a. All known sites of disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

f. Patients must have a Zubrod performance status of 0 to 2 (See Section 10.4).

g. Patients must not have undergone major surgery within 28 calendar days prior to randomization, or minor surgery/subcutaneous venous access device placement within 7 calendar days prior to randomization. The patient must not have elective or planned major surgery to be performed during the clinical trial.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must not have had prior systemic anti-cancer therapy for locally advanced or metastatic unresectable thymic carcinoma.

b. If patients have recurrent unresectable thymic carcinoma, patients may have had prior neoadjuvant or adjuvant chemotherapy if treatment concluded ≥ 6 months prior to randomization.

c. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 calendar days prior to registration. Patient must not have brain metastases unless: (1) metastases have been treated and have remained controlled for at least 2 weeks following treatment, AND (2) patient has no residual neurological dysfunction off corticosteroids for at least 1 day.

d. Patients must not be candidates for radiation therapy with curative intent. Prior palliative radiation therapy is allowed if a period of 7 days has passed since the last dose was received and the patient has recovered from any associated toxicity at the time of randomization.

5.3 Clinical/Laboratory Criteria

a. Patients must have adequate hematologic function, as evidenced by an absolute neutrophil count (ANC) ≥1500/mcL, hemoglobin ≥ 9 g/dL (5.58 mmol/L), and platelets ≥100,000/mcL documented within 28 calendar days prior to randomization.

b. Patients must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5, and a partial thromboplastin time (PTT) ≤ 5 seconds above the institutional upper limit of normal (IULN) (unless receiving anticoagulation therapy) documented within 28 calendar days prior to randomization.

Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile 14 days prior to randomization.

c. Patients must not have experienced any Grade 3 or above GI bleeding within 84 calendar days prior to randomization

d. Patients must not have a history of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered “significant”) during the 84 calendar days prior to randomization.

e. Patients must have adequate hepatic function as defined by a total bilirubin ≤1.5 x the institutional upper limit normal (IULN), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x IULN. For patients with liver metastases, total bilirubin and AST or ALT must be ≤ 5.0 x IULN These tests must be documented within 28 calendar days prior to randomization.

f. Patients must not have any of following:
- cirrhosis at a level of Child-Pugh B (or worse) (See Appendix 18.1)
- cirrhosis (any degree) and a history of hepatic encephalopathy; or
- clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.

g. Patients must have adequate renal function as defined by a serum creatinine ≤ 1.5 x IULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute (that is, if serum creatinine is >1.5 x IULN, a 24-hour urine collection to calculate creatinine clearance must be performed) documented within 28 calendar days prior to randomization.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

h. Patient urinary protein must be ≤ 1+ on dipstick or routine urinalysis (UA); if urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours). These tests must be documented within 28 calendar days prior to randomization.

i. Patients must not have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to randomization.

j. Patients must not have a history of uncontrolled or poorly controlled hypertension (defined as >160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.

k. Patients must not be pregnant or nursing due to the risk of harming fetus or infant. Women/men of reproductive potential must have agreed to use an effective contraceptive method (hormonal or barrier method of birth control; abstinence) prior to randomization, during the study participation and for 4 months after the last dose of protocol treatment. A woman is 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 period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

l. Patients must not have experienced hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to randomization or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

m. Patients must not have a prior history of gastrointestinal perforation/fistula (within 6 months of randomization) or risk factors for perforation.

n. Patients must not have a serious or nonhealing wound, ulcer, or bone fracture within 28 calendar days prior to randomization.

o. Patients must not be receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents within 7 days prior to randomization. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

5.4 Specimen Submission Criteria

a. Patients must be offered the opportunity to participate in banking of specimens for future research as described in Section 15.1.

5.5 Regulatory Criteria

a. Patients ***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 13.3 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

Not applicable for this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Study Chairs Anne Tsao, M.D. and Marianna Koczywas, M.D., at S1701Medical@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at www.swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics, or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Premedication prior to carboplatin and paclitaxel infusions are recommended per institutional standards. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at treating investigator discretion.

7.2 Treatment

Note that women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

a. Arm A

Agent	Dose	Route	Day	Schedule
Ramucirumab	10 mg/kg	IV over 60min	1	Every 21 days
Carboplatin	AUC 6 *	IV	1	Every 21 days
Paclitaxel	200 mg/m^2	IV	1	Every 21 days

Note: 1 cycle = 21 days
* See Sections 18.2 and 18.3

Carboplatin, Paclitaxel, and Ramucirumab will be administered on Day 1 of Cycles 1-6. Note that Ramucirumab will be administered first over 60 minutes. The chemotherapy combination (carboplatin and paclitaxel) will be administered per institutional guidelines.

After 6 cycles of the chemotherapy combination, patients who have not progressed will receive maintenance ramucirumab alone on Day 1 of Cycle 7 and subsequent cycles for up to 1 year after randomization.

Vital signs (temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate) are to be performed before dose administration per institutional guidelines.

b. Arm B

Agent	Dose	Route	Day	Schedule
Carboplatin	AUC 6 *	IV	1	Every 21 days
Paclitaxel	200 mg/m^2	IV	1	Every 21 days

* Note: 1 cycle = 21 days
* See Sections 18.2 and 18.3

Carboplatin and Paclitaxel may be administered according to institutional guidelines. Completion of treatment is up to a maximum of 6 cycles.

Vital signs (temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate) are to be performed before dose administration per institutional guidelines.

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2)

b. Unacceptable toxicity

c. Treatment delay for any reason > 21 days (or as noted in Section 8.0)

d. Completion of treatment

Arm A: 6 cycles of chemotherapy combination + 1 year of ramucirumab after randomization

Arm B: Maximum of 6 cycles of chemotherapy combination

e. Patients may withdraw from the study at any time for any reason

7.4 Discontinuation of Treatment

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

7.5 Follow-Up Period

All patients will be followed until death or 2 years after randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

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

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for Serious Adverse Event reporting only. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0

b. Routine toxicity reporting

This study will use the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Dose Modification Guidelines

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. The treating physician can reduce the dose of only one of the 3 drugs if the toxicity is felt to be related to only one of the drugs.

d. Once dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

e. If all drugs are held > 21 days, patient must be removed from protocol treatment. If one drug is held for > 21 days, then that drug should be permanently discontinued and the other drug could be continued as long as the treating physician believes the patient is deriving clinical benefit**.**

f. If one drug is discontinued due to toxicity, patient may remain on other study drugs as long as the remaining therapy is well tolerated and according to the treating physician the patient is still deriving clinical benefit.

8.3 Dose Reductions for Carboplatin, Paclitaxel, and Ramucirumab

Dose Level	Carboplatin (AUC)	Paclitaxel (mg/m^2)	Ramucirumab (mg/kg)
0 (Starting Dose)	6	200	10
-1	5	175	8
-2	4	150	6
-3 *	Discontinue	Discontinue	Discontinue

* Dose reductions beyond this level are not permitted.

8.4 Paclitaxel/Carboplatin Dose Modifications

a. Hematologic Toxicity

Toxicity	**Paclitaxel**	**Carboplatin**
Neutropenia		
Grade ≤ 2	No dose modification	No dose modification
Grade 3	Hold therapy and repeat labs weekly until resolution to ≤ Grade 2. Depending on symptom resolution, treatment may resume at the next lower dose or remain the same. [1]	Hold therapy and repeat labs weekly until resolution to ≤ Grade 2.
Grade 4	Hold therapy and repeat labs weekly until	Hold therapy and repeat labs weekly until

Toxicity	Paclitaxel	Carboplatin
	resolution to ≤ Grade 2. Treatment may resume at the next lower dose. [1]	resolution to ≤ Grade 2.
Neutropenic fever		
Grade ≥ 4	Hold therapy and repeat labs weekly until resolution to ≤ Grade 2. Growth factor support is recommended. Treatment may resume at the same dose with growth factor support or can resume at the next lower dose. [1]	Hold therapy and repeat labs weekly until resolution to ≤ Grade 2.
[1] 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.		
Thrombocytopenia		
Grade 1	No dose modification	No dose modification
Grade ≥ 2	Hold therapy and repeat labs weekly until resolution to ≤ Grade 1.	Hold therapy and repeat labs weekly until resolution to ≤ Grade1. Treatment may resume at the next lower dose. [2]
[2] 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. Non-Hematologic Toxicity

Toxicity	Paclitaxel	Carboplatin
Neuropathy		
Grade ≤ 1	No dose modification	No dose modification
Grade 2	Hold protocol therapy until resolution to Grade ≤ 1.	Hold protocol therapy until resolution to Grade ≤ 1.
Grade ≥ 3	Discontinue therapy	Hold therapy, until ≤ Grade 2
Other non-hematologic toxicities		
Grade ≤ 2	No dose modification	No dose modification
Grade 3 or 4	Hold therapy until ≤ Grade 2	Hold therapy until ≤ Grade 2

c. Arthralgia/Myalgia

The following dose adjustments are based on the worst grade experienced of arthralgia/myalgia of any preceding treatment course.

Arthralgia/Myalgia	Paclitaxel	Carboplatin
Grade 0-1	No dose modification	No dose modification
Grade 2	Hold treatment until resolution to ≤ Grade 1. If post-medication dexamethasone (4 mg orally BID for 3-5 days) was incorporated in regimen, reduce by 1 dose level. If no dexamethasone was used, then prior to making any dose level reductions add regimen to subsequent courses.	No dose modification
Grade 3	Hold treatment until resolution to ≤ Grade 1. If post-medication dexamethasone (4 mg orally BID for 3-5 days) was incorporated in regimen, reduce by 1 dose level. If no dexamethasone was used, then prior to making any dose level reductions add regimen to subsequent courses.	No dose modification

d. Hepatic Toxicity (Paclitaxel dose modification only)

The following dose adjustments for paclitaxel are based on ALT, AST, and bilirubin serum levels and should be obtained within 7 days of treatment.

ALT and/or AST		Bilirubin	Paclitaxel
≤ Grade 1	and/or	≤ Grade 2	No dose modification
≥ Grade 2	and/or	≥ Grade 3	HOLD*

* Hold until ALT and/or AST resolution to ≤ Grade 1 and Bilirubin is ≤ Grade 2. If recovery of toxicity exceeds 2 weeks, discontinue from all protocol therapy, and remove patient from study.

If recovery of toxicity occurs within 2 weeks, reduce dose by 1 level above for both agents (paclitaxel and ramucirumab). No dose reduction will be done for carboplatin.

e. Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Patients are encouraged to take plenty of oral fluids. If symptoms persist despite maximal anti-emetic therapy, contact provider.

Diarrhea should be managed with appropriate anti-diarrheal therapy. Patients should be encouraged to take plenty of oral fluids. If symptoms do not decrease to Grade 1 or less with adequate anti-diarrheal therapy, contact provider.

f. Hypersensitivity Reactions to Paclitaxel

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

1. Mild symptoms (e.g., mild flushing, rash, pruritus) -Complete infusion. Supervise at bedside. No treatment required.

2. Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) -Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate (20 mg/hr.) for 15 minutes. If no further symptoms, resume infusion 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 principal investigator.* Record toxicity on flow sheets.

3. Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) -Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present and is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. Patient should discontinue all protocol therapy and be removed from study. Report as serious adverse event.

g. Other Toxicities

For any Grade 2, 3 or 4 toxicities not mentioned above, excluding hemoglobin, lymphocytes, alopecia or Grade 2 nausea, the treatment should be withheld until the patient recovers to ≤ Grade 1. If an abnormal laboratory value is reported, the toxicity should be possibly related to paclitaxel and carboplatin treatment to result in dose reduction. The paclitaxel and carboplatin treatment should then be resumed at dose level (-1) (permanent dose reduction). Dose reduction will be done for the drug that is most likely to have caused the toxicity. For Grade 1 toxicities, no dose reduction should be made.

In case patients develop nausea/vomiting/diarrhea or myelosuppression, supportive medications will be prescribed as per Clinical Center and ASCO guidelines.

8.5 Ramucirumab Discontinuations due to Toxicity

Table 1: Dose Interruptions for Ramucirumab

Toxicity	Grade	Dose Interruptions	Toxicity Management
Infusion-Related Reactions	Any Grade	No dose modifications.	Manage per institutional standard at the discretion of treating investigator. Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.).
	≤ Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	-Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. -Consider premedication per institutional standard prior to subsequent doses. -Steroids should not be used for routine premedication of ≤ Grade 2 infusion reactions.
	≥ Grade 3	Permanently discontinue protocol therapy.	-Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Table 2: Dose Modifications for Ramucirumab

Toxicity	Grade	Dose Modifications
Hypertension	Grade 1	No dose modification. Consider increased BP monitoring; start anti-hypertensive medication if appropriate.
	Grade 2 Asymptomatic	No dose modification. Begin anti-hypertensive therapy and continue protocol therapy.
	Grade 2 Symptomatic	Hold protocol therapy until symptoms resolve. Start or adjust anti-hypertensive medication.
	Grade 3	Hold protocol therapy until resolution of symptoms and returns to Grade 2.
	Grade 4	Permanently discontinue protocol therapy.
Impaired Wound Healing	Prior to planned surgery	Withhold ramucirumab for at least 28 days prior to surgery.
	After surgery	Do not administer ramucirumab for at least 14 days following major surgical procedure and until adequate wound healing. The safety of resumption after resolution of wound healing has not been established.

Toxicity	Grade	Dose Modifications
	Wound-healing complications developed during study treatment	Do not administer ramucirumab for at least 14 days following major surgical procedure and until adequate wound healing. The safety of resumption after resolution of wound healing has not been established.
Proteinuria	Grade 1	No dose modification.
	Grade 2 2+ proteinuria on urine dipstick	Check 24-hour urine protein levels. • If ≥ 2 gram/24 hours, hold protocol therapy until resolution to < 2 gram/24 hours. Restart ramucirumab at the next lower dose. • If the protein level ≥2 g/24 hours reoccur, interrupt ramucirumab and reduce the dose to the next lower level once the urine protein level returns to < 2 g/24 hours.
	≥ Grade 3 ≥ 3.5 gram/24 hours	Permanently discontinue protocol therapy. If patient experiences nephrotic syndrome, permanently discontinue protocol therapy.
Other Adverse Events	Grade 4	Permanently discontinue treatment immediately, except for Grade 4 fever or Grade 4 laboratory abnormality, in which case: First occurrence: Delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, may resume ramucirumab original dose at the discretion of the treating investigator. • If NOT resolved to Grade 0-1 within21 days, discontinue ramucirumab at treating investigator's discretion. Second occurrence: Delay ramucirumab until resolved to Grade 0-1. • If resolved to Grade 0-1, reduce ramucirumab by one dose level. If NOT resolved to Grade 0-1 within 21 days, discontinue ramucirumab at treating investigator's discretion.

Table 3: Dose Discontinuations for Ramucirumab

Toxicity	Grade	Dose Discontinuation
Arterial Thromboembolic Events, Gastrointestinal Perforation, and Hemorrhage/Bleeding	≥ Grade 3	Permanently discontinue ramucirumab.
Reversible posterior leukoencephalopathy syndrome	Any Grade	Permanently discontinue ramucirumab.
Congestive heart failure	≥ Grade 3	Permanently discontinue ramucirumab.
Liver injury/liver failure or Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis	Any Grade	Permanently discontinue ramucirumab.

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact Study Chairs Anne Tsao, M.D. and Marianna Koczywas, M.D., at S1701Medical@swog.org.

8.7 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.1 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm A Carboplatin (CBDCA), Paclitaxel (Taxol®), and Ramucirumab (Cyramza™, IMC-1121B, LY3009806)

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Maintenance ¥			Off Tx	Off Tx
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	C 7	C 8	Subseq C Ω	Prior to Prog *	After Prog α
PHYSICAL																								
History & Physical Exam	X	X			X			X			X			X			X			X	X	X	X	
Weight & Performance Status	X	X			X			X			X			X			X			X	X	X	X	
Disease Assessment Ø	X							X						X						X		X Ø	X Ø	
Toxicity Notation	X				X			X			X			X			X			X	X	X	X €	X €
Vital Signs ∑	X	X			X			X			X			X			X			X	X	X		
LABORATORY																								
CBC/Hgb/Platelets	X	X ≠			X			X			X			X			X			X	X	X	X €	X €
INR and PTT £	X	X ≠			X			X			X			X			X			X	X	X £	X €	X €
Bilirubin	X	X ≠			X			X			X			X			X			X	X	X	X €	X €
AST and ALT	X	X ≠			X			X			X			X			X			X	X	X	X €	X €
Serum Creatinine/Calc CrCl	X	X ≠			X			X			X			X			X			X	X	X	X €	X €
Urine Protein Check £	X	X ≠			X			X			X			X			X			X	X	X £	X €	X €
Serum Pregnancy Test		X©																						
SCANS																								

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Maintenance ¥			Off Tx	Off Tx
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	C 7	C 8	Subseq C Ω	Prior to Prog *	After Prog α
CT or MRI for Disease Assessment Ø	X							X						X						X		X Ø	X Ø	
SPECIMEN SUBMISSION																								
Tumor Tissue (See Section 15.1)	X																							
Peripheral Blood (See Section 15.1)	X							X															X ß	X ß
TREATMENT (21 day cycle)																								
Carboplatin		X			X			X			X			X			X							
Paclitaxel		X			X			X			X			X			X							
Ramucirumab		X			X			X			X			X			X			X	X	X		

Click here for Footnotes

NOTE: Forms are found on the CTSU website (ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures, and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in the Best Practices document located at https://www.swog.org/clinical-trials/protocol-workbench.

Footnotes for Arm A Calendar

¥ After 6 cycles of the chemotherapy combination, patients who have not progressed will receive maintenance ramucirumab alone on Day 1 of Cycle 7 and subsequent cycles for up to 1 year after randomization (See Section 10.2d).

Ω During continued treatment, items marked under physical and laboratory should be performed at every subsequent maintenance treatment (every 3 weeks). Disease assessments are to take place every 9 weeks until disease progression.

* After off treatment prior to progression, patients should be followed by repeating indicated laboratory tests every 3 months for first year, and then every 6 months until 2 years from date of randomization.

α After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 3 months for first year, and then every 6 months until 2 years from date of randomization.

Ø CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.0) must be repeated every 6 weeks for the first 18 weeks and, then every 9 weeks, until disease progression.

€ Assessment should continue until resolution of all acute adverse events.

∑ Vital signs (blood pressure, heart rate, oxygen saturation, temperature, and respiratory rate) are to be performed before dose administration per institutional guidelines.

≠ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not to be repeated on Cycle 1 Day 1.

£ Urine Protein, PTT, and INR should be performed prior to every subsequent cycle throughout treatment, then as clinically required.

© Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

ß With patient's consent, peripheral blood must be collected upon removal from protocol treatment for any reason. (See Section 15.1).

9.2 Arm B Carboplatin (CBDCA) and Paclitaxel (Taxol®)

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Off Tx	Off Tx
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Prior to Prog*	After Prog α
PHYSICAL																					
History & Physical Exam	X	X			X			X			X			X			X			X	
Weight & Performance Status	X	X			X			X			X			X			X			X	
Disease Assessment Ø	X							X						X						X Ø	
Toxicity Notation	X				X			X			X			X			X			X €	X €
Vital Signs ∑	X	X			X			X			X			X			X				
LABORATORY																					
CBC/Hgb/Platelets	X	X ≠			X			X			X			X			X			X €	X €
INR and PTT	X																				
Bilirubin	X	X ≠			X			X			X			X			X			X €	X €
AST and ALT	X	X ≠			X			X			X			X			X			X €	X €
Serum Creatinine/Calc CrCl	X	X ≠			X			X			X			X			X			X €	X €
Urine Protein Check	X																				
Serum Pregnancy Test		X©																			
SCANS																					
CT or MRI for Disease Assessment Ø	X							X						X						X Ø	
SPECIMEN SUBMISSION																					

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Off Tx	Off Tx
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Prior to Prog*	After Prog α
Tumor Tissue (See Section 15.1)	X																				
Peripheral Blood (See Section 15.1)	X							X												X ß	X ß
TREATMENT (21 day cycle)																					
Carboplatin		X			X			X			X			X			X				
Paclitaxel		X			X			X			X			X			X				

Click here for Footnotes

NOTE: Forms are found on the CTSU website (https://ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures, and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in the Best Practices document located at https://www.swog.org/clinical-trials/protocol-workbench.

Footnotes for Calendar 9.2

Footnotes for Arm B Calendar

* After off treatment prior to progression, patients should be followed by repeating indicated laboratory tests every 3 months for first year, and then every 6 months until 2 years from date of randomization.

α After off treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 3 months for first year, and then every 6 months until 2 years from date of randomization.

Ø CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.0) must be repeated every 6 weeks for the first 18 weeks and, then every 9 weeks, until disease progression.

€ Assessment should continue until resolution of all acute adverse events.

∑ Vital signs (blood pressure, heart rate, oxygen saturation, temperature, and respiratory rate) are to be performed before dose administration per institutional guidelines.

≠ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not to be repeated on Cycle 1 Day 1.

© Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

ß With patient's consent, peripheral blood must be collected upon removal from protocol treatment for any reason. (See Section 15.1)

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease:** Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. A malignant lymph node is to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least 1 measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all targets 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 appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. 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).

   Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

   1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

   2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g., CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

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 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). However, non-measurable and non-target lesions are included 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. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

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: 2 or more objective statuses of CR a minimum of 4 weeks apart documented before progression or symptomatic deterioration.

b. PR: 2 or more objective statuses of PR or better a minimum of 4 weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: 1 objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: 1 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 1 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.

POINT	**DESCRIPTION**
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 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.

10.6 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective and Power Justification

The primary study objective is to compare progression-free survival between patients with unresectable locally advanced, recurrent, or metastatic Thymic Carcinoma (TC) randomized to carboplatin-paclitaxel with or without ramucirumab. Patients will be randomized with equal probability between carboplatin/paclitaxel with or without ramucirumab.

A design with 90% power to detect a hazard ratio of 0.5 (2-fold increase in medians under exponential survival) using a 1-sided 0.10 level log-rank test would require 54 PFS events. Assuming a uniform accrual rate of 2 patients per month, 18 months of follow-up, PFS is exponentially distributed, and the median PFS within the carboplatin/paclitaxel arm is 6 months, then 60 eligible patients are needed. **Accounting for an ineligible rate of 10%, the total target accrual is 66 patients accrued over 33 months.**

11.2 Secondary Objectives and Interim Analysis

With 30 eligible patients per arm, toxicity rates and other binary proportions can be estimated to be within 18% with 95% confidence. Assuming 90% of the patients will have measurable disease, response rates and disease control rates can be estimated to be within 19% with 95% confidence. Any toxicity with at least 10% prevalence is likely to be observed (with 96% probability). Binary proportions will be compared between the arms using either a Fisher's exact or Chi-squared test at the 1-sided 0.10 level. With 30 patients per arm, this design has at least 90% power to detect a 35% difference in proportions between the arms.

Overall survival will be compared between the arms also using a 1-sided 0.10 level test. However, the power to detect differences in OS will be very limited with this sample size.

An interim analysis evaluating early stopping for futility alone will be done upon the observation of 27 PFS events (50% of expected). For futility testing, the alternative hypothesis of at least 2-fold improvement in PFS for the experimental arm will be tested at one-sided level 0.025, using an extension of the log-rank test that allows for testing a relative risk not equal to 1. It is estimated that this analysis will take place approximately 27 months after initiation of accrual, when approximately 50 eligible patients have been enrolled. The approximate hazard ratio associated the boundary based on the fixed-sample p-value scale is 0.96.

11.3 Accrual

SWOG has no experience accruing to this patient population and thymic carcinoma is of definite interest in terms of rare populations to be studied in SWOG. Given our lack of experience, accrual estimates are not as well supported as our estimates in other settings.

11.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of 4 members from outside of the SWOG, 3 SWOG 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 Statistics and Data Management 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

A discipline review is not required for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Initiation of treatment must be planned to start no more than 7 calendar days after registration.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. 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 to CTEP.

a. CTEP 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)	✔	✔	✔	
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
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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 < RCRHelpDesk@nih.gov >.

b. CTSU Registration Procedures

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

1. **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 the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- 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 that are approved by the CIRB for this study are not required to submit 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 intent 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 the study.

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the **S1701** 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol #**S1701**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements for S1701 Site Registration:**

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4. **Submitting Regulatory Documents:**

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

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

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

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

5. **Checking Your Site's Registration Status:**

You can verify your site registration status on the members' section of the CTSU website.

- 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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as

outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 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.

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://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

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 and, upon enrollment, initializes the patient in the Rave database. 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):

- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. 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

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, 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 and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. 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. 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 OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 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 Requirement

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 CTSU website (https://www.ctsu.org) and (apart from the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional

information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG web site (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Time points

a. WITHIN 7 DAYS OF REGISTRATION

Submit the following:

S1701 On study Form

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Report documenting histologic confirmation of thymic carcinoma*

Submit radiology reports from all scans performed to assess disease at baseline.*

*NOTE: Upload these reports via the Source Documentation: Baseline form in Rave®.

b. WITHIN 70 DAYS AFTER REGISTRATION, IF PATIENT CONSENTS:

Submit baseline tissue, baseline blood and Cycle 3 blood specimens as outlined in Section 15.0.

c. WITHIN 14 DAYS AFTER EACH CYCLE (1 CYCLE = 21 DAYS) OF TREATMENT:

Submit the following:

S1701 Treatment Form

S1701 Adverse Event Form

d. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (see study calendar) UNTIL PROGRESSION OF DISEASE:

Submit the following:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports (Upload these reports via the Source Documentation: Follow-Up form in Rave®.)

e. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1701 Treatment Form

S1701 Adverse Event Form

If patient consents, also submit blood specimen as outlined in Section 15.0.

f. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow-Up Tumor Assessment Form (RECIST 1.1)

All radiology reports used to document progression (Upload via the Source Documentation: Follow-Up form in Rave®)

If the patient was off protocol treatment, also submit the

Follow-Up Form

g. AFTER OFF TREATMENT, SUBMIT EVERY 3 MONTHS FOR FIRST YEAR, AND THEN EVERY 6 MONTHS UNTIL 2 YEARS FROM RANDOMIZATION.

Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death. If the patient was still on protocol treatment, also submit the forms listed in Section 14.4e. If the patient was off protocol treatment, also submit the Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine and Banking (OPTIONAL FOR PATIENT)

Patients must be offered the opportunity to participate in banking of specimens for future research. Collection of specimens is critical to the interpretation of this study and should be acquired if at all possible. If the patient consents, specimens must be submitted as described in this section.

a. Archived Tumor Tissue

Within 60 calendar days after registration, submit the following:

1 or 2 paraffin-embedded tissue blocks containing formalin fixed tumor FFPE or needle aspirate slides from time of diagnosis (or subsequent, but prior to protocol therapy). If blocks are unavailable, 6-8 unstained slides, 4 to 5 microns are

acceptable alternatives. It is not necessary to perform an additional biopsy for this purpose. Paraffin blocks may be processed according to standard institutional protocols. Cytology (i.e., fine-needle aspirations) can be accepted only if they are paraffin embedded as cell blocks.

b. Buffy Coat and Plasma

Draw approximately 10 mL blood in 1-2 lavender (EDTA) tubes (depending on tube size) at the following 3 time points:

- After registration, prior to treatment on Cycle 1 Day 1
- Cycle 3 Day 1
- Upon removal from protocol treatment for any reason

Blood should be placed on wet ice immediately after collection and processed as soon as possible (preferably within 2 hours). Centrifuge vacutainer tubes at approximately 800 x g for 10 minutes (preferably in a refrigerated centrifuge, if available). Immediately after centrifugation, carefully transfer plasma to a new 15 mL conical tube using a pipette, being careful not to aspirate the interface between the plasma and the platelets (buffy coat layer). Set aside original purple top tubes for later processing. Then centrifuge plasma a second time at 1200 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 ul aliquots into 6-10 labeled 1.8-2.0 ml cryovials, being careful not to disturb the pellet in the bottom of the tube. The buffy coat, a whitish layer of cells between the plasma and red blood cell layers, should be collected from the original purple top tube(s) and transferred into 2 labeled 1.8-2.0 ml cryovials (contamination with RBC not a concern). Freeze cryovials immediately and store at or below -70° until shipping.

Blood products may be batch shipped every 3 months on dry ice.

c. Specimen Collection and Submission Instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures) Specimen must be shipped by overnight delivery, excluding Fridays.

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 (www.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. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at

https://spectrack.crab.org (select the option “SWOG – SWOG – CTSU”). SpecTrack start-up instructions (both written and demo) are available after signing in to 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. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of *tissue,* buffy coat, and plasma samples for SWOG Repository Submission biobanking is identified as follows:

Lab #201: SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201
Phone: 614/722-2865
Contact: SWOG Repository Coordinator
Email: bpcbank@nationwidechildrens.org

2. Federal guidelines for the shipment of blood products:

   a. The tube must be wrapped in an absorbent material.

   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

   c. Pack the resealable bag and tube in a Styrofoam shipping container.

   d. Pack the Styrofoam shipping container in a cardboard box.

   e. Mark the box "Biohazard".

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).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

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.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. The company, Eli Lilly and Company, will also receive a copy of the report electronically via the CTEP-AERS Web-based application.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

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 be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in Arm A of this study are ramucirumab plus carboplatin and paclitaxel. 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 Specialist at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase II and Phase III Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Ramucirumab plus carboplatin and paclitaxel, Arm A

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:

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	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[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:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

May 5, 2011

f. Expedited reporting for commercial agents

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.2. The commercial agents used in both arms of this study are carboplatin and paclitaxel. 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 Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2 Expedited reporting requirements for adverse events experienced by patients on both study arms within 30 days of the last administration of the commercial agents.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] **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.**

[b] 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 to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210/614-0006.

g. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase II and Phase III Studies Utilizing an Agent under a Non-CTEP IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210/614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

h. *Reporting Secondary Malignancy, including AML/ALL/MDS*

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a non-NCI IND to be reported via CTEP-AERS. 3 options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 calendar days by fax to 210/614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium, and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium, and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known,

accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium, and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium, and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210/614-0006. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

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18.0 APPENDIX

18.1 Child-Pugh Scoring

18.2 AUC Calculation

18.3 Carboplatin Dosing Worksheet

18.1 Child-Pugh Scoring

The score is used to assess the prognosis of chronic liver disease and employs 5 clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin, mmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s)	<4.0	4.0–6.0	> 6.0
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4

18.2 AUC CALCULATION

The area under the plasma drug concentration-time curve (AUC) reflects the actual body exposure to drug after administration of a dose of the drug and is expressed in mg*h/L.

After an I.V. bolus injection, the AUC can be calculated by the following equation:

$$AUC = \frac{C(0)}{\lambda}$$

Trapezoidal rule: It consists in dividing the plasma concentration-time profile into several trapezoids and calculating the AUC by adding the area of these trapezoids.

AUC= Area under the concentration-time curve

F = bioavailability

D = dose

CL= clearance

C(0) = extrapolated plasma concentration at time 0

λ = elimination rate constant = CL/Vd

18.3 Carboplatin Dosing Worksheet

TO CALCULATE Creatinine Clearance (CrCl) from SERUM CREATININE:

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

$$\text{CrCl} = \frac{(140 - \quad) \times (\quad)}{72 \times \_\_\_\_\_} \times 0.85 \text{ (if female)}$$

TO CALCULATE CARBOPLATIN DOSE WITH CALVERT FORMULA:

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

(AUC) (GFR + 25) = CARBOPLATIN DOSE PER CYCLE IN mg

(6) (_____+25) = _____ mg of carboplatin

This is the TOTAL DOSE of carboplatin (not mg/m^2).

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 Cockroft-Gault formula to calculate the estimated creatinine clearance for carboplatin dosing.