Protocol (3): I4T-MC-JVDA

A Phase 1 Study of Ramucirumab, a Humanized, Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Recurrent or Refractory Solid Tumors, including CNS Tumors

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CHILDREN'S ONCOLOGY GROUP

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A PHASE 1 STUDY OF RAMUCIRUMAB, A HUMAN MONOCLONAL ANTIBODY AGAINST THE VASCULAR ENDOTHELIAL GROWTH FACTOR-2 (VEGFR-2) RECEPTOR IN CHILDREN WITH REFRACTORY SOLID TUMORS, INCLUDING CNS TUMORS

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

STUDY CHAIR

For PEP-CTN Operations and Data/Statistics Contacts see: http://members.childrensoncologygroup.org

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PPD

STUDY COMMITTEE, cont.

PPD

AGENT NSC# AND IND#'s
Ramucirumab (IMC-1121B, NSC#749128, IND# 11856)

IND Sponsor: Eli Lilly

For PEP-CTN Operations and Data/Statistics Contacts see: http:members.childrensoncologygroup.org

SEE SECTION 8.7.6 and Appendix XIII FOR SPECIMEN SHIPPING ADDRESSES

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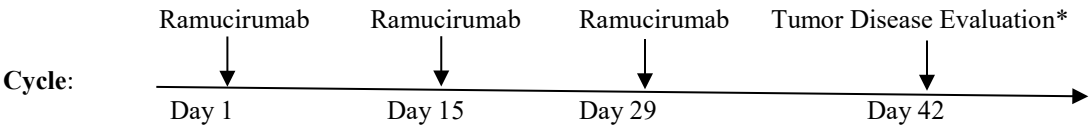
ABSTRACT

This is a Phase 1 study of ramucirumab (IMC-1121B; LY3009806), a recombinant, human monoclonal antibody of the immunoglobulin G subclass 1 developed against the vascular endothelial growth factor-2 receptor (VEGFR-2), to be conducted in children with recurrent or refractory solid tumors including CNS tumors. Ramucirumab specifically binds to the extracellular domain of human VEGFR-2 with high affinity and leads to a comprehensive inhibition of the signaling pathways activated by VEGF-A (VEGF) binding. In addition to VEGF, Ramucirumab also inhibits the binding of VEGF-C and VEGF-D to VEGFR-2. By virtue of its specificity for VEGFR-2, ramucirumab has less potential to induce "off-target" toxicities seen with VEGFR-2 tyrosine kinase inhibitors. Preclinical studies have shown that ramucirumab is efficacious as either a single agent or in combination with doxorubicin across a series of pediatric patient-derived xenograft sarcoma models including synovial, osteosarcoma, Ewings, and undifferentiated histologies and in a cell-derived neuroblastoma xenograft. It has undergone Phase 1, 2, and 3 testing in adults and has been FDA approved for advanced gastro-esophageal carcinoma and metastatic non-small cell lung cancer. The adult recommended FDA approved doses are 8 mg/kg I.V. administered every other week in gastric indications and 10 mg/kg I.V. administered every 3 weeks in non-small cell lung cancer. In Part A, we will evaluate the maximum tolerated dose (MTD) and/or RP2D of ramucirumab given intravenously every other week in children with solid tumors, excluding CNS tumors. In Part B of the study we will evaluate the tolerability and/or RP2D of ramucirumab in children with recurrent or refractory CNS tumors. In addition to pharmacokinetic and immunogenicity studies, correlative biologic endpoints will include evaluation of angiogenic proteins and circulating hematopoietic and endothelial progenitor cells.

EXPERIMENTAL DESIGN SCHEMA



* Tumor Disease Evaluations will occur at the end of cycles 1 and 2, and then every other cycle.

Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Therapy may otherwise continue up to 8 cycles or until one of the off protocol therapy criteria in Section 10.1 is met.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ramucirumab administered as an intravenous infusion over 60 minutes, every 2 weeks, to children with recurrent or refractory solid tumors.

1.1.2 To determine the tolerability of the MTD and/or RP2D of ramucirumab in children with recurrent or refractory CNS tumors.

1.1.3 To define and describe the toxicities of ramucirumab administered on this schedule.

1.1.4 To characterize the pharmacokinetics and immunogenicity of ramucirumab in children with recurrent or refractory solid tumors including CNS tumors.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of ramucirumab within the confines of a Phase 1 study.

1.3 Exploratory Aims

1.3.1 To explore the pharmacodynamics (PD) effects of ramucirumab in this pediatric population.

1.3.2 To explore potential predictive biomarkers relevant to pediatric cancers, cancer-related conditions, ramucirumab and angiogenesis.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Angiogenesis, the generation of new blood vessels from existing ones, is an essential physiological process that is deregulated in various pathological conditions including cancer.[1] Both adult and pediatric solid tumors rely on angiogenesis for growth and metastasis.[2] As a result, the pathways that mediate tumor angiogenesis have been targeted for new anti-cancer drug development. This strategy has resulted in the approval of anti-angiogenic agents with a variety of mechanisms for a number of human cancers in the last decade.[3]

The vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR-2) pathway (VEGF pathway hereafter) is considered the most important mediator of tumor angiogenesis.[4] The pathway is activated by the binding of cognate ligands, VEGF-A, VEGF-C and VEGF-D to the VEGFR-2 receptor. Activation of VEGFR-2 leads to receptor dimerization and transphosphorylation of key tyrosine residues in the cytoplasmic domain of the receptor. This event initiates several signal transduction cascades that mediate survival, migration and proliferation of endothelial cells as well as permeability of blood vessels.[5] *In situ* hybridization studies have revealed that VEGF-A mRNA is upregulated in the vast majority of human tumors including

breast, lung, thyroid, gastrointestinal tract, kidney, bladder, ovary, uterine, cervix, angiosarcoma, germ-cell, and several intracranial tumors, including glioblastoma multiforme.[6] Multiple biological agents have been developed against the VEGF pathway. These VEGF pathway inhibitors have been designed to either neutralize VEGF-A, the principal VEGFR-2 ligand, or to antagonize the protein kinase activity that initiates the downstream pro-angiogenic intra-cellular signaling pathways. For example, bevacizumab, a monoclonal antibody against VEGF-A, improved overall survival when added to chemotherapy in patients with metastatic colorectal carcinoma, resulting in its approval as the first anti-angiogenic agent almost a decade ago.[7] Several successful Phase-3 trials with bevacizumab have led to the expansion of its use in patients with advanced lung cancer,[8] recurrent glioblastoma,[9] renal cell carcinoma[10] and metastatic breast cancer.[11] Despite this initial success, there has been a lack of survival benefit in subsequent confirmatory trials among patients with breast cancer,[12] and only marginal benefit among patients with colorectal cancer.[13]

Aflibercept, a soluble decoy VEGF receptor that neutralizes VEGF-A, VEGF-B, and placental growth factor with high affinity represents an alternative approach to antagonize the VEGF pathway. While clinical benefit has not been universally demonstrated across several tumor types, the positive findings of prolonged overall survival (OS) and progression free survival (PFS) in the prospective, randomized, double-blind phase III VELOUR study (aflibercept versus placebo in combination with irinotecan and 5-FU [FOLFIRI] in the treatment of patients with metastatic colorectal cancer [mCRC] after failure of an oxaliplatin based regimen) led to the recent US approval of the aflibercept-FOLFIRI combination for use in this patient population.[14] However, the toxicity profile demonstrated that more patients on the aflibercept arm had grade 3 or 4 adverse events (83.5% vs. 62.5%). These events included not just those expected with anti-VEGF agents, such as hypertension, hemorrhage, and arterial and venous thromboembolic events, but also the potentiation of adverse effects associated with FOLFIRI.

Another therapeutic modality to inhibit angiogenesis involves targeting the VEGF pathway by using tyrosine kinase inhibitors (TKIs) to block the intracellular tyrosine kinase activity triggered by VEGF/VEGFR-2 binding. TKIs impede the downstream signals necessary for endothelial proliferation, survival, and migration that are required for tumor growth and metastasis; however, lack of absolute specificity of TKIs for VEGFR-2 results in significant "off-target" inhibition. For example, although the specific pattern of kinase inhibition varies, the TKIs sorafenib, sunitnib, cediranib, pazopanib, and motesanib all additionally inhibit VEGFRs 1 and 3, cKit and PDGFRb, while vandetanib also inhibits EGFR.[15] The lack of specificity of TKIs result in a pattern of dose-limiting toxicities that have made this class of drugs difficult to combine with chemotherapeutic regimens.[16]

The above discussion highlights the need for a novel, highly potent and selective anti-angiogenic therapy with a distinct mechanism of action. To this end, selective inhibition of the extracellular domain of VEGFR-2 has been explored. Ramucirumab, (IMC-1121B; LY3009806), is a recombinant human monoclonal, receptor-targeted antibody of the immunoglobulin G subclass 1 that specifically binds to the extracellular domain of human VEGFR-2 with high affinity (approximately 50 pM).[17,18] The binding of ramucirumab to VEGFR-2 prevents its interaction with not just VEGF-A,[15,19] the principal ligand that initiates the pro-angiogenic effects of the VEGF pathway, but also all other VEGFR-2 activating ligands including VEGF-C and VEGF-D (Preclinical, Eli

Lilly and Company, data on file). Ramucirumab thus provides a highly **specific and comprehensive inhibition of the VEGF pathway,** effectively blocking the downstream intracellular signaling, which results in proliferation, survival, and migration of endothelial cells.[20-23] Ramucirumab may further reduce signaling by inducing VEGFR-2 internalization (Preclinical, Eli Lilly and Company, data on file). Finally, by virtue of its specificity for VEGFR-2, ramucirumab has less potential to induce "off-target" toxicities seen with VEGFR-2 TKIs.

Rationale for Use in Pediatrics: Although survival for pediatric patients with solid tumors has improved with more than 75% cured, prognosis is still poor for patients with metastatic or recurrent disease. These patients need innovative therapies to combat tumor resistance. Similar to adult tumors, angiogenesis is upregulated in pediatric embryonal tumors making it an important pathway to target with novel anti-angiogenic agents. VEGF and its downstream signaling play a vital role in tumor growth and metastasis in children. Studies have shown high levels of circulating VEGF levels in children with tumors at baseline.[24,25] Neuroblastoma and Wilm's tumor tissues express VEGF, and high expression is correlated with invasion, metastasis, and risk of recurrence. [26-28] VEGF expression drives tumor angiogenesis and in some instances tumor growth and metastasis among patients with Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma.[29-31] Among osteosarcoma patients, VEGF upregulation is associated with adverse clinical outcomes.[32,33]

The pre-clinical testing of various anti-angiogenic agents in pediatric cancers has been investigated with VEGF ligand or intracellular VEGF receptor inhibition. VEGF ligand inhibition with bevacizumab and aflibercept suppresses tumor angiogenesis and growth in murine models of rhabdomyosarcoma, neuroblastoma, and hepatoblastoma. In addition, aflibercept decreased the tumor vasculature resulting in regression of established tumors and lung metastases in an orthotopic xenograft model of Wilm's tumor.[34] The anti-VEGF TKIs, cediranib, sorafenib, and sunitinib have been tested against a panel of pediatric solid tumor cell lines by the Pediatric Preclinical Testing Program (PPTP). Although complete responses were rare when tested in vivo, all 3 agents exhibited growth inhibitory activity consistent with anti-angiogenic mechanisms leading to significant prolongation of the time to event, and their response activity was rated as intermediate.[35]

Eight anti-angiogenic agents have completed Phase-1 clinical testing in children: bevacizumab,[36] aflibercept,[37] and several VEGFR-2 TKIs, including cediranib,[38] pazopanib,[39] semaxanib,[40] sorefenib,[41] sunitinib,[42] and vandetanib.[43] Compared to adult recommended dosing, those for children have ranged from reduced dosing in pediatrics, due to MTDs seen in many of the TKIs and aflibercept, to pediatric dosing that is comparable to adult dosing, as is the case for bevacizumab where an MTD was never established in the pediatric population.[16] Safety profiles of anti-angiogenics have been similar across age groups, with class effects including hypertension, proteinuria, and arterial thrombo-embolic events.[16] For children, two potential toxicities of particular interest are growth plate abnormalities and cardiotoxicity, given the prevalent use of anthracyclines in pediatric regimens. Physeal widening was observed in a single anti-angiogenic phase 1 trial with pazopanib; no other pediatric studies of VEGF pathway inhibitors have reported growth plate defects. Cardiotoxicities have been observed in some patients with prior anthracycline exposure who were treated with anti-angiogenic agents, though the pathogenesis of this cardiotoxicity and its association with VEGF pathway inhibition is not yet known. Regarding efficacy, while there is minimal data on

the anti-tumor activity of commonly used anti-angiogenic agents in children, single agent activity consisting of partial responses and stable disease have been reported in patients with soft-tissue sarcoma, Ewing's sarcoma, osteosarcoma, Wilm's tumor, hepatoblastoma, ependymoma, and gliomas.[35]

Preclinical studies have shown that anti-VEGF therapies might modify the tumor vasculature and lead to better delivery of cytotoxic agents.[44] This has prompted numerous ongoing Phase-2 combination therapy studies of bevacizumab and cytotoxic agents to assess efficacy of these novel strategies in specific types of cancer. In adult studies there has been benefit for some cancers with the addition of bevacizumab to standard chemotherapy. Early results of bevacizumab combined with standard chemotherapy have shown promise in pediatric patients with low-grade gliomas.[45] Utilizing a monoclonal antibody like ramucirumab to block not only VEGF-A but any ligand that might interact with VEGFR-2 to activate downstream angiogenic activity, offers the possibility of a more comprehensive inhibition of the VEGF pathway. For patients who acquire resistance to bevacizumab, this comprehensive blockade may prove particularly advantageous. Extrapolating from the experiences of Phase 2 and 3 studies that combined chemotherapy with various anti-VEGF therapies, monoclonal antibodies such as ramucirumab are also less likely to result in cumulative toxicities when given with cytotoxic agents, in contrast to VEGFR-2 TKIs known to have "off-target" toxicities.[46,47] Given the novel target of inhibition, and the specificity, potency, and potential for safely combining with other cytotoxic agents, ramucirumab may be an optimal candidate to treat pediatric patients with solid tumors, particularly those with recurrent or metastatic disease.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Pre-clinical studies in animal models using ramucirumab have been challenging due to its high species specificity for human VEGFR-2. Syngeneic and xenograft tumors engrafted into mice depend on expansion of murine vasculature within the host stroma precluding the use of ramucirumab in such studies. Therefore, DC101, a rat antibody targeting mouse VEGFR-2 has been used to validate the therapeutic utility of targeting VEGFR-2 *in vivo*. DC101 has pharmacological characteristics very similar to ramucirumab meeting the scientific criteria of a surrogate antibody. DC101 was evaluated in a pancreatic cancer BxPC-3 xenograft model to establish an effective dose regimen and determine the associated plasma concentration to guide subsequent studies. [48] In this model, significant tumor growth inhibition was observed at doses which were on average associated with a minimum serum drug concentration of 18 µg/mL. DC101 has demonstrated anti-tumor effect in numerous mouse xenograft solid tumor models that include gastric, hepatic, breast, colorectal, and non-small cell lung cancers.[49,50] Monotherapy with DC101 produced tumor growth inhibition (TGI) up to 59% (range: 27%-78%) and also produced additive effects when combined with chemotherapy in multiple tumor types. Importantly, single agent DC101 was active across a series of pediatric patient-derived xenograft (PDX) sarcoma models including synovial, osteo, Ewing's, and undifferentiated histologies (TGI ranging from 52 % to 88%). Significant activity of DC101 was also observed in combination with doxorubicin in PDX models of Ewings sarcoma and in a mouse cell-derived xenograft model of human neuroblastoma (TGI >100% in both cases) (Preclinical, Eli Lilly and Company, data on file). Tumor growth

inhibition in excess of 100% was also observed in a synovial sarcoma PDX model when treated with DC101 monotherapy following initial doxorubicin therapy and in combination with doxorubicin. Since the affinity of ramucirumab to human VEGFR-2 is 10-fold higher than the affinity of DC101 to mouse VEGFR-2, the *in vivo* studies of DC101 may underestimate the anti-tumor potency of ramucirumab.[21,49-51] Pre-clinical studies have shown that targeting VEGFR-2 with antibody produces tumor growth inhibition in xenografts that were resistant to the anti-VEGF TKIs.[52]

2.2.2 Animal Toxicology:

The animal toxicology studies of ramucirumab were conducted in cynomolgus monkeys. A tissue cross-reactivity study was conducted with a full panel of cynomolgus monkey and human tissues that showed that the tissue reactivity of ramucirumab observed in both tissues was similar, indicating that the cynomolgus monkey is an appropriate animal model for toxicity testing of ramucirumab. In a 5-week, 4-dose study, cynomolgus monkeys were given ramucirumab I.V. weekly at dose levels 0, 4, 12, or 40 mg/kg on Days 1, 15, 22, and 29, with a subset of monkeys sacrificed after the last dose and a second subset of monkeys entering a 6-week recovery phase for toxicity assessments. The only significant findings were mild local injection site reactions. I.V. administration was well tolerated at all dose levels and the no-observable adverse effect level was 40 mg/kg, the highest dose administered. A second toxicology study assessed the long-term (chronic) administration of ramucirumab in cynomolgus monkeys who received doses of 0, 5, 16, or 50 mg/kg administered intravenously every week for 12 or 39 weeks. The results revealed nephrotoxicity consistent with multi-focal and marked glomerulonephritis in both kidneys in monkeys receiving doses of 16 and 50 mg/kg for 39 weeks. In addition, secondary changes were also observed in the tubules, collecting ducts and the renal interstitium. Osteochondropathy and thickening of the epiphyseal growth plate was noted at all doses administered.[48]

In addition to toxicology studies, a wound healing study following a single dose of ramucirumab was also conducted at doses 5, 15, and 50 mg/kg since there is a strong role for VEGF pathway in wound healing. This study did not reveal a clinical or histological impairment of wound-healing in this cynomolgus monkey linear incision model after a single dose.[48]

2.2.3 Preclinical Pharmacokinetic Studies: Non-compartmental analysis of the concentration-vs-time data from the cynomolgus monkey studies mentioned above indicated that the PK behavior of ramucirumab was non-linear over the 4-50 mg/kg dose range. Area under the concentration-vs-time curve extrapolated to infinity ($AUC_{0\text{-}inf}$) and maximum concentration (C_{max}) increased in a greater than dose-proportional manner. Ramucirumab half-life increased and clearance decreased with increasing dose. Mean ramucirumab $AUC_{0\text{-}inf}$ in the 50mg/kg group increased between the 1st and the 39th dose, indicating drug accumulation consistent with a saturation of receptor mediated clearance. [48]

2.3 Adult Studies

2.3.1 Phase 1 Studies: Several adult Phase 1 trials have been completed using ramucirumab. They have been escalating, single-arm studies in which ramucirumab was administered as a single agent (Table 1). In addition, 3 combination studies have also been completed where a fixed dose of ramucirumab has been used in combination with other cytotoxic agents to assess safety, tolerability and efficacy (Table 2).

Table 1: Single-arm, Phase 1 Studies using escalating doses of Ramucirumab[17,26-28,48,53]

Study name	Study design	Diagnosis	Dose range	DLT	MTD
I4T-IE-JVBM	Open-label, single-arm	Advanced solid tumors	2-16 mg/kg qw X 4	Hypertension; DVT	13 mg/kg
I4T-IE-JVBN	Open-label, single-arm	Advanced solid tumors	Cohort 1-3: 6-10 mg/kg q2w X 4 Cohort 4-5: 15-20 mg/kg q3w X 4	None	None
I4T-IE-JVBI Japanese	Open-label, single-arm	Advanced solid tumors	Cohort 1: 6 mg/kg q2w Cohort 2: 8 mg/kg q3w Cohort 3: 10 mg/kg q3w	None	None

DLT: dose-limiting toxicity; DVT: deep vein thrombosis. MTD: maximum tolerated dose; qw: once a week; q2w: every 2 weeks; q3w: every 3 weeks.

The I4T-IE-JVBM study was an open-label, single-arm, dose-escalation study involving adults with advanced solid tumors. Pharmacokinetic data revealed dose-dependent elimination and nonlinear exposure consistent with saturable clearance. At all dose levels, mean trough concentrations exceeded 20 µg/mL. This was greater than the biologically significant level for target inhibition of VEGFR-2. [17,26-28] Serum VEGF-A post-treatment levels were 1.5-3.5 times higher than the baseline levels at all dose levels throughout the treatment.

Table 2: Combination studies of fixed-dose ramucirumab and chemotherapy agents in 3 different Japanese studies. [48]

Study name	Study design	Diagnosis	Dose range	Response
I4T-IE-JVBW Japanese	Open-label, single-arm	Gastric ACA (n=6)	RAM: 10 mg/kg Days 1 and 15 and PAC: 80 mg/m^2 - Days 1, 8, and 15	SD:5; PR:1
I4T-IE-JVBX Japanese	Open-label, single-arm	Breast CA (n=7)	RAM: 10 mg/kg q3w + DOC: 75 mg/m^2 q3w	SD:3; PR:4
I4T-IE-JVBY Japanese	Open-label, single-arm	Colorectal CA (n=6)	RAM: 10 mg/kg q2w + FOLFIRI	SD:4; PR:1, PD:1

ACA: adenocarcinoma; CA: carcinoma; DOC: docetaxel; FOLFIRI: folinic acid, 5-FU, irinotecan; n: sample size; PAC: paclitaxel; PR: partial response; PD: progressive disease RAM: ramucirumab; SD: stable disease; q2w: every 2 weeks; q3w: every 3 weeks.

2.3.2 Phase 2 Studies: 8 mg/kg I.V. q2 weeks as a monotherapy was selected as the adult RP2D in certain selected indications based on PK data from the Phase 1 I4T-IE-JVBM study.[17] The results of the Phase 2 studies are summarized in the Table 3.

Table 3: Response data from single-arm and double-arm Phase 2 studies[48,54-56]

Study name	Study design	Diagnosis	Dose range	ORR/PFS/OS (95% CI)
I4T-IE-JVBQ	Open-label, single-arm	Liver CA (n=43)	RAM: 8 mg/kg q2w	ORR: 9.5% (2.7-22.6%) OS: 12 (6.1-19.7)

I4-IE-JVBP	Open-label, single-arm	mRCC. (n=39)	RAM: 8 mg/kg q2w	ORR: 5.1% (0.6-17.3%) OS: 24.8 (18.9-32.6)
I4T-IE-JVBJ	Open-label, single-arm	NSCLC. (n=40)	RAM (10 mg/kg q3w) + PAC + CARBO	ORR: 55% PFS: 7.85 (5.49-9.86) OS: 16.85 (14.82-28.58)
I4T-IE-JVBH	Open-label, single-arm	mCRC. (n=48)	RAM (8 mg/kg q2w) + OXA + FA + 5-FU	ORR: 58.3% PFS: 11.5 (8.6-13.1) OS: 20.4 (18.5-25.1)
I4T-IE-JVBR	Open-label, single-arm	Ovarian/fallopian/ primary peritoneal CA (n=60)	RAM: 8 mg/kg q2w	ORR: 5% PFS: 3.5 (2.3-5.3) OS: 11.1 (8.3-17)
I4T-IE-JVBO	Open-label, double-arm	Melanoma. (n=105)	**Arm A**: RAM (10 mg/kg q3w) + DAC (1000mg/m^2) q3w **Arm B**: RAM (10 mg/kg q3w)	**Arm A**: ORR: 17.3% PFS-2.6 (1.4-5.4) OS-8.7 (7.1-12.9) **Arm B**: ORR: 4% PFS-1.7 (1.4-2.9) OS-11.1 (7.7-14.6)
I4T-IE-JVBS	Open-label, double-arm	Prostate CA. (n=66)	**Arm A**: CIXUT (6 mg/kg q3w)+ MITO+ PRED **Arm B**: RAM (6 mg/kg q3w) + MITO + PRED	**Arm A**: PFS-4.1 (2.2-5.6) OS-10.8 (6.5-13) **Arm B**: PFS-6.7 (4.5-8.3) OS-13 (9.5-16)

5-FU: 5-fluorouracil; CA: carcinoma; CARBO: carboplatin; CI: confidence interval; CIXUT: cixutumumab; DAC: dacarbazine; FA: folinic acid; mCRC: metastatic colo-rectal carcinoma; mRCC: metastatic renal cell carcinoma; MITO: mitoxantrone; n: sample size; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: median overall survival in months; OXA; oxaliplatin; PAC: paclitaxel; PRED: prednisone; PFS: median progression-free survival in months; RAM: ramucirumab; q2w: every 2 weeks; q3w: every 3 weeks.

2.3.3 Phase 3 Studies: Results from six Phase 3 trials that have been completed and summarized in Table 4 below.

Table 4: Median PFS and OS from Phase 3 trials of ramucirumab[57-62]

Study name	Study design	Diagnosis	RAM dose	Median PFS (months)	Median OS (months)
REGARD	randomized, placebo-controlled, blinded	Advanced gastric/GEJ CA	RAM: 8 mg/kg q2w + BSC	2.1 vs. 1.3 p<0.0001	5.2 vs.3.8 **p=0.047**
RAINBOW	randomized, placebo-controlled, blinded	Gastric/GEJ CA	RAM (8 mg/kg q2w) + PAC	4.40 vs. 2.86 **p<0.0001**	9.63 vs.7.36 **p=0.0169**
REVEL	randomized, placebo-controlled, blinded	NSCLC	RAM (10 mg/kg q3w) + DOC	4.5 vs. 3 **p<0.0001**	10.5 vs.9.1 **p=0.0235**
ROSE	randomized, placebo-controlled, blinded	Breast CA	RAM (10 mg/kg q3w) + DOC	9.5 vs. 8.2 p>0.05	27.3 vs. 27.2 p=0.915
REACH	randomized, placebo-	Liver CA	RAM: 8 mg/kg q2w + BSC	NS	NS

	controlled, blinded				
RAISE	randomized, placebo-controlled, blinded	Metastatic Colorectal CA	RAM (8 mg/kg q2w) + FOLFIRI	5.7 vs. 4.5 **p=0.0005**	13.3 vs. 11.7 **p=0.0219**

BSC: Best Supportive Care; DOC: docetaxel; FOLFIRI: 5-FU, folinic acid and irinotecan; GEJ CA: gastro-esophageal junction adenocarcinoma; NS: not significant; NSCLC: non-small cell lung cancer; RAM: ramucirumab; PAC: paclitaxel; q2w: every 2 weeks; q3w: every 3 weeks.

2.3.4 Safety: Adverse events (AEs) for 1199 patients who have received ramucirumab on 7 Phase 1/1b studies, 16 open-label Phase 2 studies, and 1 Phase 3 study are available. Adverse drug reactions (AEs for which a causal relationship to ramucirumab was considered at least possible) of special interest include AEs which have been associated with other anti-angiogenic agents and monoclonal antibodies and include the following categories: infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, bleeding/hemorrhagic events, and gastro-intestinal perforation.

In the Phase 3, REGARD study (n=236 ramucirumab arm), the AE profile of ramucirumab was similar to the placebo. Majority of patients received full dose of ramucirumab (dose intensity= 99.6%) with few dose delays or modifications. The most common treatment emergent AE that occurred in the ramucirumab group versus the placebo group at a higher rate (any grade) was hypertension (16.1% vs 7.8%), diarrhea (14.4% vs.8.7%), and headache (9.3% vs.3.5%). The overall incidence of Grade 3-5 treatment emergent AEs were similar between the 2 groups (56.8% vs.58.3%). The most common Grade ≥ 3 treatment emergent AE occurring in the ramucirumab group at a higher rate was hypertension (7.2% vs. 2.6% for Grade-3 hypertension). No individual Grade ≥ 3 treatment emergent AE was observed in > than 10% of patients. Serious AEs, hospitalization and supportive care use were also similar between the 2 groups indicating a good therapeutic-index profile for ramucirumab. Discontinuations due to AE were low in both groups but higher in the ramucirumab group than the placebo (10.5% vs.6%) with no specific AEs resulting in discontinuation. Deaths due to AEs were less common in ramucirumab vs. placebo group (9.3% vs.13%).

2.3.5 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacokinetic Studies: The PK of ramucirumab was first studied in patients with solid tumors administered across a range of doses from 2 to 16 mg/kg administered weekly via 1-hour I.V. infusions in I4T-IE-JVBM (IMCL CP12-0401). Apparent nonlinear PK profiles were observed between 2 and 8 mg/kg; PK profiles appeared to be linear at doses of 8 mg/kg and above, suggesting saturation of the target-mediated (VEGF Receptor 2) clearance pathway.[17]

Trough concentrations (or minimum concentrations [C_{min}]) were collected in two Phase 3 studies (REGARD and RAINBOW) in patients with gastric cancer. Following the recommended clinical dose regimen of 8 mg/kg every 2 weeks, observed C_{min} values were similar between REGARD and RAINBOW (Table 1). The geometric mean (percentage coefficient of variation [CV%]) observed trough values approached 50 μg/mL before the fourth dose, and ranged between

60 and 75 µg/mL before the seventh dose.[48]

Table 1. Summary of Observed Ramucirumab Trough Concentrations for Patients with Advanced Gastric Cancer Following Administration of 8 mg/kg of Ramucirumab Every 2 Weeks as an IV Infusion over Approximately 1 Hour Alone (REGARD) or in Combination with Paclitaxel (RAINBOW)

	Trough[a] Serum Concentrations (µg/mL)			
Dose Number	**4**		**7**	
	REGARD	RAINBOW	REGARD	RAINBOW
n_{PK}	53	203	34	142
Geo Mean	49.5	45.0	74.4	62.8
Geo CV%	81	50	58	47

Abbreviations: CV% = percentage coefficient of variation; Geo = geometric; IV = intravenous; n_{PK} = number of pharmacokinetic observations included in calculation.

a Trough concentrations were obtained prior to Doses 4 and 7. They also represent C_{min} following Doses 3 and 6.

Pharmacokinetic data from the 8 studies involving 497 patients were also pooled together for a population pharmacokinetic (PopPK) analysis. In these studies, ramucirumab was administered as a 1-hour I.V. infusion, at either 8 mg/kg once every 2 weeks on a 14- or 28-day cycle, or 10 mg/kg every 3 weeks on a 21-day cycle. The studies included patients with varying cancer indications: gastric cancer (80.5% of patients), non-small cell lung cancer (NSCLC; 8.2%), breast cancer (2.2%), colorectal cancer (CRC; 1.6%), and other tumor types (7.4%). The geometric mean of PopPK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (V_{ss}) and terminal half-life ($t_{1/2}$) were 0.0140 L/h (29.8%), 5.5 L (14.4%), and 15 days (24.1%), respectively. These parameter estimates were consistent with those observed with other human monoclonal IgG1 antibodies.[63] Results from the PopPK analyses indicate that the PK of ramucirumab following 8- and 10-mg/kg dose administrations were dose linear (absolute dose range: 169 to 1234 mg) and time independent. In addition, covariate analysis indicated that ramucirumab PK was not affected by body weight (range, 31.9 to 133.0 kg), sex, age (range, 19 to 86 years), serum albumin (range, 15.5 to 64.8 g/L), race (White and Asian), hepatic status (as assessed by alanine aminotransferase [range, 1 to 251 IU/L], aspartate transaminase [range, 1 to 276 IU/L], alkaline phosphatase [range, 31 to 2300 IU/L], and total bilirubin [range, 1.2 to 78.5 µmol/L]), and renal function (as assessed by Cockcroft-Gault creatinine clearance [range, 20.2 to 231 mL/min]).

Immunogenicity: Ramucirumab is a human monoclonal antibody with a potential to induce formation of anti-drug antibody (ADA) when administered to human. The development of ADA has been studied across 16 studies involving 1462 evaluable patients (1033 receiving ramucirumab and 429 receiving placebo) and the frequency of ADA and neutralizing ADA is low.[48]

Treatment-emergent ADA positive patients were defined as those patients whose post baseline ADA sample was greater than 4-fold higher than baseline value or with a titer > than 1:20. Overall the number of patients with treatment emergent ADA was low at 1.1% in ramucirumab-treated patients who had at least 1 post treatment sample tested (n=884). In the 321 patients who received either placebo

plus best supportive care (BSC) or placebo plus paclitaxel and who had at least 1 post-treatment sample tested, 16 patients (5.0%) had ADA detected post-treatment and 2 patients (0.6%) had treatment emergent ADA. None of these 321 patients had neutralizing antibodies detected. Overall, the rates of ADA responses and neutralizing antibody were low. No neutralizing antibodies were detected in either the RAINBOW or REGARD Phase 3 studies. [48]

Correlative and Biological Studies**:**

Pharmacodynamic circulating plasma molecular markers: Ramucirumab, (IMC-1121B, LY3009806) is a human receptor-targeted antibody that specifically blocks VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents interaction with activating ligands. Pharmacodynamic studies using ramucirumab have shown that VEGF-A levels were increased from baseline (range: 0 to 10-fold) following ramucirumab administration. Since it prevents receptor binding of circulating VEGF, this is consistent with its mechanism of action. Other VEGF ligands such as VEGF-D which also bind to VEGFR-2 were also elevated. Placental growth factor (PlGF) levels were also elevated from baseline (range: 0 to 20 fold), even though PlGF has not been shown to bind to VEGFR-2.[64,65] The mechanism of the elevation of placental growth factor levels is not known. Additionally, using newly-developed assays, correlations between pharmacodynamics changes with tumor response and survival are currently ongoing for multiple ramucirumab adult Phase 3 trials. These analyses may provide insight into ramucirumab activity that could be important to investigate in the pediatric population as well.

Circulating pharmacodynamic cellular biomarkers: To date, a consistent predictive biomarker for clinical efficacy of anti-VEGF therapy has not been identified. This produces challenges for clinicians in the upfront selection of which patients might benefit or not from anti-VEGF therapies. In adult patients with gastrointestinal stromal tumors treated with sunitinib, a rise in mature circulating endothelial cells was associated with clinical benefit[66] while results from a Phase-I pediatric study of bevacizumab showed circulating endothelial cells correlated with prolonged stable disease.[36] Circulating endothelial progenitor cells (EPCs) have been identified as predictive biomarkers of clinical efficacy for anti-angiogenic agents.[67] However, there has been a lack of consensus in defining EPCs leading to grouping various cell types under the umbrella of "EPC" and thus an inability to compare study results. Utilizing a novel multi-parametric flow cytometry (MPFC) protocol, our group has identified and defined the bona fide EPC, namely the endothelial colony forming cells (ECFCs) that are identified $CD31^{+}CD34^{bright}$ $CD45^{-}$ $AC133^{-}$ $CD14^{-}$LIVE/$DEAD^{-}$ cells, have high proliferative potential, and give rise to perfused vessels *in vivo*. [68-72] In addition, we have also enumerated circulating endothelial cells (CECs) that are identified as $CD31^{bright}$ $CD45^{-}$ $CD34^{dim}AC133^{-}$ cells which are mature, apoptotic endothelial cells sloughed off from the vessel wall during vascular remodeling and do not form perfused blood vessels *in vivo*. Finally, using MPFC we have identified a unique circulating hematopoietic stem and progenitor cell (CHSPC) population in both peripheral blood (PB) and umbilical cord blood, which is phenotypically and functionally distinct from EPCs but is still actively involved in angiogenesis.[68,73] These CHSPCs are vital for blood vessel formation in physiological and

pathological states through their interactions with mature endothelial cells and ECFCs, and are further classified into 2 distinct cellular subsets based on both cell surface antigen expression and function.[74] The pro-angiogenic CHSPCs (pCHSPCs) express AC133, while the non-angiogenic CHSPCs (nCHSPCs) do not, otherwise they are identical in their phenotypic definition showing the expression of $CD31^{+}$ $CD34^{bright}$ $CD45^{dim}$ $CD14^{-}$ $LIVE/DEAD^{-}$. The ratio of the pCHSPCs to nCHSPCs is a way to normalize variability in the total number of CHSPCs, with normal ratios between 1.2-1.8. An increased pCHSPC: nCHSPC ratio (>2.0) is associated with tumor-induced angiogenesis.[74-76] Further, using an anti-VEGF TKI suntinib in a Phase-II study among chemotherapy naïve subjects with metastatic breast cancer, results showed a decrease in the pCHSPC: nCHSPC ratio among women who responded to treatment.[76] Therefore, the pCHSPC: nCHSPC ratio, CECs and the ECFCs are the circulating, cellular markers are of particular interest for further investigation in additional Phase 1 and 2 studies, in order to evaluate their potential role as novel predictive, cellular biomarkers of anti-angiogenic agents, which have been elusive so far.

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There is no prior experience with ramucirumab in children.

2.5 Overview of Proposed Pediatric Study

Ramucirumab is a highly selective human monoclonal antibody directed against VEGFR2. Six Phase 3 pivotal trials of ramucirumab in combination with chemotherapy have been completed in adults and 3 additional Phase 3 trials are ongoing. The recommended dose in adults is 8 mg/kg IV administered over 1 hour every 2 weeks for patients with gastric cancer. For patients with NSCLC, the recommended dose in adults is 10 mg/kg IV administered over 1 hour every 3 weeks. No dose limiting toxicity is reported using these doses and schedules in adults. The toxicity profile is consistent with class effect, including dose-limiting hypertension at 10 mg/kg IV weekly, and deep venous thrombosis at 16 mg/kg IV weekly. Similar to other monoclonal antibodies, ramucirumab has a long half-life and is expected to accumulate. Based on adult PK studies, steady state is anticipated to be achieved after the third dose administered q 2 weeks. Initial PK studies in adults demonstrated non-dose proportional exposure at dose levels 2- 8 mg/kg weekly. At 8 mg/kg q week and above, systemic clearance decreased indicating a saturable receptor mediated clearance mechanism such as binding to VEGFR-2. The target trough concentration established in vitro was 18 µg/mL. However, in the pivotal Phase 3 trials, REGARD (8 mg/kg I.V. q 2 weeks, as monotherapy) and RAINBOW (8 mg/kg IV q 2 weeks in combination with paclitaxel) exposure-efficacy analyses indicated that improvements in OS and PFS were associated with increasing ramucirumab exposure. In RAINBOW (N=321), patients with ramucirumab exposure greater than the median (in the 3^{rd} and 4^{th} quartiles) were associated with longer OS and PFS and significantly better treatment effects (smaller HR) as compared to patients with ramucirumab exposure lower than the median (in the 1^{st} and 2^{nd} quartiles). The median OS times for 1^{st}, 2^{nd}, 3^{rd}, and 4^{th} exposure quartiles were 6.5, 8.6, 11.0, and 12.9 months, respectively, and the hazard ratios were 1.04, 0.84, 0.69, and 0.53, respectively, in ramucirumab plus paclitaxel arm. Similar exposure-efficacy trend

was observed in REGARD despite of smaller samples size (N=72). Further PKPD modelling and simulation analysis indicated EC_{50} value (in terms of minimum concentration at steady state, $C_{min,ss}$) was ~ 50 ug/mL, which was also the approximate median$C_{min,ss}$ value in RAINBOW. It is therefore of interest to identify a dose which will produce $C_{min,ss}$ of 50 ug/mL or higher in a majority of patients, and identify a safety profile so as to assist in the selection of a potentially efficacious dose for pediatric populations entering Phase 2 studies and beyond.

Based on the safety profile in adults and the lack of DLTs at 8 mg/kg IV q 2 week dose level, we propose a dose finding study that, in the absence of DLTs, the recommended dose of ramucirumab in children and adolescents will be based on achieving a $C_{min,ss} \geq$ 50 µg/mL after 3 doses of ramucirumab administered every 2 weeks (C_{min} will be obtained course 1 day 42 ±2 days, *ie* 2 weeks after dose 3 and just before dose 4). A rolling 6 design will be used. Starting dose will be 8 mg/kg IV every 2 weeks x 3 doses per 42 day course. In this pediatric trial in the absence of dose limiting toxicity that defines a maximum tolerated dose, we propose a dose escalation to achieve a $C_{min,ss}$ of 50 µg/mL in children and adolescents with relapsed or refractory solid tumors. One observation from the RAINBOW and REGARD trials was a tendency for concentrations to be decreased in the lower body weight quartiles in population PK analysis. The planned dose escalation in children and adolescents will permit evaluation of a higher dose to achieve comparable serum exposures seen in adults [personal communication with Eli Lilly]. If the MTD is not exceeded (0 or 1 DLT/6 fully evaluable patients) at 8 mg/kg dose level, a second dose level will be explored at the escalated dose of 12 mg/kg IV q 2 weeks x 3 doses per course. After accrual to Dose Level 2 is completed, PK comparisons from dose levels 1 and 2 will be performed. If PK analysis indicates that more than one patient treated at 12 mg/kg dose level has a day 42 C_{min} significantly less than 50 µg/mL, and the MTD has not been exceeded, additional dose levels will be considered. The next dose level will be established based on C_{min} from children who received 8 mg/kg/dose and 12 mg/kg/dose on this trial, and will not exceed 16 mg/kg per dose q 2 weeks x 3 doses (*adult MTD: 13 mg/kg weekly).* If the MTD in children and adolescents is exceeded at 8 mg/kg IV q 2 weeks x 3 doses within the 42 day evaluation period for toxicity during course 1, de-escalation to 6 mg/kg will be considered, and the recommended dose will be based on the MTD. An expansion cohort will accrue at the lowest tolerable dose at which C_{min} of ≥ 50 ug/mL has been achieved in at least 5 out of 6 evaluable patients, to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). If at least 10 out of the total 12 evaluable patients have a steady state concentration of ramucirumab greater than 50 µg/mL, then the RP2D has been defined.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at < https://ctepcore.nci.nih.gov/iam/index.jsp>). This is the same account (user id and

password) used for credentialing in the CTSU members' web site. To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. 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. Registrars must hold a minimum of an AP registration type.

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 position 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.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

3.2 IRB Approval

NCI Pediatric CIRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study.

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 3000

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions, call the CTSU General Helpdesk at 1-888-823-5923 or contact CTSU by email at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made through the OPEN website and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) an IRB-approved institutional screening protocol or b) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed

from the institutional pathology report prior to submission.

3.9 **Study Enrollment**

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age: Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Diagnosis:

Part A: Patients with recurrent or refractory non-CNS solid tumors are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except patients with extra-cranial germ-cell tumors who have

elevations of serum tumor markers including alpha-fetoprotein or beta-HCG. Patients in Part A cannot have CNS metastases.

Part B: Patients with recurrent or refractory CNS tumors will be eligible and must have a histological verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with CNS-germ cell tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

4.1.3 Disease Status: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy.

a. Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
d. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
e. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. (See table on DVL homepage listing monoclonal antibody half-lives.)
f. XRT: At least 14 days after local palliative XRT (small port); At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation.

g. Stem Cell Infusion without TBI: No evidence of active graft vs. host disease and at least 84 days must have elapsed after transplant or stem cell infusion.
h. Patients must not have received prior exposure to ramucirumab.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:
- Urine protein: ≤ 30 mg/dl in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 h urine sample.
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

- Serum albumin ≥ 2 g/dL.

4.1.7.4 Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study.

4.1.7.5 Adequate Blood Pressure Control Defined as:
A blood pressure (BP) ≤ the 95th percentile for age, height, and gender (Appendix VIII) measured as described in Section 6.4, and not receiving medication for treatment of hypertension. Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP.

4.1.7.6 Adequate Coagulation Defined as:
- INR ≤ 1.5

4.1.8 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.9 Tissue blocks or slides must be sent per Section 8.10. If tissue blocks or slides are unavailable, the study chair must be notified prior to enrollment.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use a highly effective method of contraception during protocol therapy and for at least 3 months after the last dose of ramucirumab. A highly effective method of contraception is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly. Barrier methods used alone are not highly effective methods of contraception. For female patients, if a barrier method is used, a hormonal method must be used with it to ensure that pregnancy does not occur. Abstinence is an acceptable method of birth control. Those who become pregnant while on treatment with ramucirumab must discontinue immediately and consult their treating physician.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.2.4 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.2.5 Anti-inflammatory agents: Patients who are chronically receiving aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs are not eligible.

4.2.2.6 Anti-platelet agents: Patients who are currently receiving anti-platelet agents are not eligible.

4.2.2.7 Anti-hypertensives:
Patients who are receiving anti-hypertensive medications for control of blood pressure at the time of enrollment are not eligible for this trial.

4.2.2.8 Anti-coagulation: Patients who are currently receiving therapeutic anti-coagulation with heparin, low-molecular weight heparin or coumadin are not eligible for this trial.

4.2.2.9 Belimumab: Patients who are currently receiving belimumab (a monoclonal antibody for systemic lupus erythematosus) are not eligible.

4.2.2.10 Bisphosphonate derivatives: Patients who are currently receiving bisphosphonate derivatives are not eligible.

4.2.3 Surgery: Patients who have had or are planning to have the following invasive procedures are not eligible:

- Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrollment.
- Central line placement or subcutaneous port placement is not considered major surgery. External central lines must be placed at least 3 days prior to enrollment and subcutaneous ports must be placed at least 7 days prior to enrollment
- Core biopsy within 7 days prior to enrollment.
- Fine needle aspirate within 7 days prior to enrollment.
- Surgical or other wounds must be adequately healed prior to enrollment

NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

4.2.4 Bleeding and Thrombosis:

- Patients with evidence of active bleeding: intratumoral hemorrhage by current imaging, or bleeding diathesis are not eligible.
- Patients with known or prior history in prior 3 months of esophageal varices are not eligible.

- Patients with a history of CNS arterial/ venous thromboembolic events including transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to study enrollment are not eligible.
- Patients with a history of deep vein thrombosis (including pulmonary embolism) within 3 months prior to study enrollment are not eligible.
- Patients with a history of hemoptysis or other signs of pulmonary hemorrhage within 3 months prior to study enrollment are not eligible.
- Patients with a history of ≥ Grade 3 bleeding disorders, vasculitis, or had a significant (≥ Grade 3) episode from gastrointestinal bleeding, within 6 months prior to enrollment are not eligible.
- For Part B: Patients with CNS tumors and evidence of new CNS hemorrhage of more than punctate size and/or more than three foci of punctate hemorrhage on baseline MRI obtained within 14 days prior to study enrollment are not eligible. Note: ECHO Gradient MRI sequences per institutional guidelines are required for patients with CNS tumors

4.2.5 Patients with known cardiac disease per the New York Heart Association definition such as myocardial infarction, severe or unstable angina, peripheral vascular disease, or congestive heart failure or peripheral vascular disease are not eligible.

4.2.6 Patients who have a history of fistula, gastrointestinal ulcer or perforation, or intra-abdominal abscess within 3 months of study enrollment are not eligible.

4.2.7 Patients with a history of hypertensive crisis or hypertensive encephalopathy within 6 months of study enrollment are not eligible.

4.2.8 Patients who have non-healing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrollment are not eligible.

4.2.9 Immunocompromised patients (other than that related to the primary oncologic diagnosis or to the use of corticosteroids) including patients known to be HIV positive are not eligible.

4.2.10 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.11 Patients who have received a prior solid organ transplantation are not eligible.

4.2.12 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Treatment Schedule Table		
Day	**Ramucirumab (i.v. over 60 minutes)**	**Disease Evaluation**
1	**X**	
15	**X**	

29	**X**	
42		**X**

A cycle of therapy is considered to be 42 days. A cycle may be repeated for a total of 8 cycles, up to a total duration of therapy of approximately 12 months. This is an open-label study.

Effort should be made to begin protocol therapy on Monday through Thursday if possible to accommodate correlative sample shipments.

Drug doses should be adjusted based on actual weight measured within 7 days prior to the beginning of each cycle.

Update: With the release of Amendment #2A, the dose escalation portion of the study is complete. Given this, Part B will open to patients with relapsed or refractory CNS tumors.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 42 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0.

5.3 Dose Escalation Schema (Completed)

5.3.1 Inter-Patient Escalation for Part A:

Part A of the study is an open-label, Phase 1, dose-escalation study. Ramucirumab will be administered as an intravenous infusion over 60 minutes every other week for 3 infusions over a 6-week period constituting a cycle. The anticipated maximum number of evaluable subjects required to complete Part A is 24 patients (See Section 11.1).

Patients should receive diphenhydramine (1 mg/kg, maximum dose 50 mg) (or alternative antihistamine) within 30 to 60 minutes prior to each infusion with ramucirumab. Anaphylactic precautions should be observed during ramucirumab administration. If ≥ Grade 2 infusional reaction occurs, the infusion should be stopped and supportive care given as per institutional guidelines.

See Section 6.3 for management and dose modification guidelines for infusional reactions (IRR). For the first infusion, vital signs should be monitored prior to infusion, every 30 (± 5) minutes during the infusion, and every 30 (± 5) minutes for a one-hour observation period after the completion of the infusion. If there is no evidence of an IRR during the initial 2 infusions of ramucirumab, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the one-hour observation period should be reinstituted.

The starting dose of ramucirumab will be 8 mg/kg (dose level 1) with dose levels for subsequent groups of patients as follows.

Dose Level	Dose (mg/kg)

-1	6
1*	8
2	12
3^	≤ 16

* Starting Dose Level

^ Escalation to Dose level 3 will only be considered after evaluation of PK and toxicity at dose Level 2. If $C_{min,ss}$ of ≥ 50 µg/mL has not been achieved in at least 5 out of 6 evaluable patients from dose level 2, and if the MTD has not yet been reached, then dose level 3 will be considered.

Ramucirumab will be provided by Eli Lilly and Company. **Do not use commercial supply.**

There will be no escalations beyond dose level 3 (16 mg/kg). If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 6 mg/kg (dose level -1). If dose level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

Defining RP2D: After accrual to dose level 2 is completed, PK comparisons from dose levels 1 and 2 will be performed. An expansion cohort will accrue at the lowest tolerable dose at which C_{min} of ≥ 50 ug/mL has been achieved in at least 5 out of 6 evaluable patients to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). If at least 10 out of the total 12 evaluable patients have a steady state concentration of ramucirumab greater than 50 µg/mL, then the RP2D has been defined. If $C_{min,ss}$ of ≥ 50 µg/mL has not been achieved in at least 5 out of 6 evaluable patients from dose level 2, and if the MTD has not yet been reached, then dose level 3 will be considered.

Update: The RP2D was determined to be 12 mg/kg.

5.3.2 **Part B**: Once the RP2D has been determined in Part A, Part B will open to enroll children with relapsed or refractory CNS tumors who will receive ramucirumab at the MTD or RP2D. Part B of the study will require up to 6 evaluable patients enrolled at the MTD or RP2D as determined in Part A (See Section 11.1).

5.3.3 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes

of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 Non-hematological dose-limiting toxicity

5.5.1.1 Any Grade 3 or Grade 4 non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea, vomiting, diarrhea, or constipation < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix X for toxicity grading table.
- Grade 3 fever < 5 days duration
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation

5.5.1.2 Dose-limiting hypertension

- Any Grade 4 hypertension
- A blood pressure > 25 mmHg above the 95th percentile for age, height, and gender (Appendix VIII) confirmed by repeated measurement is dose limiting.
- In patients who begin antihypertensive therapy a blood pressure > 10 mmHg but ≤ 25 mmHg above the 95th percentile for age, height, and gender (Appendix VIII) for > 14 days is dose limiting.

5.5.1.3 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles will be considered dose-limiting.

5.5.1.4 Proteinuria: Urine protein/creatinine (P/C) ratio > 1 and < 1.9 confirmed with a second measurement within 72 hours will be considered a DLT (See Section 6.5)

5.5.1.5 Any gastrointestinal perforation event will be considered a DLT and require removal from protocol therapy.

5.5.1.6 Grade ≥ 2 wound complication or wound dehiscence will be considered a DLT and require removal from protocol therapy.

5.5.1.7 Grade ≥ 3 hepatic failure will be considered a DLT and require removal from protocol therapy.

5.5.1.8 Grade ≥ 2 reversible posterior leukoencephalopathy syndrome (RPLS) will be considered a DLT and require removal from protocol therapy.

5.5.1.9 Grade ≥ 3 congestive heart failure will be considered a DLT and

require removal from protocol therapy.

5.5.1.10 Any toxicity that is possibly related to the study medication that requires removal from protocol therapy. Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

5.5.2.1 In patients evaluable for hematological toxicity (see Section 4.1.7.1), hematological dose limiting toxicity is defined as:

- Grade 4 neutropenia for > 7 days
- Platelet count < 20,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

5.5.2.2 Other hematological dose-limiting toxicities:

- Any arterial thromboembolic event (including cerebrovascular ischemia, peripheral or visceral arterial ischemia)
- Any ≥ Grade 3 venous thromboembolic event
- Any thrombotic event requiring systemic anti-coagulation
- Any ≥ Grade 3 hemorrhage

5.5.2.3 Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have dose-limiting thrombocytopenia will have their treatment held. Counts should be checked every 3-4 days for thrombocytopenia during this time. If the toxicity resolves to meet eligibility criteria parameters within 14 days, the patient may resume subsequent infusions at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.2 Patients who have dose-limiting neutropenia will have their treatment held. Counts should be checked every other day for neutropenia during this time. If the toxicity resolves to meet eligibility criteria parameters within 14 days, the patient may resume subsequent infusions at the next lower dose level. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.3 Patients who experience dose-limiting thrombocytopenia or neutropenia after two dose reductions must be removed from protocol therapy.

6.1.4 If, within a cycle, a dose-limiting hematological toxicity does not resolve to meet eligibility criteria within 14 days as stipulated in Sections 6.1.1 and 6.1.2 above, the patient must be removed from protocol therapy. In addition, patients who have a dose-limiting hematological toxicity that does not resolve to eligibility criteria within 21 days after the planned start of the *next* treatment cycle must be removed from protocol therapy.

6.1.5 Patients who experience any of the following events must be removed from protocol therapy:

- Any arterial thromboembolic event (including cerebrovascular ischemia, peripheral or visceral arterial ischemia)
- Any ≥ Grade 3 venous thromboembolic event
- Any thrombotic event requiring systemic anti-coagulation
- Any ≥ Grade 3 hemorrhage

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent infusions at the next lower dose level, except as outlined in Sections 6.4 and 6.5. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.2 If the same non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility criteria within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.3 Dose Modifications for Infusion-Related Reactions

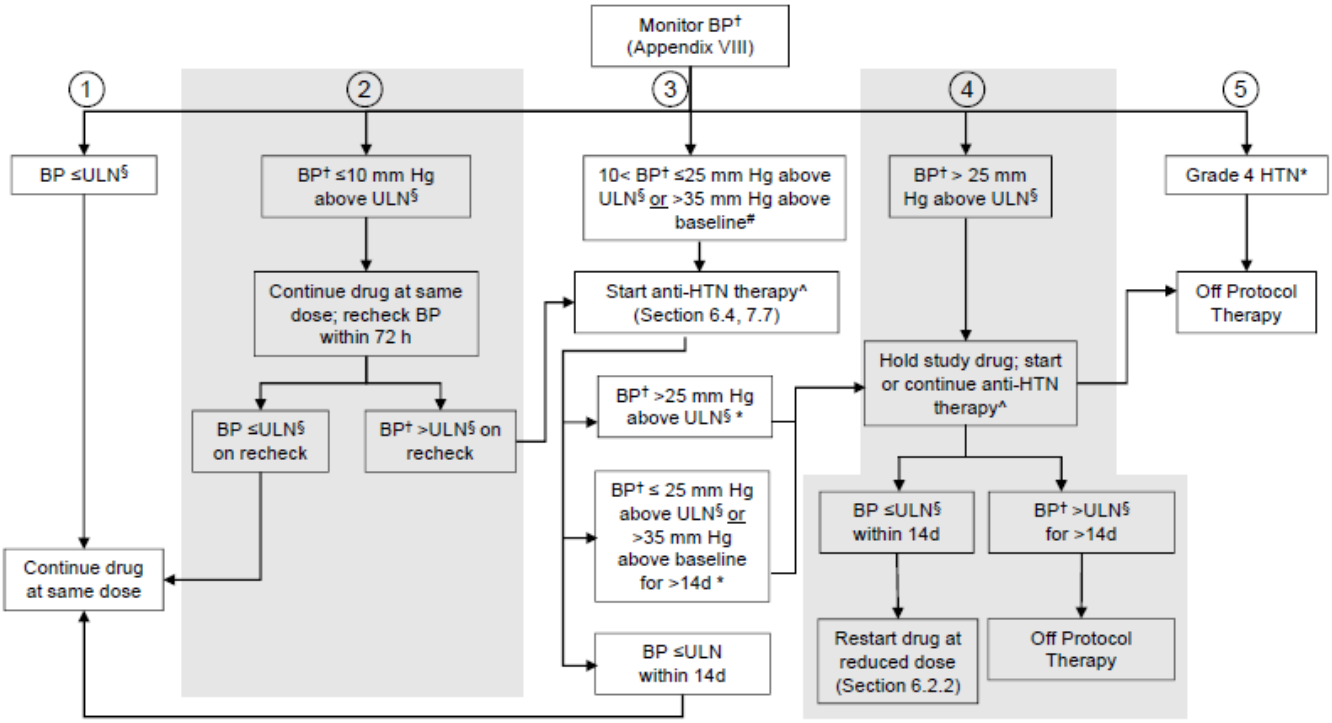
For patients who have allergic or acute infusion reactions to ramucirumab, therapy modifications based on grade should be as follows.

Grade Infusion Related Reaction	Action
Grade 1 Transient flushing or rash, drug fever < 38° C	• Monitor patient until recovery from symptoms; infusion rate may be slowed. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor patient closely. The following prophylactic premedications are recommended: diphenhydramine 1 mg/kg with max 50 mg (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg) at least 30 minutes before additional ramucirumab administrations, slowing infusion rate as above.
Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ⩾ 38°C	• Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor patient closely. • If symptoms recur, then no further ramucirumab will be administered at that visit. Administer diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent), and remain at bedside and monitor the patient until resolution of symptoms. The following prophylactic premedications are recommended: diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and acetaminophen (10-15 mg/kg, max 1000 mg) should be administered at least 30 minutes before additional ramucirumab administrations. If clinically indicated, corticosteroids (recommended dose: 1-2 mg/kg/day methylprednisolone IV or equivalent) may be used.
Grade 3 or 4 Symptomatic bronchospasm with	• Immediately discontinue infusion of ramucirumab. • Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to

or without urticaria, allergy related edema/angioedema, hypotension; Anaphylaxis	1 mg of a 1:1,000 solution for subcutaneous administration, 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, 0.01 mg/kg of 1:1000 dilution (0.01 ml/kg/dose) for intramuscular administration, and/or diphenhydramine 1 mg/kg with max 50 mg IV with 1-2 mg/kg/day methylprednisolone IV (or equivalent), as needed. • Patient should be monitored until the investigator is comfortable that the symptoms will not recur. • Ramucirumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids).

6.4 Dose Modifications for Hypertension

- **Baseline blood pressure** (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows: 1) Obtain 3 serial blood pressures from the same extremity with the patient in the same position at rest with an appropriately sized cuff. Measures must be obtained at least 5 minutes apart. Avoid using the lower extremity if possible. 2) Average the systolic blood pressure from the 2nd and 3rd measurements. 3) Average the diastolic blood pressure from the 2nd and 3rd measurements. 4) The baseline BP is the average of the systolic over the average of the diastolic measurements.
- **Elevation** in either the systolic or diastolic blood pressure should be considered when following the algorithm below.
- **The upper limit of normal (ULN)** is defined as a BP equal to the 95th percentile for age, height, and gender. See Appendix VIII.
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. If confirmed, patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage ramucirumab- related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.



Elevations in BP are based on systolic or diastolic pressures.

† Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix VIII)

* If BP >25 mm Hg above ULN for age (verified) or Grade 4 HTN at any time, hold drug. Study drug should also be held for BP ≤ 25 mm Hg above the ULN age for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.

^ Anti-hypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

Baseline BP is defined in Section 6.4.

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue ramucirumab at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue ramucirumab at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue ramucirumab at the same dose.
  - If the BP remains above the ULN on recheck, then start antihypertensive therapy (Section 7.7) and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start anti-hypertensive therapy (see Section 7.7), continue ramucirumab at the same dose, and monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue ramucirumab at the same dose and continue anti-hypertensive therapy.
  - If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the institution of anti-hypertensive therapy,

hold ramucirumab, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that ramucirumab is held. The antihypertensive therapy should be continued until the BP is less than the ULN.
  - If the BP returns to ≤ ULN within 14 days, restart ramucirumab at a reduced dose (Section 6.2).
  - If the BP remains > ULN for more than 14 days, patient is Off Protocol Therapy.
- If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** ramucirumab, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that ramucirumab is held.
  - If the BP is ≤ ULN within 14 days, ramucirumab may be restarted at a reduced dose (Section 6.2).
  - If the BP is > ULN for > 14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the 95% for age, height, and gender **hold** ramucirumab, monitor BP and administer anti-hypertensive therapy as clinically indicated.
  - If the BP returns to ≤ ULN within 14 days, ramucirumab may be restarted at a reduced dose (Section 6.2).
  - If the BP is > ULN for >14 days, the patient is Off Protocol Therapy (Section 10.1).

Arm 5 of algorithm:

- If the participant develops Grade 4 hypertension, **discontinue** ramucirumab, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy (Section 10.1).

6.5 Dose Modifications for Proteinuria

If urinalysis shows ≥ trace protein then obtain Urine Protein to Creatinine (UPC) concentrations (See Appendix IX).

Proteinuria: UPC Ratio	Action
If < 1	Continue protocol therapy
If 1-1.9	Hold next infusion. A second measurement should be obtained within 72 hours. A second confirmation of urine protein/creatinine (P/C) ratio 1-1.9 will be considered a DLT. If resolves to <1 within 14 days, resume protocol therapy. Subsequent infusions will be given at a lower dose as outlined in Section 6.2. Monitor the UPC weekly for 2 consecutive weeks once protocol therapy resumes. UPC ≥ 1 that persists ≥ 14 days will require removal from protocol therapy.
If > 1.9	Off protocol therapy

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 7.6 for drugs that should not be used concomitantly due to potential interactions with ramucirumab.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy. The Study Chair should be notified before growth factors are initiated in subsequent cycles.

7.5 Surgery

Patients should not have elective surgical procedures while on therapy. For patients who require emergent or urgent procedures, therapy should be held and may not be restarted until 28 days after major procedures and 7 days after minor procedures such as line replacement (3 days for external lines [e.g. Hickman or Broviac]), as detailed in Section 4.2.3.

7.6 Concomitant Medications

Anticoagulation: Use of therapeutic anticoagulation with heparin, low-molecular weight heparin, or warfarin should be avoided.

Anti-platelet agents: Use of aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs or anti-platelet agents for chronic use is not allowed while on study therapy.

Anti-hypertensives: Patients who develop hypertension while on study therapy may be treated with anti-hypertensive agents and may remain on therapy as long as hypertension is well controlled on medication (See Section 7.7).

The use of belimumab (a monoclonal antibody for systemic lupus erythematosus) and bisphosphonate derivatives are prohibited while the patient is on study therapy.

7.7 Concurrent Anti-Hypertensive Therapy

The algorithm in Section 6.4 will be used to grade and manage ramucirumab- related hypertension. Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine, which are permissible without discussion with the study chair) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Section 6.4.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Subsequent Cycles^	Off Protocol Therapy (30 days after last dose)
History	X	Weekly		X
Physical Exam with vital signs	X	Weekly	X	X
Pregnancy Test[1]	X		X	
Height, weight	X		X	
Performance Status	X			X
Blood Pressure[2]	X	Weekly	Every other week	X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	Weekly[4]	X
Urinalysis[5]	X	Every 2 weeks	X	X
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X	X
Creatinine, ALT, bilirubin	X	Weekly	X	X
Albumin	X		X	X
INR	X		X	X
Tumor Disease Evaluation[6]	X	End of Cycle 1	End of Cycle 2, then every other cycle	
Plain radiograph tibial growth plate[7]	X		Prior to cycles 2, 5 and every 6 months	X
ECHO or gated radionuclide study	X			X
Pharmacokinetic (PK) Studies[8]	X	X		X
Immunogenicity Studies[9]	X	X		X
Circulating Plasma Molecular Marker Studies[10]	X	X		X
Pharmacogenomic Studies[11]		X		
Peripheral Blood Flow-Cytometry (PBFC) Studies (Part A Only)[12]	X			
Tumor Tissue Studies[13]	X			

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

[1] Women of childbearing potential require a negative pregnancy test prior to starting treatment and before starting each subsequent cycle; sexually active patients must agree to use a highly effective method of contraception during protocol therapy and for at least 3 months after the last dose of ramucirumab. Abstinence is an acceptable method of birth control.

[2] Blood pressure will be measured with an appropriate sized cuff at rest. Blood pressure measurement will be repeated within the same day if the blood pressure (BP) is elevated (> the 95th percentile for age, height, and gender). Please note that 3 serial blood pressures should be obtained and averaged to determine baseline BP (See Section 6.4). If both BP measurements are >95th percentile for age, height, and gender, follow the guidelines in Section 6.4. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the 95th percentile for age, height, and gender (See Appendix VIII).

[3] If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

[4] If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3.

[5] See Appendix IX for UPC rationale and calculation and Section 6.5 for dose modifications if UPC > 1. If patient is being followed for prior proteinuria and UPC is obtained at the scheduled time points, urinalysis is not also required. If patient has proteinuria (urine protein/creatinine (P/C) ratio >1), a second measurement should be obtained within 72 hours.

[6] Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically. For patients with CNS disease (Part B), ECHO gradient MRI sequences per institutional standards are required to evaluate for hemorrhage (See Appendix X).

[7] Plain radiographs of at least one tibial growth plate should be obtained in all patients prior to first dose of protocol therapy. In patients with open growth plates, follow-up plain radiographs of the same growth plate(s) should be obtained according to Section 8.2.1.

[8] See Section 8.4 and Appendix III for timing and details of PK studies.

[9] See Section 8.5 and Appendix IV for timing and details of Immunogenicity studies.

[10] See Section 8.6 and Appendix V-A for timing and details of the pharmacodynamic Circulating Plasma Molecular Marker studies.

[11] See Section 8.7 and Appendix V-B for details of Pharmacogenomic studies.

[12] See Section 8.8 and Appendix VI for details of Peripheral Blood Flow-Cytometry (PBFC) cellular marker studies.

[13] See Section 8.10 and Appendix VII for details of Tumor Tissue studies.

8.2 Monitoring for Specific Toxicities

8.2.1 Growth Plate Toxicity

Patients will have a plain AP radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

a. If patients are found to have a closed tibial growth plate, no further radiographs will be required.

b. If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be obtained prior to cycles 2, 5 and every 6 months.

- Patients with evidence of growth plate thickening or other changes should have a knee MRI performed to further assess the degree of physeal pathology and undergo more frequent x-ray follow up at least every 3 cycles or as clinically indicated. MRI should be performed without contrast.
- Patients with knee MRI changes should be managed in an individualized manner. Decisions regarding continuation of ramucirumab should be

made after discussion with the Study Chair or Study Vice-Chair and DVL Leadership, taking into account the presence of any symptoms referable to the knee as well as the patient's response to ramucirumab. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue ramucirumab or not.

8.3 Radiology Studies

8.3.1 Bone Age/Knee MRI

All tibial radiographs and knee MRIs (if obtained) should be submitted for review.

8.3.2 Central Radiology Review for Response

Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 3 cycles) on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1416) and date and shipped to Syed Aamer at the address below:

8.4 Pharmacokinetics (Required)

8.4.1 Description of Studies and Assay:

Pharmacokinetic analysis to determine ramucirumab concentration in serum will be conducted by Eli Lilly and Company using validated ELISA assay.

8.4.2 Sampling Schedule

Blood samples (2 ml of whole blood) will be obtained prior to drug administration and at the time points outlined in Appendix III. In the event an infusion-related reaction is experienced, an additional blood sample for PK and Immunogenicity will be collected as close to the onset of the infusion-related

reaction, at the time of its resolution, and approximately 30 days after resolution of the event.

8.4.3 Sample Collection and Handling Instructions (Appendix III)
Blood samples (2 ml) will be collected in 2 mL red top serum tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.4.4 Sample Processing
1. Immediately after collection, gently invert each blood sample > 5 times and allow blood to clot for 30-45 minutes at room temperature (20-25°C, 60 min. max).
2. Centrifuge samples at room temperature for 15-20 minutes at ~1500-2000 x g.
3. Transfer serum into appropriately labeled transfer tube.
4. Store the serum samples immediately at -20°C until shipment on dry ice to Covance.

8.4.5 Sample Labeling
Each tube must be labeled with the patient's I.D. and accession number and the study I.D. (ADVL1416).

8.4.6 Sample Shipping Instructions
Refer to lab manual for detailed instructions regarding shipment of these specimens.

8.4.7 Sample Storage
Bioanalytical samples collected to measure ramucirumab concentration will be retained for a maximum of 1 year following study publication.

8.5 Immunogenicity Studies (Required)

8.5.1 Description of Studies and Assay:
Immunogenicity analysis to determine antibody production against ramucirumab will be conducted by Eli Lilly and Company using validated ELISA assay in serum.

8.5.2 Sampling Schedule
Blood samples (2.5 ml of whole blood) will be obtained prior to drug administration and at the time points outlined in Appendix IV. In the event an infusion-related reaction is experienced, an additional blood sample for PK and Immunogenicity will be collected as close to the onset of the infusion-related reaction, at the time of its resolution, and approximately 30 days after resolution of the event.

8.5.3 Sample Collection and Handling Instructions (Appendix IV)
Blood samples will be collected in 2.5 mL gold top serum tube at a site distant

from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.5.4 Sample Processing

1. Immediately after collection, thoroughly mix the blood with the clotting activation agent by inverting the tube not less than five times.
2. Allow blood to clot for 30 minutes (tube standing upright).
3. Centrifuge samples for 15-20 minutes at ~1500-2000 x g until clot and serum are well separated by a well formed polymer barrier.
4. Use pipette provided to transfer equally the serum into three appropriately labeled transfer tubes
5. Freeze serum samples at -20°C or colder until shipment on dry ice to Covance.

8.5.5 Sample Labeling

Each tube must be labeled with the patient's I.D. and accession number and the study I.D. (ADVL1416).

8.5.6 Sample Shipping Instructions

Refer to lab manual for detailed instructions regarding shipment of these specimens.

8.5.7 Sample Storage

Samples may be stored for a maximum of 15 years after study completion to enable further analysis of immune responses to ramucirumab and allow the sponsor to respond to regulatory requests related to ramucirumab.

8.6 Circulating Plasma Molecular Marker Studies

8.6.1 Description of Studies: Plasma samples will be collected as part of the ongoing efforts to understand the relationship between cancer, genetics/biology, and response to therapy, this study may analyze biomarkers relevant to pathways associated with cancer-related conditions, the mechanism of action of ramucirumab, and/or angiogenesis, and may also be used for related research methods or validation of diagnostic tools or assay(s). Potential pharmacodynamics and/or circulating markers may include, but are not limited to, placental growth factor, vascular endothelial growth factor A (VEGF-A), VEGF-C, VEGF-D, soluble vascular endothelial growth factor receptors 1, 2 and 3 (sVEGFR-1,VEGFR-2, and sVEGFR-3).

8.6.2 Sampling Schedule

Blood samples will be obtained prior to drug administration and at the time points outlined in Appendix V-A.

8.6.3 Sample Collection and Handling Instructions (Appendix V-A)

Blood samples (4 ml) will be collected in 4 mL lavender top EDTA tubes at a site distant from the infusion. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.6.4 Sample Processing

1. Immediately after collection, thoroughly mix the blood by gently inverting tube at least 8 to 10 times.
2. Centrifuge samples at ~1500-2000 x g until clot for 15 minutes until cells and plasma are well separated.
3. Use pipette provided to transfer plasma equally into three appropriately labeled transfer tubes
4. Freeze serum samples at -20°C until shipment on dry ice to Covance.

8.6.5 Sample Labeling

Each tube must be labeled with the patient's I.D. and accession number and the study I.D. (ADVL1416).

8.6.6 Sample Shipping Instructions

Refer to lab manual for detailed instructions regarding shipment of these specimens.

8.6.7 Sample Storage

The samples will be coded with the patient number and stored for up to a maximum 15 years after the study completion at a facility selected by the sponsor.

8.7 Pharmacogenomic Studies

8.7.1 Description of Studies: A blood sample will be collected for pharmacogenetic analysis. These samples are not being collected to create a biobank for unspecified disease or population genetic research either now or in the future. Samples may be periodically assessed and used to investigate variable response to ramucirumab and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of adverse events or differences in efficacy.

8.7.2 Sampling Schedule

A single blood sample (0.5 mL) will be collected in 0.5 mL lavender top microtainer and spotted on a FTA card.

8.7.3 Sample Collection and Handling Instructions: (Appendix V-B)

Record the exact time that the sample is drawn along with the exact time that the drug is administered.

Blood will be spotted onto a DBS or FTA card:

- Always use sterile technique when handling the FTA card.
- Collect 0.5 ml whole blood in a tuberculin syringe and immediately transfer to the K_2EDTA lavender top tube. Gently mix blood by inverting 10-15 times.
- Using enclosed pipette and FTA card, transfer 1 drop of K_2EDTA whole blood into each of the four circles on the FTA card, taking precaution not to contaminate the FTA card.
- Attach the bar code label containing patient identifier information in the designated area of the FTA card.

- Allow the blood spots to air dry for at least one hour at room temperature.
- After the sample has dried, carefully fold the flap over the specimen.
- Place the FTA card into the pre-labeled, foil-lined pouch provided in the kit, and seal the pouch.
- Store ambient and ship to Covance with next ambient shipment.

8.7.4 Sample Labeling
Each tube must be labeled with the patient's I.D. and accession number and the study I.D. (ADVL1416).

8.7.5 Sample Shipping Instructions
Refer to lab manual for detailed instructions regarding shipment of these specimens.

8.7.6 Sample Storage
Samples will be retained for a maximum of 15 years after study completion. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available. Genotyping data generated will be used only for the specific research scope described here, will not be used for any other purpose and will be otherwise destroyed.

8.8 Peripheral Blood Flow-Cytometry (PBFC) Studies (Part A Only)

8.8.1 Description of Studies:
The Peripheral Blood Flow –Cytometry (PBFC) cellular marker assay must be performed within 24 hours after PB collection. The Angio BioCore located at Indiana University will perform the PBFC studies.

8.8.2 Sampling Schedule (See Appendix VI)
Samples will be collected at baseline on **Day 1** of Cycle 1 prior to the 1st infusion and on **Day 43**, 2 weeks following the 3rd infusion (Cycle 2, Day 1).

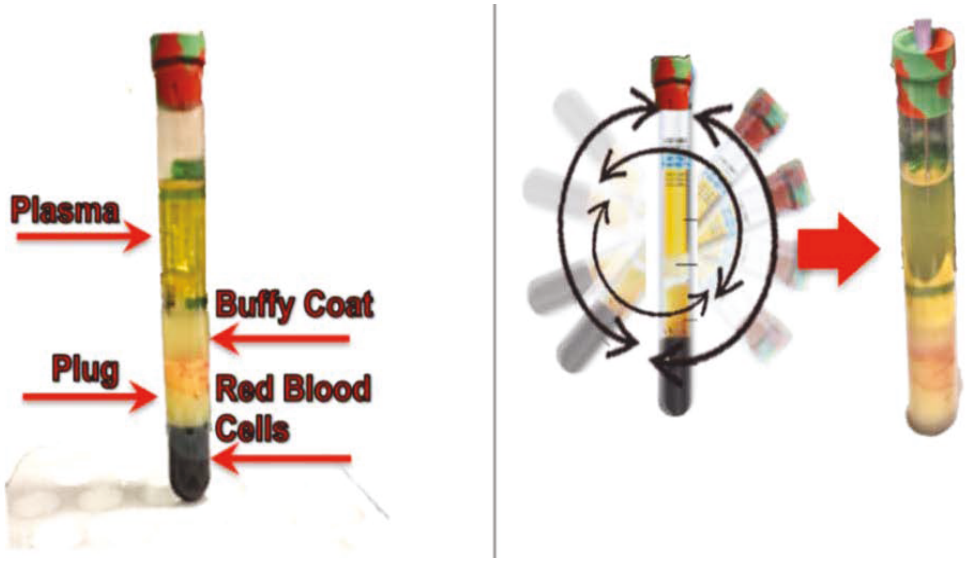
8.8.3 Sample Collection and Handling Instructions
Blood samples (8 ml) will be collected in 2 six-ml K_2EDTA tubes for flow cytometry quantification of progenitor cells. Record the exact time that the sample is drawn.

8.8.4 Sample Processing
1. Invert at least 5 times gently to avoid hemolyzing the sample.
2. Transfer blood from the K_2EDTA tubes into the CPT tube by pouring the blood gently into the CPT tube.
3. Replace the cap on the CPT and be sure that the cap is secure. CPTs should remain upright at room temperature at all times. Discard the K_2EDTA tube.
4. Centrifuge the CPT at 1500-1800 x g for 30 minutes at room temperature. Centrifugation should occur within 2 hours of drawing blood into the lavender top K_2EDTA tube. A CPT tube filled with water will be used as a balance tube. The same centrifuge should be used for all specimens if possible.

Note: The speed for centrifugation is very important. If your centrifuge only has setting for RPM, you will need to calculate the correct RPM setting.

PPD

5. Transfer the plasma and buffy coat as shown in the figure from the CPT tube by first gently rotating the CPT tube a few times and then gently pouring the supernatant into a new K_2EDTA tube ready for shipment. The red cells and the plug should remain in the CPT tube that is discarded.



8.8.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Peripheral Blood Flow-Cytometry Study Form (Appendix VI), which must accompany the sample(s).

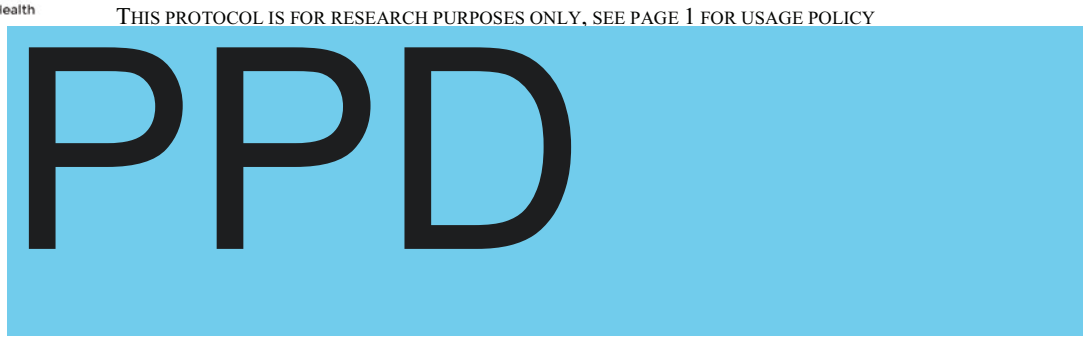
Replace the cap on the K_2EDTA tube and be sure the cap is secured TIGHT. Use parafilm or tape around the cap.

Place the labelled K_2EDTA tube along with the correlative study form in a sealed biohazard labeled plastic bag. Place plastic bag in the Styrofoam box to ship as given below.

8.8.6 Sample Shipping Instructions

Effort should be made to begin protocol therapy on Monday through Thursday if possible to accommodate correlative sample shipments. On Monday through Thursday, ship box at room temperature overnight via Federal Express Priority Overnight to the following address. **No Friday shipment should be made**.

PPD



8.9 **Tissue Studies**

8.9.1 Description of Studies

Archival tumor tissue should be submitted for all patients (10 unstained slides or a paraffin block [whole or partial]) using the Archive Tumor Tissue kit from Covance. Slides should be prepared with 5 micron tissue thickness per slide. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

Tumor samples from patients may be used for research on the drug target, disease process, pathways associated with cancer, mechanism of action of ramucirumab, and/or research method or in validating diagnostic tools or assay(s) related to cancer and will not be used for anything else.

8.9.2 Sample Labeling (Appendix VII),

Each tube must be labeled with the patient's I.D. and accession number and the study I.D. (ADVL1416). The date and time the slides were prepared should be recorded.

8.9.3 Sample Shipment

The blocks or slides of tumor material should be sent at room temperature via courier. During the warmer months (June – August), it is advisable to ship the block(s) with an ice-pack in order to prevent the melting of paraffin-embedded tissue blocks during transit. Ensure cold pack is not in direct contact with specimen. Slides should be shipped ambient to Covance immediately after they are prepared.

8.9.4 Sample Storage

The samples will be coded with the patient number and stored for up to a maximum 15 years after the study completion at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

9.0 AGENT INFORMATION

9.1 **Ramucirumab**

(Cyramza®, IMC-1121B LY3009806) NSC#749128 IND#11856

9.1.1 Description

Ramucirumab is an anti-VEGF Receptor 2 recombinant human monoclonal antibody of the IgG1 subclass. It is composed of 4 polypeptide chains, 2 identical heavy (γ) chains consisting of 446 amino acids each, and 2 identical light (κ) chains consisting of 214 amino acids each. The antibody contains 1 conserved N-linked glycosylation site at each heavy chain, in the Fc region. All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

9.1.2 Supplied by: Eli Lilly and Company. **Do not use commercial supply.**

9.1.3 Formulation

Ramucirumab is supplied in single-use, 50-mL nominal volume, United States Pharmacopeia (USP) Type I 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. 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. The osmolality is 285 mmol/kg.

9.1.4 Storage

Store intact vials of ramucirumab refrigerated at 2-8 °C (36-46°F). Protect from light. DO NOT FREEZE OR SHAKE. The formulation contains no preservatives.

Prepared dosing solution should be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared ramucirumab dosing solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F), for a duration not to exceed 24 hours. If the prepared solution is stored at room temperature (below 25°C [77°F]), it must be used within 4 hours. Store protected from light. Brief exposure to ambient light is acceptable while preparation and administration is taking place. DO NOT FREEZE AND/OR SHAKE PREPARED RAMUCIRUMAB FOR INFUSION.

9.1.5 Solution Preparation

Ramucirumab is compatible with common infusion containers. The use of a low protein binding 0.22 micron in–line filter is required. Aseptic technique is to be used when preparing and handling ramucirumab for infusion. Drug doses should be adjusted based on actual weight measured within 7 days prior to the beginning of each cycle. Based on the calculated volume of ramucirumab, add (or remove from pre-filled [with 0.9% normal saline] I.V infusion container) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to a concentration > 0.4 mg/mL by making the total volume 100 mL for patients weighing 8-25 kg, and total volume 250 mL for patients weighing > 25 kg. For patients < 8 kg total volume should be at least 50 mL and concentration should be > 0.4 mg/mL. Do not use dextrose containing solutions. The container should be gently inverted to ensure adequate mixing.

9.1.6 Stability

Prepared solutions of ramucirumab are stable for up to 24 hours refrigerated (2 – 8° C). If the prepared solution is stored at room temperature (below 25°C [77°F]), it must be used within 4 hours.

9.1.7 Administration

See Treatment and Dose Modification sections of the protocol.

Patients should receive premedication with diphenhydramine or alternative antihistamine within 30 to 60 minutes prior to each infusion with ramucirumab (see Section 5.3.1). The infusion should be delivered via infusion pump over 60 minutes. The infusion rate should not exceed 25 mg/minute. Infusions of duration longer than 60 minutes are permitted in specific circumstances (that is, for larger patients in order to maintain an infusion rate that does not exceed 25 mg/minute, or in the setting of prior ramucirumab infusion-related reaction); the infusion duration must always be accurately recorded. The infusion set must be flushed post infusion with sterile sodium chloride 0.9% equal to or greater than infusion set holdup volume to ensure delivery of the calculated dose.

9.1.8 Ramucirumab Toxicities

The toxicities in the table below are based on version 15.0 of the Investigator's Brochure and US prescribing information data from single agent trials. The following events have been observed in patients receiving single agent ramucirumab in clinical trials or are potential toxicities for anti-angiogenic agents.

Incidence	Toxicities
Common (>20% of patients)	**Gastrointestinal**: Abdominal pain
Occasional (4-20% of patients)	**Cardiovascular**: Hypertension **Blood and Lymphatic System Disorders:** Neutropenia **Gastrointestinal:** Diarrhea **Metabolism & Nutrition Disorders:** Hypokalemia, Hyponatremia **Nervous System Disorders:** Headache **Respiratory, Thoracic, & Mediastinal Disorders:** Epistaxis **Skin and Subcutaneous Tissue Disorders:** Rash
Rare (≤ 3% of patients)	**Blood and Lymphatic System Disorders:** Severe bleeding **Cardiovascular**: Arterial thromboembolic events **Gastrointestinal**: Intestinal obstruction, Gastrointestinal perforation, **General Disorders and Administration Site Conditions:** Infusion-related reactions, Impaired wound healing* **Hepatic disorders:** Worsening Liver failure** **Renal and urinary disorders:** Proteinuria
Pregnancy & Lactation	**Pregnancy** Discontinue use in pregnant women. Animal studies have not been specifically conducted to evaluate the effect of ramucirumab on female reproduction and fetal development, and there are no studies in pregnant women. Based on ramucirumab's mechanism of action, it is likely to inhibit angiogenesis and may potentially result in adverse effects during pregnancy and postnatal development. Patients (male and female) of childbearing potential must agree to use highly effective

	birth control methods during and for 3 months after participation in this study. **Lactation** There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with ramucirumab.

* Potential toxicity for anti-angiogenic class of agents
**Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome was reported in patients with Child-Pugh B or C cirrhosis who received single-agent ramucirumab.

9.2 Agent Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Eli Lilly or disposed, if approved, will be maintained by the clinical site. Before destroying any unused inventory, site should contact the Operations Center to confirm that it should not instead be returned to Eli Lilly. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all ramucirumab received from Eli Lilly. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers.

All unused or expired ramucirumab will be returned to Eli Lilly or if authorized, disposed of at the study site and documented. All material containing ramucirumab will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.3 Obtaining the Agent

Ramucirumab will be supplied by Eli Lilly. Ramucirumab can be obtained by following the instructions on the agent request form provided on the ADVL1416 protocol page of the COG website (https://members.childrensoncologygroup.org/).

The drug supply must be stored in a locked limited access area. Ramucirumab is for investigational use only, and is to be used only within the context of this study. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section 6.0).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 8 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of ramucirumab (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) Patient did not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

The study will be completed in 2 parts. Part A will be a dose-escalation phase including patients with non-CNS solid tumors, and Part B will include a safety and imaging evaluation in patients with CNS tumors.

A minimum of 2 evaluable patients will be entered at each dose level for determination of MTD. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory solid tumors without restrictions on hematologic evaluability may be enrolled to acquire PK data in a representative number of young patients (e.g six patients < 12 years old and six patients ≥12 years old). Review of the enrollment rate into previous COG new agent studies indicates that 1-2 patients per month are available. The anticipated maximum number of evaluable subjects required to complete Part A is 24 patients. Assuming a 20% inevaluable rate, 29 patients may be enrolled and the study would be expected to be completed within 15-29 months. A maximum of 51 patients may be required in the unlikely event that each of the three dose levels are expanded to 12 because two DLTs of different types are observed at each of the three dose levels, 6 additional patients are needed for PK analysis, and a 20% inevaluable rate. The maximum of 51 would be completed within 26-51 months.

Part B of the study will require up to 6 evaluable patients enrolled at the MTD or RP2D as determined in Part A. Allowing for 20% inevaluability, 8 patients may be enrolled, and this would be expected to be completed within 4-8 months. If Part B is expanded to 12 because of two different classes of DLTs, then up to 15 patients could be enrolled. The maximum of 15 patients is expected to be completed within 8-15 months.

11.2 Definitions

11.2.1 Evaluable For Adverse Effects

Any patient who receives at least one dose of the study drug(s) and who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, during Cycle 1, patients must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and do not receive at least 85% of the prescribed dose within the first cycle for reasons other than toxicities (e.g. progressive disease) will not be considered evaluable for toxicity and will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.2.3 Recommended Phase 2 Dose (RP2D):

After accrual to dose level 2 is completed, PK comparisons from dose levels 1 and 2 will be performed. An expansion cohort will accrue at the lowest tolerable dose at which C_{min} of ≥ 50 ug/mL has been achieved in at least 5 out of 6 evaluable patients to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). If at least 10 out of the total 12 evaluable patients have a steady state concentration of ramucirumab greater than 50 µg/mL, then the RP2D has been defined. If $C_{min,ss}$ of ≥ 50 µg/mL has not been achieved in at least 5 out of 6 evaluable patients from dose level 2, and if the MTD has not yet been reached, then dose level 3 will be considered.

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study. [82] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*

3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
** If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule). If there are no further dose escalations based on toxicity assessment, then the Recommended Phase 2 Dose (RP2D) will be confirmed as per Section 11.2.3.

In addition to determination of the MTD or RP2D, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of ramucirumab will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics.

While the primary aim of this study is to evaluate the toxicity of ramucirumab, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

All these analyses will be descriptive in nature.

11.6 Statistical methods

11.6.1 Analysis Sets

Safety Analysis Set (SAS) will consist of subjects who receive any amount of study drug.

11.6.2 **Dose Evaluable Set (DES)** will consist of: 1) subjects who receive any amount of study drug and then experience DLT during Cycle 1; and 2) subjects who receive at least 85% of the prescribed dose in Cycle 1 and have an adverse event assessment in the first cycle. DES will be used for evaluation of each dose level for dose-escalation.

11.6.3 **Pharmacokinetic Analysis Set** (PAS) will include subjects who have sufficient PK data to derive at least one PK parameter.

11.6.4 **Efficacy Analyses:**

Preliminary efficacy analyses will also be performed by dose cohort for the Safety Analysis Set. Data cut-off for primary study analysis will occur when all enrolled subjects have completed 6 cycles of treatment or discontinued study drug administration. After the final analysis, additional analyses may be performed as appropriate.

11.6.5 **Pharmacokinetic Analyses**

Serum concentrations of Ramucirumab will be tabulated and summarized by dose level and time. Ramucirumab PK parameters will be derived from serum concentrations by non-compartmental analyses using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, and AUC ($t_{½}$, CL, and Vd_{ss} will be calculated only if the data permit). Additional analysis utilizing the population pharmacokinetic approach may also be conducted if deemed appropriate.

11.6.6 **Immunogenicity Analyses**

Immunogenicity incidence will be tabulated, and correlation of immunogenicity to ramucirumab drug level, activity, and safety will be assessed as appropriate.

11.6.7 **Statistical Analyses**

Baseline demographics and baseline disease characteristics will be summarized for all enrolled patients who had at least one dose of study therapy.

Listing of patients including those treated at the MTD will be generated.

Treatment-emergent CTCAEs will be summarized by each dose level and for

overall population by each CTCAE grade separately.

Best overall response, duration of response, and duration of stable disease will also be summarized descriptively by each dose level.

Listing of deaths on study or 30 day post-discontinuation will be provided. Listing of SAEs will also be produced. Listing of AEs leading to treatment discontinuation will be provided.

CTCAEs possibly study drug related or regardless of causality will be presented separately.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.1.1 **Adverse Event (AE or Adverse Experience):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of Unrelated ["unrelated", "unlikely"] or Related ["possible", "probable", or "definite"]). (International Conference on Harmonisation [ICH] E2A, E6).

12.1.2 **All AEs for which a CTCAE term exists must be reported routinely as outlined in the protocol** (see Section 13.5). All Serious AEs (as defined in Table A in Section 13.1) must be reported expeditiously. For detailed AE reporting guidelines refer to the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs": **http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.**

12.1.3 **Safety Assessments**

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v 4.0 grades (for both increasing and decreasing severity) and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs; and the performance of physical examinations.

12.2 Response Criteria for Patients with Solid Tumors

See the table in section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained the next consecutive cycle following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable for response. For all other patients, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

12.2.1.2 Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

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

Note: 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. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to

reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.2.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

12.2.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

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

12.2.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

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

12.2.5 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease
The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.3.2 Complete Response
Disappearance of all evaluable disease.

12.3.3 Partial response
Partial responses cannot be determined in patients with evaluable disease

12.3.4 Stable Disease (SD)
That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.3.5 Progressive Disease
The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.3.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 MIBG Positive Lesions
Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.4.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

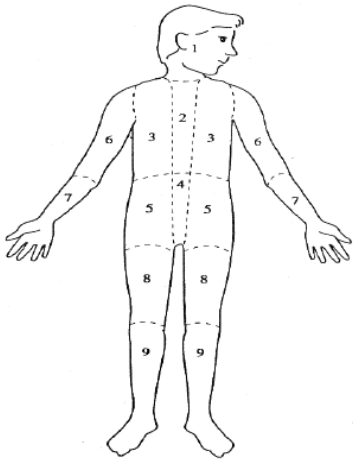
12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.3.2 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or

aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.

2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 5 in Section 12.7.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 14 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.5.2 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes

of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.7.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** ≥50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.
- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

12.6.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.6.6 Response criteria for tumor markers (if available):
Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment
The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

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

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target	**Non-Target**	**New**	**Overall**	**Best Overall Response**

Lesions	Lesions	Lesions	Response	when Confirmation is Required*
CR	CR	No	CR	≥28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

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

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 3. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

Table 4: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD

Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

Table 5: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only
If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

12.7.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). This will be described by descriptive measures of duration of response as opposed to standard time to event analysis.

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. This will be described by descriptive measures of duration of stable disease as opposed to standard time to event analysis.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

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

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

All CTCAE v 5.0 codable AEs are considered reportable for this study. For detailed AE reporting guidelines refer to the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs": http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring;

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed as Related (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated (Unrelated, Unlikely); Related (Possible, Probable, and Definite).

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **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 via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization	24-Hour, 7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization		

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.
- "24-Hour; 7 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 7 calendar days of the initial 24-hour report.

Important note: In the narrative of the CTEP-AERS Report, please provide an explanation of the investigator's opinion regarding the determination of seriousness and indicate whether the reported event(s) is related or unrelated to any protocol procedures aside from the investigational agent (e.g required observations in Table 8.1).

[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 3, 4, and Grade 5 AEs

Expedited 24-hour notification followed by complete report within 7 calendar days for:

- Grade 1 and Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

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- Any medical event that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected.

- Any adverse event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects or exposure to study drug through breastfeeding must be reported via CTEP-AERS if the event occurs following treatment with the study drug.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed as Related (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) via the web at http://ctep.cancer.gov (email the ADVL1416 COG Study Assigned Research Coordinator within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in 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 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event

Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at https://eapps-ctep.nci.nih.gov/ctepaers/. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Email supporting documentation to the ADVL1416 COG Study Assigned Research Coordinator. **ALWAYS include the ticket number on all emailed documents**.

13.3.2 Reporting to Eli Lilly

The ADVL1416 COG Study Assigned Research Coordinator will automatically forward SAE reports via email to Eli Lilly within 24 hours of receipt from the site.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG data submission forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2)

should be reported at the end of each cycle using the forms provided in the CRF packet (See Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials). The CTEP-AERS reports will be filed with Eli Lilly Global Patient Safety (GPS) by the Operations Center. Eli Lilly will retain responsibility for global reporting and distribution of all such reports to the health authorities, ethics committees and investigators.

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

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

Secondary Malignancy:

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.

All secondary malignancies that occur following treatment must be reported via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) 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.

13.7 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1416 COG Study Assigned Research Coordinator along with any additional medical information along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy 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"*** **System Organ Class (**SOC**)**.

- Pregnancy should be followed until the outcome is known. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.7.2 Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE as "Death in utero."

- Any pregnancy loss should be reported expeditiously, as **Grade 4** ***"Pregnancy loss"*** under the ***"Pregnancy, puerperium and perinatal conditions"*** **SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE as ***"Newborn deaths occurring during the first 28 days after birth"*** 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 "Death neonatal" under the "General disorders and administration" SOC **when the death is the result of a patient pregnancy or pregnancy in partners of men on study**

- Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 Access to Rave for Data Submission/ Data Reporting

Data collection for this study will be done 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, the site user 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 COG or COGC roster at the enrolling site.

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 user name 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 site 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 1-888-823-5923 or by e-mail at ctsucontact@westat.com, or by email to the COG Study Assigned Data Manager.

14.3 CDUS

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. This is not a responsibility of institutions participating in this trial.

14.4 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chair will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the COG PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

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CCI

APPENDIX II: CORRELATIVE STUDIES GUIDE

Correlative Study	Appx.	Tube Type	Blood Volume per Sample	Total Volume Cycle 1	Total Volume
Pharmacokinetics	III	Refer to manual	2 mL	**24 mL**	**34 mL**
Immunogenicity	IV	Refer to manual	2.5 mL	**7.5 mL**	**15 mL**
Circulating Plasma Molecular Marker Studies	V-A	Refer to manual	4 mL	**4 mL**	**12 mL**
Pharmacogenomics	V-B	Refer to manual	0.5 mL	**0.5 mL**	**0.5 mL**
Peripheral Blood Flow-Cytometry Studies (Part A Only)	VI	K_2EDTA tube	8 mL	**8 mL**	**16 mL**
Total Volume for All Studies				**44 mL**	**77.5 mL**
Tumor Tissue	VII				

APPENDIX III: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ACC # _____
Please do not write patient names on this form or on samples.

Weight: _____kg Dose Level: _____mg/kg Total Dose: _____mg

Blood samples (2 mL) will be collected for pharmacokinetic studies at the time points listed in the table below. Record the exact date and time each sample is drawn and the time of the ramucirumab administration. If this form will be used as a source document, the site personnel who collected the samples or research staff responsible for the research specimen must initial in the table below, next to the respective sample.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Ramucirumab Time Point	Actual Date Sample Collected or Dose Given	Actual Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
1	**Cycle 1, Day 1**	**Prior to Infusion**		___/___/___	|__|__|:|__|__|	
			Cycle 1, Day 1	___/___/___	|__|__|:|__|__|	
2	**Cycle 1, Day 1**	End of Infusion (EOI) on Cycle 1, Day 1		___/___/___	|__|__|:|__|__|	
3	**Cycle 1, Day 1**	1 hour after EOI on Cycle 1, Day 1		___/___/___	|__|__|:|__|__|	
4	**Cycle 1, Day 3 ± 1**	48 (± 24) hours after Cycle 1, Day 1 dose		___/___/___	|__|__|:|__|__|	
5	**Cycle 1, Day 8 ± 1**	7 (± 1) days after Cycle 1, Day 1 dose		___/___/___	|__|__|:|__|__|	
6	**Cycle 1, Day 15**	**Prior to Infusion**		___/___/___	|__|__|:|__|__|	
			Cycle 1, Day 15	___/___/___	|__|__|:|__|__|	
7	**Cycle 1, Day 15**	1 hour after EOI on Day 15		___/___/___	|__|__|:|__|__|	
8	**Cycle 1, Day 29**	**Prior to Infusion**		___/___/___	|__|__|:|__|__|	
			Cycle 1, Day 29	___/___/___	|__|__|:|__|__|	
9	**Cycle 1, Day 29**	End of Infusion (EOI) on Day 29		___/___/___	|__|__|:|__|__|	
10	**Cycle 1, Day 29**	1 hour after EOI on Day 29		___/___/___	|__|__|:|__|__|	
11	**Cycle 1, Day 31 ± 1**	48 (± 24) hours after Day 29 dose		___/___/___	|__|__|:|__|__|	
12	**Cycle 1, Day 36 ± 1**	7 (± 1) days after Day 29 dose		___/___/___	|__|__|:|__|__|	
13*	**Cycle 2, Day 1***	14 (± 1) days after Day 29 dose (Prior to dose on Cycle 2, Day 1)		___/___/___	|__|__|:|__|__|	
			Cycle 2, Day 1	___/___/___	|__|__|:|__|__|	
14	**Cycle 2, Day 1**	1 hour after EOI on Cycle 2, Day 1		___/___/___	|__|__|:|__|__|	
15	**Cycle 3, Day 1**	**Prior to Infusion**		___/___/___	|__|__|:|__|__|	
16	**Cycle 5, Day 1**	**Prior to Infusion**		___/___/___	|__|__|:|__|__|	
FOLLOW-UP: Date of last dose of Ramucirumab: ___/___/___ Cycle #_____						
Sample No.	**Scheduled Sample Collection Time**			**Date Sample Collected**	**Time Sample Collected (24-hr clock)**	
17	**~ 30 days after last dose of ramucirumab**			___/___/___	|__|__|:|__|__|	

*** Patients who are removed from therapy during Cycle 1 after receiving the dose should have this sample collected on Day 42 ± 1 of Cycle 1.**

In the event an infusion-related reaction is experienced, an additional blood sample for each PK and Immunogenicity will be collected if possible as close to the onset of the infusion-related reaction, at the time of its resolution, and approximately 30 days after resolution of the event.

Sample No.	Time Point	Scheduled Sample Collection Time	Date of IRR Onset/Resolution	Date Sample Collected	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
IRR-1	**Onset of IRR**	unscheduled	___/___/___	___/___/___	|__|__|:|__|__|	
IRR-2	**Resolution of IRR**	unscheduled	___/___/___	___/___/___	|__|__|:|__|__|	
IRR-3	**~30 Days Post-Resolution**	unscheduled		___/___/___	|__|__|:|__|__|	

Sample Collection and Processing: Refer to manual for sample processing and shipping details.

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. See manual for detailed guidelines for packaging and shipping PK samples to Covance.

APPENDIX IV: IMMUNOGENICITY FORM: ANTI- RAMUCIRUMAB ANTIBODY STUDIES

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Weight: _____kg **Dose Level: _____ mg/kg** **Total Dose: _____mg**

Sample Collection: Blood samples (2.5 ml) will be obtained at the time points listed in the table below. Record the exact date and time each sample is drawn and the time of the ramucirumab administration. If this form will be used as a source document, the site personnel who collected the samples or research staff responsible for the research specimen must initial in the table below, next to the respective sample.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Ramucirumab Time Point	Date Sample Collected or Dose Given	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
1	Cycle 1, Day 1	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 1	___/___/___	Start time |__|__| : |__|__|	
2	Cycle 1, Day 15	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 15	___/___/___	Start time |__|__| : |__|__|	
3	Cycle 1, Day 29	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 29	___/___/___	Start time |__|__| : |__|__|	
4	Cycle 3, Day 1	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 3, Day 1	___/___/___	Start time |__|__| : |__|__|	
5	Cycle 5, Day 1	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 5, Day 1	___/___/___	Start time |__|__| : |__|__|	
FOLLOW-UP: Date of last dose of Ramucirumab: ___/___/___ Cycle #_____						

Blood Sample No.	Scheduled Sample Collection Time	Date Sample Collected	Time Sample Collected (24-hr clock)	
6	~ 30 days after last dose of ramucirumab	___/___/___	|__|__| : |__|__|	

In the event an infusion-related reaction is experienced, an additional blood sample for PK and Immunogenicity will be collected as close to the onset of the infusion-related reaction, at the time of its resolution, and approximately 30 days after resolution of the event.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Date of IRR Onset/Resolution	Date Sample Collected	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
IRR-1	Onset of IRR	unscheduled	___/___/___	___/___/___	|__|__| : |__|__|	
IRR-2	Resolution of IRR	unscheduled	___/___/___	___/___/___	|__|__| : |__|__|	
IRR-3	~30 Days Post-Resolution	unscheduled		___/___/___	|__|__| : |__|__|	

Sample Processing Procedures: Refer to manual for sample processing and shipping details.

One copy of this Immunogenicity Study Form should be uploaded into RAVE. See manual for detailed guidelines for packaging and shipping Immunogenicity samples to Covance.

APPENDIX V-A: CIRCULATING PLASMA MOLECULAR MARKER STUDIES FORM

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Weight: _____kg **Dose Level: _____ mg/kg** **Total Dose: _____mg**

Blood samples (4 mL) will be obtained at the time points listed in the table below. Record the exact date and time each sample is drawn and the time of the ramucirumab administration. If this form will be used as a source document, the site personnel who collected the samples or research staff responsible for the research specimen must initial in the table below, next to the respective sample.

Sample Collection:

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Ramucirumab Time Point	Date Sample Collected or Dose Given	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
1	Cycle 1, Day 1	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 1	___/___/___	Start time |__|__| : |__|__|	
2*	Cycle 2, Day 1	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 1	___/___/___	Start time |__|__| : |__|__|	
FOLLOW-UP: Date of last dose of Ramucirumab: ___/___/___ Cycle #_____						
Blood Sample No.	Scheduled Sample Collection Time			Date Sample Collected	Time Sample Collected (24-hr clock)	
3	~ 30 days after last dose of ramucirumab			___/___/___	|__|__| : |__|__|	

* Patients who are removed from therapy during Cycle 1 after receiving the dose should have this sample collected on Day 42 of Cycle 1.

Sample Processing Procedures: Refer to manual for sample processing and shipping details.

One copy of this Circulating Plasma Molecular Marker Studies Form should be uploaded into RAVE. See manual for detailed guidelines for packaging and shipping Circulating Molecular Biomarker samples to Covance.

Notification of sample shipping:
Notification of sample shipment is necessary.

APPENDIX V-B: PHARMACOGENOMICS STUDY FORM

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Weight: _____kg **Dose Level: _____ mg/kg** **Total Dose: _____mg**

A single blood sample (0.5 mL) will be obtained in consenting patients. Effort should be made to collect the sample prior to infusion on Cycle 1 Day 1. See Section 8.7 for sample collection and processing details. If this form will be used as a source document, the site personnel who collected the samples or research staff responsible for the research specimen must initial in the table below, next to the respective sample.

Sample Collection:

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Date Sample Collected or Dose Given	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
1	**Cycle 1, Day 1**	Prior to infusion*	___/___/___	|__|__| : |__|__|	

*If sample is not collected at Cycle 1 Day 1, please collect at a later visit using the Retest Kit provided by Covance.

One copy of this Pharmacogenomics Form should be uploaded into RAVE. See manual for detailed guidelines for packaging and shipping Pharmacogenomics samples to Covance.

Notification of sample shipping:
Notification of sample shipment is necessary.

APPENDIX VI: PERIPHERAL BLOOD FLOW CYTOMETRY SETUDIES FORM (PART A ONLY)

COG Pt ID # _____ ACC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Weight: _____kg **Dose Level: _____ mg/kg** **Total Dose: _____mg**

Sample Collection: Samples will be collected in consenting patients at baseline on Day 1 of Cycle 1 prior to the 1st infusion and on Day 43 (Cycle 2, Day 1), 2 weeks following the 3rd infusion. See Section 8.8 for sample collection and processing details. If this form will be used as a source document, the site personnel who collected the samples or research staff responsible for the research specimen must initial in the table below, next to the respective sample.

Blood Sample No.	Time Point	Scheduled Sample Collection Time	Scheduled Ramucirumab Time Point	Date Sample Collected or Dose Given	Time Sample Collected or Dose Given (24-hr clock)	Staff Initials
1	**Cycle 1, Day 1**	Prior to infusion		___/___/___	|__|__| : |__|__|	
			Cycle 1, Day 1	___/___/___	Start time |__|__| : |__|__|	
2	**Cycle 2, Day 1**	Prior to infusion*		___/___/___	|__|__| : |__|__|	

* Patients who are removed from therapy during Cycle 1 after receiving the dose should have this sample collected on Day 42 of Cycle 1.

One copy of this Peripheral Blood Flow Cytometry Studies Form should be uploaded into RAVE. A second copy should be sent with the samples to PPD or Children at the address listed in Section 8.8.6.

APPENDIX VII: TISSUE STUDIES FORM

COG Pt ID # _____ **ACC #** _____ **Date:**_____
(Please do not write patient names on this form or on samples)

Sample Labeling:
Samples should be labeled with the following information:

Protocol number: **ADVL1416**
Institution: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
Site of Acquired Tissue: _____

Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse ☐Subsequent Resection/Biopsy

Tissue sample is from a:
☐ Resection or ☐ Biopsy

Archived paraffin-embedded tissue must be available for any previous resections for that patient (approximately 10 unstained slides or tumor block). The blocks or slides of tumor material should be sent at room temperature via courier. During the warmer months (June – August), it is advisable to ship the block(s) with a frozen gel ice-pack in order to prevent the melting of paraffin-embedded tissue blocks during transit. Ensure cold pack is not in direct contact with specimen.

All blocks or slides must be labeled with the patient's study registration number (COG Patient ID #), the study I.D. (ADVL1416), and the sample collection date. Data should be recorded on this Tissue Studies Form, which must accompany the sample(s).

One copy of this Tissue Studies Form should be uploaded into RAVE. See lab manual for detailed guidelines for packaging and shipping Pharmacogenomics samples to Covance.

One copy of this form should be uploaded into RAVE. If this form will be used as a source document, the site personnel responsible for samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel responsible for samples)

APPENDIX VIII: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for BOYS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.5.1 for definition of dose limiting hypertension, Section 6.4 for management and grading of hypertension, and Section 7.7 for medical treatment of ramucirumab related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.5.1 for definition of dose limiting hypertension, Section 6.4 for management and grading of hypertension, and Section 7.7 for medical treatment of ramucirumab related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX IX: URINE PROTEIN TO CREATININE (UPC) RATIO

Clinical Meaning of UPC

There is a good correlation between the ratio of urine protein to creatinine concentrations (UPC) in a random urine sample and the amount of protein excreted in a 24-hour urine collection period.[83] Thus, the UPC allows for an estimation of the 24-hour urine protein excretion from a random sample. The creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate:

- Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day
- Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day
- Normal protein excretion is <100 mg to 150 mg per 24 hours.
- The UPC ratio is roughly equal to the 24 hour urine protein excretion in g/day

Calculating UPC Ratio

UPC ratio = (Urine protein [mg/dL]) / (urine creatinine [mg/dL]) = numerically equivalent to grams (g) protein excreted in urine over 24 hours.

Example: If a subject has a urine protein of 90 mg/dL and urine creatinine of 30 mg/dL,
then UPC ratio = $\frac{90\ (mg/dL)}{30\ (mg/dL)} = 3$
Result UPC is 3 correlating to roughly 3g of protein excretion in a 24-hour period.

Units for UPC ratio

UPC is a calculated ratio. The guidelines in the protocol are based on having urine protein and urine creatinine measured in the same units (e.g., mg/dL). The SI units for urine protein and urine creatinine are not the same, so these must be converted to mg/dL before calculating the ratio. For reference, the conversion factors for commonly used units for protein and creatinine are provided below.

Starting units	Conversion to mg/dL
Protein (g/L)	Multiply by 100
Creatinine (μmol/L)	Divide by 88.4
Creatinine (mmol/L)	Multiply by 11.3

APPENDIX X: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN- 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for SGOT is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX XI: CTEP AND CTSU 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 >.

CTSU Registration Procedures

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

IRB Approval:
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to 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.

ites 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.

Requirements For ADVL1416 Site Registration:

- 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)
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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