This study J1S-MC-JV01 (NCT04145349) is a sub-study of Master Protocol J1S-MC-JAAA (NCT05999994)

Protocol J1S-MC-JV01 Version (g)

A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults With Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor

NCT04145349

Approval Date: 13-Dec-2021

1. Protocol Addendum J1S-MC-JV01(g) A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor

LY900023 (JAAA CAMPFIRE Protocol); Ramucirumab (LY3009806)

This addendum is to be performed in addition to all procedures required by Protocol J1S-MC-JAAA or any subsequent amendments to that protocol.

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Protocol Addendum JV01 Electronically Signed and Approved by Lilly on 7 December 2018
Protocol Addendum Amendment JV01(a) Electronically Signed and Approved by Lilly on 23 January 2019
Protocol Addendum Amendment JV01(b) Electronically Signed and Approved by Lilly on 2 August 2019
Protocol Addendum Amendment JV01(c) Electronically Signed and Approved by Lilly on 26 September 2019
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Protocol Addendum Amendment JV01(e) Electronically Signed and Approved by Lilly on 18-May-2020
Protocol Addendum Amendment JV01(f) Electronically Signed and Approved by Lilly on 09-Oct-2020
Protocol Addendum Amendment JV01(g) Electronically Signed and Approved by Lilly on date provided below.

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3. Protocol J1S-MC-JV01(g) Addendum

3.1. Synopsis

Protocol Title:

A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor

Rationale:

Study J1S-MC-JV01 (JV01) is designed to investigate the efficacy of ramucirumab in combination with low-dose cyclophosphamide and vinorelbine for the treatment of pediatric and young adult patients with Desmoplastic Small Round Cell Tumor (DSRCT).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT.	PFS
Secondary	
To evaluate the safety and tolerability of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT.	SAEs, AEs, safety laboratory assessments, and vital signs
To evaluate the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	ORR, DoR, CR
To characterize the PK of ramucirumab when co-administered with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	C_{max} and C_{min}
To assess the immunogenicity of ramucirumab when co-administered with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	Incidence of immunogenicity

Abbreviations: AE = adverse event; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DSRCT= desmoplastic small round cell tumor; DoR = duration of response; ORR = overall response; PFS = progression-free survival; PK = pharmacokinetics; SAE = serious adverse event.

Overall Design:

Study JV01 is a randomized, open-label Phase 1/2 study evaluating ramucirumab in combination with low-dose cyclophosphamide and vinorelbine in pediatric and young adult patients with relapsed, recurrent, or refractory DSRCT.

Number of Patients:

Approximately 30 patients will be enrolled.

The study must enroll a minimum of 10 patients ≤17 years old with DSRCT.

Treatment Arms and Duration:

Treatment period: patients will receive treatment until evidence of disease progression or other discontinuation criteria have been fulfilled.

Follow-up period (post-discontinuation): approximately 30 days.

	Dose and Schedule (q 28 days)			
Arm	**Ramucirumab IV, D1, and D15**	**Cyclophosphamide PO, QD**	**Vinorelbine IV, D1, D8, and D15**	**Number of Cycles**
1	12 mg/kg	25 mg/m^2	25 mg/m^2	Treatment will continue until a discontinuation criterion is met.
2	NA	25 mg/m^2	25 mg/m^2	

Abbreviations: D = day; IV = intravenous; PO = by mouth; q = every; QD = daily.

3.2. Schedule of Activities

Table JV01.1. Baseline Schedule of Activities

Day Relative to C1D1	**≤28**	**≤7**	
Procedure			**Instructions**
Informed consent	X		ICF must be signed before any protocol-specific procedures are performed
Inclusion/exclusion criteria	X		
Physical examination		X	Including height, weight, and vital signs (temperature, blood pressure, and pulse rate).
ECOG/Lansky/Karnofsky performance status		X	
Medical history	X		Including assessment of preexisting conditions, historical illnesses, and habits.
Prior and current anticancer therapy	X		
Concomitant medications	X		
AE collection	X		CTCAE, Version 5.0
Radiologic imaging and measurement of palpable or visible lesions; and chest, abdomen, and pelvis CT	X		• Perform according to RECIST 1.1 criteria • See Section 3.9.1
Plain anteroposterior radiograph of a single proximal tibial growth plate	X		Only for patients <18 years of age. See Section 3.9.3.1.2.
ECHO/MUGA	X		
ECG	X		Local testing.
Hematology		X	See Attachment 2 for designation of local or central testing.
Coagulation		X	See Attachment 2 for designation of local or central testing.
Clinical chemistry		X	See Attachment 2 for designation of local or central testing.
Urinalysis		X	See Attachment 2 for designation of local or central testing.
Pregnancy test		X	Serum or urine per institutional standard. Applies only to female of childbearing potential. See Attachment 2 for designation of local or central testing.
TSH and FreeT4		X	See Attachment 2 for designation of local or central testing.
Sample collection for:			
Pharmacokinetics	See Attachment 3		
Immunogenicity	See Attachment 3		

Genetics	See Attachment 3	
Biomarkers	See Attachment 3	

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); Free T4 = thyroxine; ICF = informed consent form; MUGA = multigated acquisition; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); TSH = thyroid-stimulating hormone.

Table JV01.2. On-Study-Treatment Schedule of Activities

For C1D1, evaluations must be done on the day of visit or within 7 days prior. For all subsequent visits, evaluations must be done on the day of visit or within 3 days prior. In case of dose interruption, these evaluations will also be done at a minimum frequency every 28 days.

	Treatment Period 28-Day Cycle						
	Cycle 1			Cycle 2-n			
Day within cycle	1	8	15	1	8	15	
Procedure							**Instructions**
Physical examination	X	X	X	X			Perform prior to administering study drug(s).
Weight and height	X			X			Perform prior to administering study drug(s). Height to be collected for patients <18 years of age only.
Vital Signs	X	X	X	X	X	X	Perform prior to administering study drug(s). • Including temperature, blood pressure, and pulse rate.
Concomitant medication	X	X	X	X	X	X	
AE collection	X	X	X	X	X	X	CTCAE, Version 5.0. To be performed before treatment.
ECOG/Lansky/ Karnofsky performance status	X			X			
Radiologic imaging and measurement of palpable or visible lesions; and chest, abdomen, and pelvis CT	Perform every 8 wk (±7 days)						• Perform according to RECIST 1.1 criteria, by the same method used at baseline, q 8 wk (±7 days) starting from C1D1 until documented disease progression per RECIST 1.1 criteria, death, or study completion, whichever occurs first. • After third evaluation of stable disease (or better) or following complete resection, may obtain every 3 months (±14 days) thereafter. • Perform as scheduled, even if study treatment is delayed or omitted. • Local testing. • See Section 3.9.1

	Treatment Period 28-Day Cycle						
	Cycle 1			Cycle 2-n			
Day within cycle	1	8	15	1	8	15	
Procedure							**Instructions**
Plain anteroposterior radiograph of a single proximal tibial growth plate (only for patients randomized to ramucirumab and with open growth plate at baseline)	See Instructions						Perform every 4 months according to Section 3.9.3.1.2. Patients must be followed for duration of study or until closure of growth plate. In some geographies, an MRI of the knee may be an alternate option instead of plain radiograph.
ECG							Single, at baseline. Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. Local testing.
Hematology	X	X	X	X	X	X	For C1D1: ≤7 days prior; subsequent collections: ≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated (Refer to Section 3.7.4 for Dose Modifications). See Attachment 2 for designation of local or central testing.
Coagulation	X			X			For C1D1: ≤7 days prior; subsequent collections: ≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated. See Attachment 2 for designation of local or central testing.
Clinical chemistry	X	X	X	X	X	X	For C1D1: ≤7 days prior; subsequent collections: ≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated. See Attachment 2 for designation of local or central testing.
Urinalysis	X		X	X		X	For C1D1: ≤7 days prior; subsequent collections: ≤3 days prior to administration of study treatment, unless more frequent assessment is clinically indicated. See Attachment 2 for designation of local or central testing.
Pregnancy test	X			X			Serum or urine per institutional standard. Applies only to females of childbearing potential. Where required by local law or regulation, perform monthly/once every 28 days (±7 days) prior to administration of study treatment. See Attachment 2 for designation of local or central testing.
Administer ramucirumab (investigational arm)	X		X	X		X	Premedicate according to Section 3.7.1.1. Patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions for the first 2 infusions (see Section 3.7.6.1.8.1).

	Treatment Period 28-Day Cycle						
	Cycle 1			Cycle 2-n			
Day within cycle	**1**	**8**	**15**	**1**	**8**	**15**	
Procedure							**Instructions**
Administer cyclophosphamide	X						
Administer vinorelbine	X	X	X	X	X	X	
Sample collection for:							
Pharmacodynamics	See Attachment 3						
Pharmacokinetics	See Attachment 3						
Immunogenicity	See Attachment 3						
Genetics	See Attachment 3						
Biomarkers	See Attachment 3						

Abbreviations: AE = adverse event; C1D1 = Cycle 1 Day 1; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); hr = hour; IV = intravenous; q = every; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); wk = week.

Table JV01.3. Post-Study-Treatment Follow-Up Schedule of Activities

Visit	Short-Term Follow-Up[a] 801	Long-Term Follow-Up 802-8XX	
Procedure			**Instructions**
Physical examination	X	X (only for patients with abnormal growth plate findings at V801)	Short-Term Follow-up: Including weight and vital signs (temperature, blood pressure, and pulse rate) Include height only for patients being followed with open growth plates on study. Long-Term Follow-up: continue to obtain height periodically at investigator's discretion until resolution of growth plate abnormalities or growth plate closure.
Concomitant medication	X		
AE collection	X		CTCAE, Version 5.0
Lansky/Karnofsky/ECOG performance status	X		
Radiologic imaging and measurement of palpable or visible lesions; and chest, abdomen, and pelvis CT	See instructions		• Perform q 8 week (±7 days) according to RECIST 1.1 criteria or q 3 months (±14 days) after third evaluation of stable disease or following surgical resection with clean margins, by the same method used at baseline and throughout the study, until one of the following occurs: o the patient has documented disease progression o patient has started new anti-cancer therapy o the study's primary/final analysis of OS.
Plain anteroposterior radiograph of a single proximal tibial growth plate for patients randomized to ramucirumab with open growth plates at baseline being followed on study	X	X (only for patients with abnormal growth plate findings at V801)	In some geographies, an MRI of the knee may be an alternate option instead of plain radiograph. Long-Term Follow-Up: Frequency of radiographs in Long-Term Follow-Up is per the investigator's discretion according to Section 3.9.3.1.2. Continue to perform until resolution of growth plate abnormalities or growth plate closure.
Collection of survival information		X	Perform q 3 months (±14 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone until death or study completion.
Collection of poststudy-treatment anticancer therapy information	X	X	Perform q 3 mo (±14 days) for the first 2 years after discontinuation from study treatment and q 6 months (±14 days) thereafter until death or study completion.
Hematology	X		See Attachment 2 for designation of local or central testing.

Visit	Short-Term Follow-Up[a] 801	Long-Term Follow-Up 802-8XX	
Procedure			**Instructions**
Coagulation	X		See Attachment 2 for designation of local or central testing.
Clinical chemistry	X		See Attachment 2 for designation of local or central testing.
Urinalysis	X		See Attachment 2 for designation of local or central testing.
TSH and FreeT4	X		See Attachment 2 for designation of local or central testing.
Sample collection for:			
Pharmacodynamics	See Attachment 3		
Pharmacokinetics	See Attachment 3		
Immunogenicity	See Attachment 3		
Genetics	See Attachment 3		
Biomarkers	See Attachment 3		

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); Free T4 = thyroxine; OS = overall survival; q = every; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); TSH = thyroid-stimulating hormone.

[a] Short-term follow-up begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Table JV01.4. Continued Access Schedule of Activities

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE, Version 5.0
PK, IG, and hypersensitivity labs for IRR events (including hypersensitivity reactions)	See instructions		In the event of an IRR (including hypersensitivity reactions), blood samples will be collected as outlined in Section 3.7.6.1.8.1 and Attachment 3.
Administer ramucirumab (investigational arm)	X		Premedicate according to Section 3.7.1.1.
Administer cyclophosphamide	X		
Administer vinorelbine	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); IG = immunogenicity; IRR = infusion-related reaction; IV = intravenous; PK = pharmacokinetics; PO = by mouth.

[a] Continued-access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3.3. Introduction

3.3.1. Study Rationale

Angiogenesis is a biologic process that is important for cancer growth and metastasis. As a result, the pathways that mediate angiogenesis are considered important targets in cancer drug development. Vascular endothelial growth factors (VEGFs; including VEGF-A, VEGF-B, VEGF-C, and VEGF-D) and placental growth factor have emerged as key regulators of angiogenesis. VEGF-A is distinct within the VEGF ligand family in that it acts as a dominant endothelial cell-specific mitogen during angiogenesis. VEGF Receptor 2 is the primary mediator of proangiogenic effects of VEGF A and experimental evidence suggests that the VEGF-A/VEGF Receptor 2 interaction plays an important role in tumor angiogenesis. Therefore, disruption of the interaction between VEGF-A and VEGF Receptor 2 may have therapeutic application in the treatment of cancer.

Angiogenesis is upregulated in pediatric embryonal tumors, making it an important pathway. 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 (Blann et al 2001; Holzer et al 2001).

Tumor angiogenesis is a prime process involved in tumor growth and requires the interaction of various cell factors, cells, and tissues (Ellis and Hicklin 2008). Targeting multiple processes, such as angiogenesis and cell cycle control, is known to effectively treat many cancers (DeVita et al. 1975; Sawyers 2004; Knight et al. 2010; Carmeleit and Jain 2011).

Soft tissue sarcomas (STSs) have been shown to express VEGF and/or VEGFR-2 to varying degrees. Multiple clinical trials targeting the VEGF pathway with mAb agents or tyrosine kinase inhibitors (TKIs) have been conducted in patients with STSs and demonstrated activity (George et al. 2009; Maki et al. 2009; Sleijfer et al. 2009; Fox et al. 2010; van der Graaf et al. 2012; Glade Bender et al. 2013; Chisholm et al. 2017). The PALATTE study, a randomized, double-blind, placebo-controlled Phase 3 trial, investigating the use of pazopanib in adult patients with advanced non-adipocytic STS, demonstrated improved median progression-free survival (PFS) in the TKI arm (van der Graaf et al. 2012). The BERNIE trial, a pediatric, open-label, randomized Phase 2 study, investigated the addition of bevacizumab to standard front-line chemotherapy and maintenance therapy versus chemotherapy and maintenance alone for patients with metastatic rhabdomyosarcoma (RMS) and non-rhabdomyosarcoma STS (NRSTS). While the study did not meet its primary end point of event-free survival (EFS) across all patients with STS, a subset analysis identified a potentially compelling benefit in the NRSTS cohort with the addition of the anti-VEGF agent. Furthermore, the safety profile of the anti-VEGF inhibitor in combination with standard front-line chemotherapy and maintenance therapy in pediatric patients with STSs was consistent with the known safety profile in adults and did not enhance toxicity in the very dense chemotherapy protocol (Chisholm et al. 2017).

In preclinical patient-derived xenograft studies using DSRCT (CTG-0926, CTG-1458) and synovial sarcoma (SS) (CTG-0331, CTG-1173) models, a mouse surrogate inhibitor targeting

VEGF Receptor 2 (DC101) had better tumor efficacy in combination with standard of care treatments (doxorubicin, docetaxel/gemcitabine, or cyclophosphamide) versus standard of care alone.

Therefore, Studies JV01 and J1S-MC-JV02 (JV02) are Phase 1/2 studies evaluating ramucirumab in pediatric patients and young adults with relapsed, recurrent, or refractory DSRCT (JV01) or SS (JV02) in combination with known chemotherapy backbones used in these settings. Tumor-specific conclusions regarding improvements in efficacy will be made for each study. As adding ramucirumab may similarly improve outcomes for patients with both diseases, the statistical analysis will also incorporate a formal mechanism to adaptively borrow information regarding relative benefit observed across both studies.

This addendum (JV01) describes the hypothesis and details of the DSRCT investigation. When relevant to the discussion, references to the synovial sarcoma investigation (JV02) will be included.

3.3.2. Background

3.3.2.1. Desmoplastic Small Round Cell Tumor

Desmoplastic Small Round Cell Tumor (DSRCT) is a rare tumor that is primarily found in adolescents and young adults typically involving the abdominal and pelvic peritoneum. DSRCT, originally described as a mesenchymal entity, is diagnosed based on the histological and immunohistochemically features of the tumor and contains the molecular hallmark of the EWS-WT1 fusion protein that results from the t(11;22)(p13;q12) translocation (Gerald and Rosai 1989; Iyer et al. 2013). Patients diagnosed with DSRCT have a median survival ranging from 17 to 25 months and long-term survival is uncommon (Dufresne et al. 2012). Irrespective of the stage of disease, age, and treatment received, the prognosis of patients with DSRCT is poor, with a 5-year survival of <20%, and an overall median survival time of 2.1 years (Lal et al. 2005; Honoré et al. 2015; Bent et al. 2016). For patients of all ages, aggressive surgical debulking (removal of at least 90% of the tumor burden) is the mainstay of the treatment strategy. The most commonly used treatment plans include multimodality treatment (radiation, chemotherapy, and surgery). Desmoplastic small round cell tumor has been shown to be chemosensitive and regimens designed for treatment of Ewing's disease are most often followed for initial treatment. However, no defined standard treatment regimens exist for the treatment of either upfront or relapsed DSRCT.

3.3.2.2. Ramucirumab

Ramucirumab is a human receptor-targeted monoclonal antibody (mAb) that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases. This neutralizes ligand-induced proliferation and migration of human endothelial cells and ultimately inhibits tumor growth and propagation.

Ramucirumab has not been approved in pediatrics; however, is being studied in the ongoing I4T-MC-JVDA (JVDA) trial. In adults, ramucirumab has improved outcomes, including overall survival, in multiple indications as both a monotherapy and in combination with other agents. Ramucirumab is approved as monotherapy or in combination with paclitaxel in the United States (US), the European Union (EU), Japan, and other countries for the treatment of adult patients with advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior platinum and/or fluoropyrimidine chemotherapy. The approvals were based on the clinical efficacy and safety demonstrated in 2 global, randomized, double-blind, and placebo-controlled Phase 3 studies, REGARD (Fuchs et al. 2014) and RAINBOW (Wilke et al. 2014).

In the US and the EU, ramucirumab in combination with FOLFIRI (irinotecan, 5-fluorouracil, and folinic acid) is approved for the treatment of metastatic colorectal cancer in adult patients with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE; Tabernero et al. 2015).

In the US, ramucirumab in combination with docetaxel is approved for the treatment of advanced non-small cell lung cancer (NSCLC) in adult patients with disease progression on or after platinum-based chemotherapy (REVEL; Garon et al. 2014).

3.3.2.3. Cyclophosphamide and Vinorelbine

Vinorelbine is a cell-cycle-dependent vinca alkaloid agent with a proven broad spectrum of activity. Pilot studies have reported vinorelbine activity in STSs such as rhabdomyosarcoma (RMS), osteosarcoma, Ewing's sarcoma, and in some brain tumors (Casanova et al. 2002; Biassoni et al. 2006; Minard-Colin et al. 2012). A Phase 1 Children's Oncology Group (COG) trial of vinorelbine demonstrated that the spectrum of hematologic and other types of toxicity in pediatric patients was much the same as in adults (Johansen et al. 2006).

Cyclophosphamide is active in the majority of pediatric malignancies, including sarcomas. Low-dose continuous oral dosing of cyclophosphamide has been used in adult and pediatric studies, usually in combination with other cytotoxic agents, with minimal toxicity (Bolis et al. 1980; Casanova et al. 2004).

The combination of vinorelbine and low-dose cyclophosphamide has been investigated in pediatric sarcomas and demonstrated tolerability in children and adolescents (Casanova et al. 2004; Ferrari et al. 2007; Minard-Colin et al. 2012; Chisholm et al. 2017). Case reports describing use of a low-dose cyclophosphamide with vinorelbine regimen have demonstrated benefit and efficacy in DSRCT patients specifically, justifying further exploration (Ferrari et al. 2007).

The European pediatric Soft tissue Sarcoma Group (EpSSG) piloted a study that assessed the combination and its efficacy in pediatric sarcoma. The maximum tolerated vinorelbine dose was found to be 30 mg/m^2, with neutropenia identified as the dose-limiting toxicity (DLT). At the recommended vinorelbine dose (25 mg/m^2), Grade 3 or 4 neutropenia was observed in 37% of all cycles, but no other major toxic events were noted. The overall acceptability and feasibility of the study regimen are supported by the finding that no patient had treatment discontinued on

account of toxicity and by the observation that many patients were treated for an extended duration, with 40% of all patients receiving at least 6 cycles of therapy (Casanova et al. 2004). Consequently, the recommended dose was oral daily cyclophosphamide 25 mg/m^2 for 28 days and intravenous (IV) vinorelbine 25 mg/m^2 on Days 1, 8, and 15.

In Minard-Colin et al. (2012), vinorelbine and continuous low-dose cyclophosphamide was evaluated in children and young adults with relapsed or refractory malignant solid tumors. The combination provided evidence for the efficacy of vinorelbine 25 mg/m^2 on Days 1, 8, and 15 administered IV in combination with oral cyclophosphamide 25 mg/m^2 per day over 28 days. Myelosuppression was the main treatment-related toxicity. Grade 3/4 neutropenia occurred in 38% of patients and 15% of patients experienced febrile neutropenia. Grade 3/4 non-hematologic toxicities were limited, occurring in <5% of patients.

In the randomized, multicenter BERNIE study of 154 pediatric patients with STS conducted by EpSSG and the European Innovative Therapies for Children with Cancer consortium, the backbone was a standard induction chemotherapy course followed by surgery and/or radiation and a maintenance therapy of low-dose cyclophosphamide and vinorelbine (Chisholm et al. 2017). The addition of bevacizumab to the chemotherapy backbone to the experimental arm was well tolerated. Overall, the median EFS for patients with all STS patients receiving chemotherapy with bevacizumab (n=74) was 20.6 months compared to 14.9 months for patients receiving chemotherapy alone (n=80; HR 0.93 95% CI: 0.61 to 1.41; p=.72), which did not meet the primary EFS endpoint to demonstrate a statistically significant improvement with the addition of bevacizumab across the entire population. However, in a subset analysis, a potentially meaningful benefit in EFS in the NRSTS cohort (n=49) was suggested, with the addition of the anti-VEGF agent (17.2 months vs 7.4 months; HR 0.64; 95% CI: 0.32 to 1.26), whereas in the RMS cohort (n=103) no difference in EFS was observed (21.3 months vs 20.1 months; HR 1.24; 95% CI: 0.73 to 2.09). Of note, DSRCT patients made up a quarter of the NRSTS population (n=12). The response rate for DSRCT patients was 40% (2 of 5 patients) in those treated with bevacizumab plus chemotherapy compared to 16.7% (1 of 6 patients) in those treated with chemotherapy alone (Chisholm et al. 2016). When considering the potential benefit a VEGF pathway inhibitor might add for patients with relapsed or refractory metastatic DSRCT, these data support exploration of the combination of ramucirumab with a non-induction chemotherapy regimen such as low-dose cyclophosphamide and vinorelbine in the relapsed and refractory setting.

3.3.3. Benefit/Risk Assessment

DSRCT is a rare tumor that is primarily found in adolescents and young adults, typically involving the abdominal and pelvic peritoneum. Currently, there is no standard of care for treating pediatric and young adult patients with DSRCT in the relapsed setting, and the outcomes are unsatisfactory, with a 5-year survival of <20%, and an overall median survival ranging from 17 to 38 months (Lal et al. 2005; Dufresne et al. 2012; Honoré et al. 2015; Bent et al. 2016). Thus, even with the common use of regimens such as cyclophosphamide and vinorelbine, there is still need for more effective treatments (Scheer et al. 2019). As DSRCT tumors display robust expression of VEGF pathway components, including VEFGR-2, VEGF-A, -C, and -D, there is

the potential for therapeutic benefit for patients resulting from VEGFR-2 inhibition with ramucirumab. Improved efficacy with ramucirumab in combination with cyclophosphamide and vinorelbine chemotherapy is expected to enhance these effects within evolving tumors by impeding the VEGF pathway's maintenance of vascular endothelial cell survival and ability to drive angiogenesis. Compelling efficacy and acceptable safety findings have also been observed when the related VEGF pathway inhibitor bevacizumab was added to a cyclophosphamide and vinorelbine backbone in 2 prospective STS studies in pediatric and young adult patients (Mascarenhas et al. 2014; Chisholm et al. 2017;).

Gastrointestinal (GI) perforation and severe bleeding including GI hemorrhage are considered key risks for the overall benefit/risk assessment of ramucirumab in the treatment of patients. However, the overall reporting rate of these events is low, and these risks are mitigated in the JV01 protocol through ongoing surveillance, identification (and exclusion) of patients with high bleeding risk, and dose modification or discontinuation of ramucirumab if a patient experiences a GI perforation/hemorrhage. In addition, the currently available data from Study JVDA indicate that the pediatric safety profile of ramucirumab is consistent with that observed in adults, and the majority of events are low grade, monitorable, and manageable. These risks, along with the potential pediatric-specific concerns of osteochondropathy of the epiphyseal growth plate and effects on renal function, which are monitored in the study, are considered acceptable when weighed against survival benefits for patients in this disease setting for which there are no other approved alternatives and a very short survival is expected. Combining ramucirumab with cyclophosphamide and vinorelbine chemotherapies—all with well-established safety profiles—is anticipated to offer improved therapeutic benefit in an area of unmet medical need and with a manageable safety profile that will be closely monitored throughout the study. Therefore, the benefit/risk assessment for ramucirumab in combination with cyclophosphamide and vinorelbine is considered favorable and supports the conduct of this trial.

3.4. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT.	PFS
Secondary	
To evaluate the safety and tolerability of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	SAEs, AEs, safety laboratory assessments, and vital signs
To evaluate the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	• ORR • DoR • CR
To characterize the PK of ramucirumab when co-administered with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	C_{max} and C_{min}
To assess the immunogenicity of ramucirumab when co-administered with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT	Incidence of immunogenicity
Exploratory	
To explore additional measures of the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in pediatric and young adult patients with DSRCT.	• OS • PFS2 • Difference in proportion of patients who become eligible for surgical resection of lesions due to documented tumor response while on study therapy
To explore the associations between biomarkers, disease state, and clinical outcomes	Biomarkers may be assessed from blood and tumor tissue samples, unless precluded by local regulations

Abbreviations: AE = adverse event; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DSRCT = desmoplastic small round cell tumor; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event.

3.5. Study Design

3.5.1. Overall Design

Study JV01, combined with Protocol J1S-MC-JAAA (hereinafter referred to as the CAMPFIRE Master Protocol), is a Phase 1/2 randomized investigation in pediatric patients and young adults diagnosed with relapsed, recurrent, or refractory DSRCT evaluating ramucirumab in combination with low-dose cyclophosphamide and vinorelbine. Patients will be randomized at a ratio of 2:1 to receive either experimental or control therapy, respectively.

The primary endpoint of the study (PFS) will be evaluated via a Bayesian analysis incorporating information regarding historical control outcomes as well as effect-size observed in Study JV02. This design allows for a reduced proportion of patients to be randomized to control therapy while

maintaining power in light of sample-size limitations associated with the underlying rarity of the disease. Details of the Bayesian analysis are provided in the Statistical Analysis Plan (SAP), Section 6.6.1.

The study design is illustrated in Figure JV01.1.

Safety Lead-in Period: To assess excessive toxicity associated with the experimental ramucirumab-based combination, a safety lead-in period will be observed via the rolling six decision framework of Skolnik et al. (2008). Based on the first 2 to 6 DLT-evaluable patients randomized in the ramucirumab arm at the planned 12-mg/kg dose (on a D1, D15 every 28 day schedule), the ramucirumab dose will be de-escalated to 8 mg/kg (on a D1, D15 every 28 day schedule) for Study JV01 should any of the 'de-escalate' criteria (Table JV01.5) be met, based on the totality of the data for which the DLTs are attributable to ramucirumab exposure. Otherwise, enrollment will continue as planned. If the dose is de-escalated, Study JV01 will be terminated for safety should any of the criteria for terminating the study be met due to DLTs observed at 8 mg/kg (Table JV01.6) based on the totality of the data. Otherwise, enrollment will continue with ramucirumab dosing at 8 mg/kg as planned. Enrollment in Study JV01 may be temporarily paused in certain circumstances in which 6 ramucirumab patients have enrolled at the current dose, but DLT data are pending in more than one patient (Table JV01.5). Patients that complete the lead-in period will continue until one of the discontinuation criteria is met. See Section 3.7.1.3 for determination of DLTs.

Table JV01.5. Rolling Six Rules (Ramucirumab at 12 mg/kg)

Number Enrolled	Number with DLT	Number without DLT	Number Pending DLT Data	Safety Lead-In Rules
2	0,1	Any	Any	Continue Lead-In at 12 mg/kg
2	**2**	0	0	**De-Escalate to 8 mg/kg**
3	0	0,1,2	3,2,1	Continue Lead-In at 12 mg/kg
3	0	3	0	Lead-In Period Ends
3	1	Any	Any	Continue Lead-In at 12 mg/kg
3	**≥2**	Any	Any	**De-Escalate to 8 mg/kg**
4	0	0,1,2,3	4,3,2,1	Continue Lead-In at 12 mg/kg
4	0	4	0	Lead-In Period Ends
4	1	Any	Any	Continue Lead-In at 12 mg/kg
4	**≥2**	Any	Any	**De-Escalate to 8 mg/kg**
5	0	0,1,2,3,4	5,4,3,2,1	Continue Lead-In at 12 mg/kg
5	0	5	0	Lead-In Period Ends
5	1	Any	Any	Continue Lead-In at 12 mg/kg
5	**≥2**	Any	Any	**De-Escalate to 8 mg/kg**
6	0	<5	≥2	Pause Enrollment for DLT Data
6	0	5,6	1,0	Lead-In Period Ends
6	1	<5	≥2	Pause Enrollment for DLT Data
6	1	5	0	Lead-In Period Ends
6	**≥2**	Any	Any	**De-Escalate to 8 mg/kg**

Abbreviation: DLT = dose-limiting toxicity.

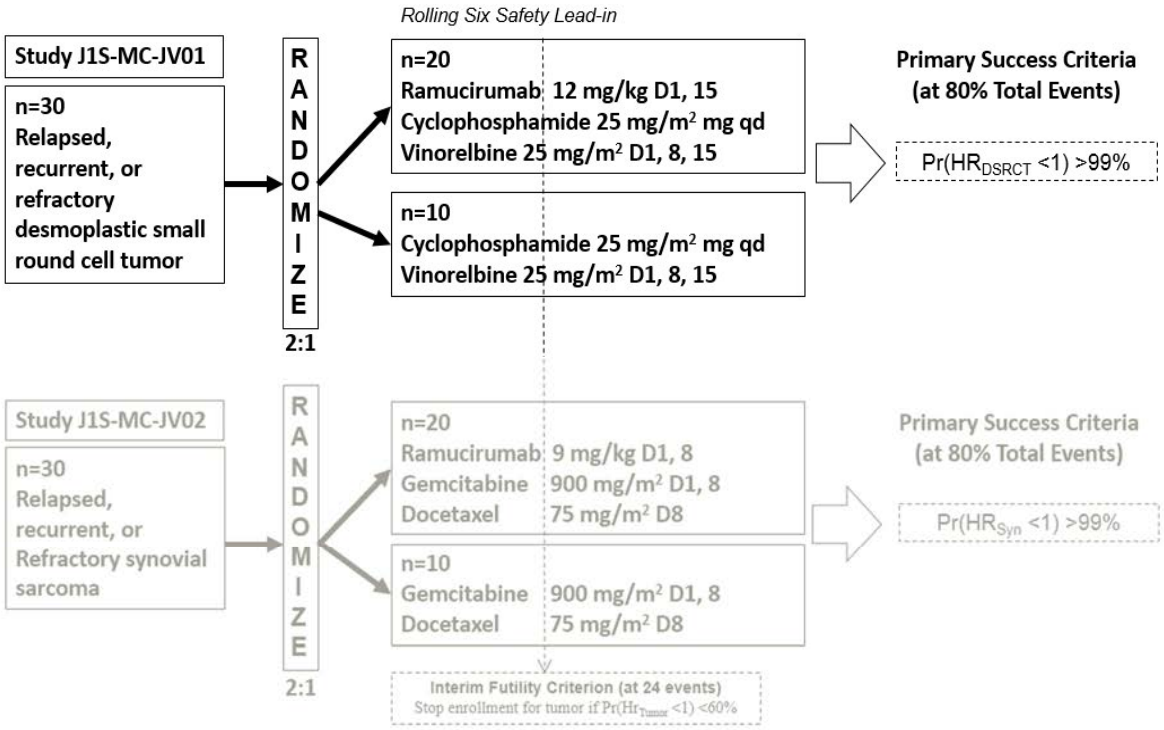
Table JV01.6. Rolling Six Rules (Ramucirumab at 8 mg/kg)

Number Enrolled	Number with DLT	Number without DLT	Number Pending DLT Data	Safety Lead-In Rules
2	0,1	Any	Any	Continue Lead-In at 8 mg/kg
2	2	0	0	**Terminate**
3	0	0,1,2	3,2,1	Continue Lead-In at 8 mg/kg
3	0	3	0	Lead-In Period Ends
3	1	Any	Any	Continue Lead-In at 8 mg/kg
3	≥2	Any	Any	**Terminate**
4	0	0,1,2,3	4,3,2,1	Continue Lead-In at 8 mg/kg
4	0	4	0	Lead-In Period Ends
4	1	Any	Any	Continue Lead-In at 8 mg/kg
4	≥2	Any	Any	**Terminate**
5	0	0,1,2,3,4	5,4,3,2,1	Continue Lead-In at 8 mg/kg
5	0	5	0	Lead-In Period Ends
5	1	Any	Any	Continue Lead-In at 8 mg/kg
5	≥2	Any	Any	**Terminate**
6	0	<5	≥2	Pause Enrollment for DLT Data
6	0	5,6	1,0	Lead-In Period Ends
6	1	<5	≥2	Pause Enrollment for DLT Data
6	1	5	0	Lead-In Period Ends
6	≥2	Any	Any	**Terminate**

Abbreviation: DLT = dose-limiting toxicity.

Interim Futility Analysis: An interim futility analysis for Study JV01 will be triggered when approximately 24 total PFS events have been observed across Study JV01 and Study JV02, with a minimum of 8 events in each study. At the interim futility look, the Bayesian analysis must provide a minimum of 60% confidence in treatment superiority (PFS hazard ratio [HR] <1 for DSRCT patients) in order for enrollment on Study JV01 to continue. Otherwise, enrollment on Study JV01 will be stopped.

Primary Analysis: If Study JV01 passes the futility analysis (and thus continues enrollment), the primary analysis will be triggered when PFS events have occurred for approximately 80% of the enrolled patients (across both Study JV01 and Study JV02, regardless of whether Study JV02 passed its futility look). In order to conclude success for the investigation in DSRCT, Study JV01 must carry a minimum of 99% confidence in treatment superiority (PFS HR<1 for DSRCT patients) evaluated via the Bayesian analysis.



Abbreviations: d = day; n = approximate number of patients per group; qd = daily.
Note: PFS to be analyzed via Bayesian analysis, which includes adaptive borrowing on effect-size between JV01 and JV02 and augmentation of control arms with historical data.

Figure JV01.1. Illustration of Study JV01 and Study JV02 Designs

3.5.2. Number of Patients

Approximately 30 patients older than 12 months and ≤29 years of age will be enrolled in Study JV01. The study must enroll a minimum of 10 patients ≤17 years old with DSRCT.

Patients will be allocated between the ramucirumab and control arm at a 2:1 ratio.

3.5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2) for the last patient.

3.5.4. Scientific Rationale for Study Design

There is currently no standard of care or approved agents for treating relapsed or recurrent DSRCT in either the pediatric or adult setting. Superiority of any one regimen has not been determined for DSRCT, though many systemic treatment regimens have been tried, likely chosen in part due to patients' past exposure, toxicity profiles, access to agents, and regional treatment preferences for pretreated sarcomas. Reports have described activity using cyclophosphamide and vinorelbine for DSRCT, with and without temsirolimus (Ferrari et al. 2007; Tarek et al. 2018).

Given DSRCT is a disease that straddles adolescence into early adulthood, with little to no expectation of difference in clinical presentation or outcome, Study JV01 will include children, adolescents, and young adult patients ≤29 years of age to ensure the study is feasible. Emphasis will be placed on enrolling patients younger than 18 years old by partnering with investigators and consortia that focus on treating pediatric patients.

3.5.5. Justification for Dose

A ramucirumab dosing regimen of 12 mg/kg once every 2 weeks (Q2W) in combination with cyclophosphamide (25 mg/m^2 once daily [QD]) and vinorelbine (25 mg/m^2 on Days 1, 8, and 15 of a 28-day [4 weeks] cycle) will be evaluated in DSCRT patients in Study JV01.

Ramucirumab dosing and schedule are based on the recommended Phase 2 dose (RP2D) dose determined in Part A of Study JVDA in conjunction with the schedule of the cyclophosphamide/vinorelbine backbone being used.

To optimize the dosing regimen sought to treat pediatric and young adult patients, the RP2D in Study JVDA was defined as the dose achieving the steady-state minimum concentration (C_{min}) of ≥50 µg/mL in a majority of patients, assuming a maximally tolerated dose was not reached. Justification for this target was based on the observed association between ramucirumab exposure and an improvement in OS and PFS in Phase 3 studies, in which exposure-response analysis across the studies indicated an EC_{50} value of ~50 µg/mL. A minimum of 50 µg/mL was therefore used as the targeted efficacious concentration level for selection of the RP2D in Study JVDA.

Results of the dose-finding component of Study JVDA identified the RP2D for pediatric and young adult patients as 12 mg/kg when administered as monotherapy on a Q2W schedule. The safety profile at the RP2D was also found to be acceptable and consistent with ramucirumab's well-characterized safety profile in the approved adult dosing regimens of 8 mg/kg Q2W and 10 mg/kg Q3W. Of interest, the 12-mg/kg Q2W ramucirumab dosing regimen has also been shown to be well tolerated in adult studies when given as monotherapy (Study JVDB) and in combination with paclitaxel (Study JVCZ) in patients with gastric cancer. As the RP2D of 12 mg/kg Q2W follows a 28-day cycle like the cyclophosphamide/vinorelbine backbone regimen-planned Study JV01, this ramucirumab regimen of 12 mg/kg Q2W has been chosen for treatment of patients with DSRCT.

To verify the weight-based dosing approach for ramucirumab in the age range proposed for Study JV01, preliminary pharmacokinetic (PK) data from Study JVDA was evaluated (ages: 3 to 21 years; body weight: 11 to 91 kg). A higher exposure was generally observed in patients receiving the 12-mg/kg dose as compared to those receiving an 8-mg/kg dose (data on file). The exposures observed in Study JVDA were similar to those observed in adult patients (data on file). Moreover, within each dose level, similar ramucirumab exposures were observed across the age and body weight ranges studied in Study JVDA (data on file), indicating the body weight-based dosing regimen is expected to produce comparable exposure levels for patients within the age range from 3 to 21 years old. The PK data from adult patients also suggested a

similar exposure level for patients from 21 to 29 years following the same body weight-based dosing regimen. Of note, PK data is not available for patients less than 3 years old.

Safety data from the non-central nervous system (CNS) arm of JVDA (Part A) includes data from 23 patients. There were no deaths or life-threatening events reported due to treatment-emergent adverse events (TEAEs) during the study. One patient experienced a dose-limiting toxicity (DLT) at each dose level. Both events were Grade 2 proteinuria, which resulted in each patient discontinuing treatment on their respective dose level. No other patients discontinued treatment due to TEAEs.

Nine out of 23 patients experienced at least 1 serious adverse event (SAE) (39.1%), 2 (25.0%) at Dose Level 1 and 7 (46.7%) at Dose Level 2. The most frequently reported SAEs were pyrexia (3 patients) and dyspnoea and hypoxia (2 patients each), all reported at Dose Level 2. Other relevant SAEs were pulmonary hemorrhage, lung infection, and possible infection (1 patient each). The SAEs reported were Grades 2 and 3, none of which required patients to discontinue from treatment. Most SAEs were consistent with the expected courses for the underlying diseases and/or for patients on ramucirumab treatment.

All patients experienced at least 1 TEAE. A higher incidence of individual TEAEs was observed at Dose Level 2 compared with Dose Level 1 for the majority of events reported; however, most of the TEAEs were low-grade (Grade 1 or 2), with a similar number of Grade 3 events in both dose levels. Overall, the most common TEAEs, occurring in >40% of patients, were aspartate aminotransferase (AST) increased (13 patients), anaemia and nausea (11 patients each), and vomiting and headache (10 patients each). A total of 13 patients (56.5%) experienced Grade 3 TEAEs, 5 patients in Dose Level 1 (62.5%) and 8 patients in Dose Level 2 (53.3%). The most common Grade 3 TEAEs included lymphocyte count decreased and pyrexia and hypoxia (2 patients each).

Adverse events of special interest (AESIs) typically seen in adult patients treated with ramucirumab, including bleeding/hemorrhage, hypertension, and proteinuria, were also observed in pediatric and young adult patients, and were primarily Grade 1 or 2 events.

As these are recognized events occurring with ramucirumab, the JV01 study incorporates risk minimization measures for these AESIs including exclusion of patients at higher risk of these events, i.e., those with uncontrolled hypertension, increased risk for bleeding, or high levels of urine protein at baseline. In addition, throughout the study there is routine and frequent monitoring, with guidelines for supportive care, dose modifications, and treatment discontinuation to assist in the management of these events.

To further mitigate potential safety risks and ensure the proposed regimen maintains an acceptable safety profile in DSCRT patients, a safety lead-in will be conducted to assess the safety and tolerability of ramucirumab administered IV at a dose of 12 mg/kg every 2 weeks in combination with cyclophosphamide and vinorelbine, since the selected combination has not been previously studied. Based upon the review of the early safety analysis, study modifications may be warranted.

In summary, the dosing regimen of ramucirumab 12 mg/kg IV on Day 1 every 2 weeks in combination with cyclophosphamide (25 mg/m^2 QD) and vinorelbine (25 mg/m^2 on Days 1, 8, and 15 of a 28-day [4 weeks] cycle) was selected for this study to potentially maximize clinical benefit, and is anticipated to produce a favorable benefit-risk profile in DSCRT patients.

3.6. Study Population

3.6.1. Inclusion Criteria

Patients are eligible to be included in the Study JV01 only if they meet all of the inclusion criteria in Section 6.1 of the **CAMPFIRE Master Protocol** and the following criteria:

[14] Patients must be 12 months to ≤29 years of age at the time of study enrollment.

a) In the European Union (EU) countries participating in Voluntary Harmonization Procedure (VHP, see Attachment 1), patients must be 36 months to ≤29 years of age, >11 kg at the time of study enrollment, and must be able to swallow cyclophosphamide tablets.

[15] Patients with relapsed, recurrent, or refractory DSRCT.

[16] Patients must:

- have measurable disease by RECIST 1.1.
- have received at least one prior line of systemic treatment (including neoadjuvant and adjuvant chemotherapy). This prior treatment must include approved therapies for which they are eligible, unless the patient is not a suitable candidate for the approved therapy.
- not be eligible for surgical resection at time of enrollment.

[17] Patients must not have received prior exposure to ramucirumab.

[18] Adequate cardiac function, defined as:

- Shortening fraction of ≥27% by echocardiogram, or
- Ejection fraction of ≥50% by gated radionuclide study.

[19] Adequate blood pressure (BP) control, defined as:

- Patients ≥18 year-old:
  - The patient has controlled hypertension defined as systolic BP≤150 mmHg or diastolic BP≤90 mmHg where standard medical management is permitted. Please note that ≥2 serial BP readings should be obtained and averaged to determine baseline BP.
- Patients <18 years-old:
  - A BP≤95th percentile for age, height, and gender measured as described in NHBPEPWG on High Blood Pressure in Children and Adolescents (2004), where standard medical management is permitted. Please note that ≥2 serial BP readings should be obtained and averaged to determine baseline BP.

[20] The patient has an adequate coagulation function as defined by International Normalized Ratio ≤1.5 or prothrombin time ≤1.5×ULN, and partial thromboplastin time ≤1.5×ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their therapeutic use. Patients must have no history of clinically significant active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).

3.6.1.1. Exceptions to the CAMPFIRE Master Protocol Inclusion Criteria

For Study JV01, the below inclusion criteria should be used in place of the CAMPFIRE Master Protocol inclusion criteria of the corresponding number.

[4] Patients must have discontinued all previous treatments for cancer or investigational agents ≥7 days after the last dose or as shown below, and must have recovered from the acute effects to ≤Grade 2 for alopecia and decreased tendon reflex and to ≤Grade 1 for all other effects at the time of enrollment, unless otherwise noted. For agents with known AEs occurring beyond the required wait period outlined in the table, this period must be extended until after the time during which the AE is known to occur. Consult with the Lilly CRS/CRP for the appropriate length of time prior to the first dose of study treatment on additional therapies not mentioned.

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Cytotoxic and myelosuppressive chemotherapy	≥14 days after the last dose of cytotoxic or myelosuppressive chemotherapy (or ≥42 days if prior nitrosourea)
Hematopoietic growth factors	≥14 days after the last dose of a long-acting growth factor (for example, pegfilgrastim) or ≥48 hours for short-acting growth factor
Cellular therapy	≥42 days after the completion of any type of cellular therapy (eg modified T cells, NK cells, dendritic cells, etc.) agent
Interleukins, interferons, and cytokines (other than hematopoietic growth factors)	≥21 days after the completion of interleukins, interferon, or cytokines (other than hematopoietic growth factors)
Antibody therapy	≥21 days after the last infusion of antibody therapy. For patients in the EU countries participating in VHP, the washout-period after previous antibody therapy is defined as 4 half-lives after the last dose of the antibody.
Radiotherapy	≥ 14 days since local palliative radiation therapy (RT) (small port); craniospinal XRT, or 50% or greater pelvic radiation; ≥ 42 days for other substantial radiation (such as metaiodobenzylguanidine therapy)
Radiopharmaceutical therapy (eg, radiolabeled	≥42 days after systemically administered

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
antibody, 131I-MIBG)	radiopharmaceutical therapy
Stem cell infusion without TBI	≥84 days must have elapsed after auto-transplant or stem cell infusion
Corticosteroids	≥14 days for patients who have received a course of systemic corticosteroids (≥5 days) to modify immune AEs related to prior therapy. Note: Patients who are on chronic replacement dose for endocrine disorders or are on a stable or decreasing dose for indications other than treating the underlying cancer, may still be eligible (consult Lilly CRP/CRS)
Live vaccines	≥28 days after last live vaccine

[5] The patient has adequate hematologic, organ, and coagulation function ≤1 week (7 days) prior to first dose of study drug:

System	**Laboratory Value**
Hematologic	
ANC	≥750/μL (≥1500/μL for patients in the EU countries participating in VHP) G-CSF permitted up to 48 hours prior. Patients with documented history of benign ethnic neutropenia or other conditions could be considered with a lower ANC after discussion with and approval from the Lilly CRP/CRS
Platelets	≥75,000/mm^3 (≥100,000/mm^3 for patients in the EU countries participating in VHP) Platelet transfusion permitted up to 72 hours prior.
Hemoglobin	≥8 g/dL (≥80 g/L)
	Transfusions to increase the patient's hemoglobin level to at least 8 g/dL are permitted; however, study treatment must not begin until 7 days after the transfusion, and CBC criteria for eligibility are confirmed within 24 hr of C1D1
Hepatic	
Total bilirubin	≤1.5×ULN Except patients with document history of Gilbert Syndrome who must have a total bilirubin level of <3.0×ULN
ALT and AST	≤2.5×ULN **OR** ≤5.0×ULN if the liver has tumor involvement

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; G-CSF = granulocyte-colony stimulating factor; ULN = upper limit of normal.

Adequate renal function, defined as:

- Creatinine clearance or radioscope glomerular filtration rate (GFR) ≥60 mL/min/m^2 (Appendix 4) OR

- Serum creatinine meeting the following parameters:
    - for patients ≥18 years of age serum creatinine ≤1.5×upper limit of normal (ULN);

    - for patients <18 years of age, 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	1.0	1.0
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
16 to <18 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (Appendix 4).

- Urine protein meeting the following parameters:
    - for patients ≥18 years of age: <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <2 g of protein in 24 hours or the urine protein to creatinine (UPC) ratio from a random urine sample can be calculated and must be <1 to allow participation in the study.
    - for patients <18 years of age: ≤30 mg/dl urine analysis or <2+ on dipstick. If urine dipstick or routine analysis indicates proteinuria >30mg/dl or ≥2+, then either a 24-hour urine can be collected and must demonstrate <1 g of protein in 24 hours or the urine protein to creatinine (UPC) ratio from a random urine sample can be calculated and must be <1 to allow participation in the study.

[7] Both female and male patients of childbearing potential must agree to use highly effective contraceptive precautions during the trial, <u>for at least</u> 3 months following the last dose of <u>ramucirumab and vinorelbine, and 12 months following the last dose of cyclophosphamide</u> in order to prevent pregnancy.

Females of child-bearing potential (FOCBP) and males who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with someone of the opposite sex. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception.

Females: FOCBP participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine or serum pregnancy test at the screening visit. Two forms of effective contraception, where at least one form is highly effective (less than 1% failure rate; includes combination oral contraceptives, implanted contraceptives, or intrauterine devices) must be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, or female condom with spermicide). It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Males: Males, regardless of their fertility status, with nonpregnant FOCBP partners must agree to use condoms as well as one additional highly effective method of contraception (less than 1% failure rate; includes combination oral contraceptives, implanted contraceptives, or intrauterine devices) for the duration of the study and up to 3 months following the last dose of study drug, or longer, if appropriate for other study drugs according to their label in order to prevent pregnancy.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined. Males with pregnant partners should use condoms during intercourse for the duration of the study and for at least 3 months after the last dose of study drug, or longer, if appropriate for any study drug according to the label.

3.6.2. Exclusion Criteria

Patients will be excluded from Study JV01 if they meet any of the exclusion criteria in Section 6.2 of the **CAMPFIRE Master Protocol** or the following criteria:

[21] Are currently taking any prohibited medications outlined in Attachment 5.

[22] Bleeding and thrombosis:

- Patients with evidence of active bleeding or a history of significant (≥Grade 3) bleeding event within 3 months prior to enrollment are not eligible.
- Patients with a bleeding diathesis or vasculitis are not eligible.
- Patients with known or prior history in the prior 3 months of esophageal varices are not eligible.
- Patients with a history of deep vein thrombosis requiring medical intervention (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.

[23] Cardiac:

- Patients with a history of central nervous system (CNS) arterial/venous thromboembolic events (VTEs) including transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to study enrollment are not eligible.
- Patients with myocardial infarction or unstable angina within the prior 6 months.
- Patients with New York Heart Association Grade 2 or greater congestive heart failure (CHF).
- Patients with serious and inadequately controlled cardiac arrhythmia.
- Patients with significant vascular disease (eg, aortic aneurysm, history of aortic dissection).
- Patients with clinically significant peripheral vascular disease.

[24] Patients who have a history of fistula, gastrointestinal (GI) ulcer or perforation, or intra-abdominal abscess within 3 months of study enrollment are not eligible.

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

[26] 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.

[27] Patients previously treated and progressed on combination cyclophosphamide and vinorelbine regimen. Patients who received combination as maintenance therapy, without progression, would be eligible.

[28] Patients with a known hypersensitivity to ramucirumab, cyclophosphamide, vinorelbine or any of the excipients of the medicinal products.

[29] Hepatic impairment:

- Severe liver cirrhosis Child-Pugh Class B (or worse)
- Cirrhosis with a history of hepatic encephalopathy

- Clinically meaningful ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis
- History of hepatorenal syndrome.

[30] The patient has a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (eg, hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

[31] The patient has a urinary outflow obstruction

[32] The patient has Grade 2 hematuria or non-infectious cystitis at the time of screening.

[33] Patients with CNS involvement are ineligible.

3.6.2.1. Exceptions to the CAMPFIRE Master Protocol Exclusion Criteria

There are no exceptions to the CAMPFIRE Master Protocol exclusion criteria.

3.6.3. Lifestyle Restrictions

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on cytochrome P450 (CYP)3A4 and the potential for toxicities related to cyclophosphamide.

3.7. Treatments

3.7.1. Treatments Administered

A delay of a dose due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of ±3 days and not counted as a protocol deviation. However, clinical assessment time frames relative to drug administration, as shown in the schedule of activities, must be maintained.

3.7.1.1. Premedication

All premedication administered must be adequately documented in the electronic case report form (eCRF).

3.7.1.1.1. Ramucirumab

Patients should receive premedication with diphenhydramine or an alternative antihistamine within 30 to 60 minutes prior to each infusion with ramucirumab.

3.7.1.2. Dosing Schedule

The following treatments will be administered in this study every 4-week (28-day) cycle:

Table JV01.7. Treatment Regimens/Dosing Schedule

Study Drug	Arm	Dose	Route	Timing
Ramucirumab[a]	1	12 mg/kg[b]	IV	Approximately 1-hour infusion on Days 1 and 15 of each 28-day cycle.
Cyclophosphamide	1 and 2	25 mg/m^2	PO	Daily on Days 1-28 of each 28-day cycle
Vinorelbine	1 and 2	25 mg/m^2	IV	Days 1, 8, and 15 of each 28-day cycle

Abbreviations: kg = kilogram; IV = intravenous; mg = milligram; PO = by mouth.

[a] Patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions for the first 2 infusions (see Section 3.7.6.1.8.1).

[b] During the rolling-six safety lead-in, de-escalation of ramucirumab to 8 mg/kg may be necessary per Table JV01.5.

A cycle is defined as an interval of 28 days.

For patients on the ramucirumab arm, ramucirumab is to be administered first, followed by vinorelbine on days when both are to be given. During the first two ramucirumab infusions, patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions prior to being administered vinorelbine (see Section 3.7.6.1.8.1). On these visits, cyclophosphamide must also be taken in clinic following the ramucirumab infusion observation period. On all other days, including days of study treatment, cyclophosphamide may be taken at home prior to clinic visits. In addition, vinorelbine may be given without the post-ramucirumab observation period after the first two ramucirumab infusions, unless an infusion-related reaction (IRR) has occurred.

Cyclophosphamide will be administered orally at a dose of 25 mg/m^2 every day (no rest between cycles) in the morning. It is recommended patients take cyclophosphamide with adequate fluid intake (at least 1 L/m^2 per day) in order to minimize damage to the transitional epithelium. If oral cyclophosphamide is administered in capsules/tablets of 50 mg, which cannot be cut into smaller capsules/tablets, the doses should be divided over an adequate number of days to maintain an average daily dose over 28 days (or 1 cycle) within the 10% margin for body surface area (BSA) as per institutional guidelines. There should be no more than 2 planned days between consecutive doses of cyclophosphamide capsules/tablets. For example, in the case of a patient with a BSA of 1.3 m^2, the daily dose should be 32.5 mg, corresponding to about 100 mg every 3 days; therefore, one entire capsule/tablet (50 mg) should be given for two consecutive days followed by one day off.

Cyclophosphamide may be reconstituted to a concentration of 2 mg cyclophosphamide per mL in aromatic elixir, USP for oral administration for subjects who are unable to swallow tablets. The oral administration may be prepared by dissolving cyclophosphamide for injection in aromatic elixir, USP, which is a compendial product with a defined composition of a suitable essential oil, sucrose syrup, talc, ethyl alcohol, and purified water. Such preparations should be stored under refrigeration in glass containers and used within 14 days. See the pharmacy manual for more information.

After the start of a cycle, treatment should continue on schedule if possible, but a variance of ±3 days may be allowed to accommodate holidays, weekends, inclement weather, or other justifiable events. If the patient's weight fluctuates by more than ±10% from the weight used to calculate the prior dose, the dose of study drugs must be recalculated. Study treatment may be modified according to Section 3.7.4.

If ramucirumab Day-1 dose is delayed, a minimum of 2 weeks between ramucirumab administration is required.

Intravenous study drugs can only be administered at the investigational site, at-home administration is not permitted in this study. In the event of treatment delays of IV study drugs that is greater than 1 treatment cycle (28 days), unrelated to AEs but due to unforeseeable circumstances (e.g., COVID-19 pandemic resurgence) and in the principal investigator's discretion the patient has experienced clinical benefit, a discussion with Lilly CRP/CRS should occur before resuming IV study drugs. In addition, all on-treatment SoA as in Table JV01.2 must resume.

If a dose de-escalation is deemed appropriate during the safety lead-in period due to DLTs (Table JV01.5), the dose of ramucirumab will de-escalate from 12 mg/kg to 8 mg/kg intravenous (IV). No changes to the procedures will be affected with the exception of the dose of ramucirumab.

During the course of study treatment, patients may become eligible and undergo surgical resection of their disease. These patients may continue to receive study treatment if deemed beneficial in consultation with the Lilly CRP/CRS. Treatment should be held before surgery and resume at least 14 days postsurgery when acute toxicities of surgery are recovered per investigator discretion. Patients should continue to follow study procedures outlined in the protocol including radiologic evaluation.

Ramucirumab contains 0.1 mg of polysorbate 80 in each 1 ml of medicinal product, which is equivalent to 0.12 mg/kg per dose. Rarely, patients can experience severe allergic reactions to polysorbates. Each ramucirumab 10 ml vial contains 17 mg of sodium which is less than 1 mmol sodium (23 mg), that is, essentially 'sodium free.'

See guidelines on supportive care (Section 3.7.6.1) while administering study treatment. For any specific concerns not discussed in the guidelines, investigators should consult the PI for additional precautions.

3.7.1.3. Dose-Limiting Toxicity Determination

A DLT is defined as one of the following adverse events (AEs) reported during Cycle 1 of the rolling six safety lead-in (Table JV01.5), if considered to be definitely, probably, or possibly related to ramucirumab by the investigator; and fulfills any one of the following criteria using NCI CTCAE Version 5.0:

1. Hepatic biochemical tests will be considered DLTs as follows:

Patients with normal or near normal alanine aminotransferase (ALT) or AST at baseline (<1.5x ULN):

- ALT or AST ≥8× ULN on 2 or more consecutive tests (at least 2 days apart) in the absence of a clear cause of hepatic injury other than the study drug.
- ALT or AST ≥3× ULN and TBL ≥2× ULN on 2 or more consecutive tests (at least 2 days apart) in the absence of significant cholestasis and in the absence of a clear cause of hepatic injury other than the study drug.

Patients with elevated ALT or AST at baseline (≥1.5x ULN):

- ALT or AST ≥5× baseline on 2 or more consecutive tests (at least 2 days apart) in the absence of a clear cause of hepatic injury other than the study drug.
- ALT or AST ≥3× baseline and TBL ≥2× ULN on 2 or more consecutive tests (at least 2 days apart) in the absence of significant cholestasis and in the absence of a clear cause of hepatic injury other than the study drug.

2. Any other nonhematologic toxicity Grade ≥3 will be considered as DLT with the following exceptions:

   a) Grade 3 nausea, vomiting, diarrhea, and constipation that can be controlled with treatment. If persisting more than 72 hours despite maximal supportive intervention, considered a DLT.

   b) Asymptomatic transient Grade 3 electrolyte disturbance that can be controlled with oral substitution therapy or by IV infusions, and does not require hospitalization.

   c) Grade 3 fatigue.

   d) Grade 3 fever or Grade 4 fever <48 hours.

   e) Grade 3 infection.

   Note: Allergic reactions are NOT considered a DLT, even if necessitating discontinuation of a study drug.

3. The following hematologic toxicities will be considered DLTs:

   a) Grade 4 anemia, persistent despite maximal supportive intervention
   b) Platelet count <20,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7-day period
   c) Platelet count <50,000/mm^3 if associated with medically relevant bleeding
   d) Absolute neutrophil count (ANC) <500/mm^3 for >7 days
      - Note: Febrile neutropenia will only be considered a DLT if the ANC<500/mm^3 for >7 days.
   e) Myelosuppression that causes a delay of >14 days in initiating Cycle 2.
   f) Other hematological DLTs:

• Any arterial thromboembolic event (ATE; including cerebrovascular ischemia, peripheral or visceral arterial ischemia)

• Any ≥Grade 3 VTE

• Any thrombotic event requiring systemic anti-coagulation

• Any ≥Grade 3 hemorrhage

4. Hypertension:

a) Patients ≥18 years old: Grade 3 or 4 as defined in the CTCAE v5.0
b) Patients <18 years old:
   - Any Grade 4 hypertension
   - BP>25 mmHg above the 95th percentile for age, height, and gender confirmed by repeated measurement is dose-limiting
   - In patients who begin and are compliant on antihypertensive therapy BP>10 mmHg, but ≤25 mmHg, above the 95th percentile for age, height, and gender (NHBPEPWG on High Blood Pressure in Children and Adolescents, 2004) for >14 days despite appropriate management with antihypertensive therapy is dose-limiting.

5. Proteinuria:

a) Patients ≥18 years old: 24-hour urine protein of 2 to 3 g/24 hours confirmed with a second measurement within 72 hours; or ≥3 g/24 hours on first assessment.
b) Patients <18 years old: urine protein/creatinine (P/C) ratio of >1 and <1.9, calculated from a random urine collection and confirmed with a second measurement within 72 hours; or a UPC ratio >1.9 on first assessment.

6. Any GI perforation event

7. Grade ≥2 posterior reversible encephalopathy syndrome (PRES)

8. Grade 5 toxicity (that is, death), if considered related to study treatment

9. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose-limiting, for example:

   a) Any toxicity that is possibly related to study treatment that requires the withdrawal of the patient from the study during observation period

   b) A delay of >14 days due to persistent Grade ≥2 treatment-related toxicities in Cycle 1 with the exception of fatigue

Other potentially reversible risk factors for the AE should be identified and addressed as appropriate. Potential DLTs that are reasonably anticipated AEs for concomitant medication should be reviewed by the treating investigator and Lilly CRP before final determination as a DLT. Review and discussion may include additional participating investigators. Such review may determine that confounding factors render the case to be not evaluable for the purposes of dose selection.

A DLT-evaluable patient is considered to be one who either completed 1 cycle of treatment or discontinued from the treatment due to a DLT. A DLT-non-evaluable patient is considered one who experienced disease progression, was noncompliant, discontinued for reasons other than AEs within the first cycle of treatment, or did not complete the safety monitoring for the DLT Assessment Period for any reason other than a DLT. Additional patients may be included in the safety lead-in to replace any patient deemed non-evaluable.

3.7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to receive study treatment. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the site will register the patient by assigning the patient a unique study identification number via the Interactive Web-Response System (IWRS), which is accessible 24 hours a day. Study treatment will be allocated to patients using the IWRS.

Patients who meet all criteria for enrollment will be randomly assigned to receive cyclophosphamide and vinorelbine with or without ramucirumab.

Approximately 30 patients will be randomized in a 2:1 ratio (ramucirumab arm versus control, respectively).

Randomization will be stratified by staging at relapse (metastatic disease versus locally advanced).

3.7.3. Blinding

This is an open-label study.

3.7.4. Dose Modification

Dose adjustments (suspensions, reductions, or discontinuations) will be made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study treatment per investigator judgment). The CTCAE v 5.0 will be used to assess AEs. Treatment may be suspended for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. Other potentially reversible risk factors for the AE should be identified and addressed as appropriate. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be considered for permanent discontinuation from study treatment. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS.

In general, dose adjustments of one study drug (ramucirumab, cyclophosphamide, or vinorelbine) due to toxicity guidances outlined in Section 3.7.4.1 will not necessitate suspensions, reductions, or discontinuation of the other unrelated study drug(s). However, close consideration must be made by the investigator to administer all study treatments per the schedule outlined in Section 3.7.1.

Any patient who requires a dose reduction for drug-related toxicity will continue to receive the reduced dose for the remainder of the study. For ramucirumab, cyclophosphamide, or vinorelbine, any patient who has had 2 dose reductions in the same agent and who experiences a toxicity that would cause a third dose reduction must be discontinued from that study treatment. If cyclophosphamide is held, patients may restart on the same day as recovery from the AE, irrespective of when in the cycle that might be. If an IV agent is held, patients may restart upon resolution of the AE at the next scheduled dose. If both IV agents are held beyond the duration of one cycle, when reinitiated deem that Day 1 of the subsequent cycle.

Table JV01.8 presents the dose reduction for ramucirumab, cyclophosphamide, and vinorelbine. Dose adjustments required for hematologic and nonhematologic toxicities due to ramucirumab, cyclophosphamide, or vinorelbine are presented in Table JV01.10 and Table JV01.11, respectively.

Table JV01.8. Dose Reductions for Treatment-Related Toxicities

	Starting Dose	Dose Reduction	
Study Drug		**First**	**Second**
Ramucirumab	12 mg/kg	10 mg/kg	8 mg/kg
if de-escalated	**8 mg/kg**	**6 mg/kg**	**5 mg/kg**
Cyclophosphamide	25 mg/m^2	20 mg/m^2	15 mg/m^2
Vinorelbine	25 mg/m^2	20 mg/m^2	15 mg/m^2

3.7.4.1. Guidelines for Hematological and Nonhematological Dose Modifications

In general, ramucirumab therapy does not need to be altered for either cyclophosphamide- or vinorelbine-related toxicity. Similarly, cyclophosphamide or vinorelbine do not need to be altered for ramucirumab-related toxicity. Investigators will interpret and document whether or not an AE has a reasonable possibility of being related to each of the study drugs, taking into account the disease, concomitant treatments, or pathologies, in order to individually adjust study drug doses.

In the case of toxicity for which the relative roles of each agent are impossible to separate, it is expected that omissions and/or dose reductions of all involved agents would result. Thus, it is expected such toxicity would result in omissions and/or dose reductions of involved agents. In cases in which AEs, in the opinion of the investigator, are more likely due to 1 drug than another, adjustment of 1 of the agents and not the others are permissible. General guidelines for study treatment dose modifications due to toxicities are presented in

Table JV01.9. Dose adjustment guidelines for specific hematologic and nonhematologic toxicity due to cyclophosphamide, vinorelbine, and/or ramucirumab are presented in Table JV01.10 and Table JV01.11, respectively.

See Section 3.7.4.2 and Table JV01.12 for additional requirements and dose adjustment guidelines related to potential IRRs and adverse events of special interest (AESIs) that may occur during or following ramucirumab administration.

Table JV01.9. General Guidelines for Study Treatment Dose Modification Due to Toxicities Related to Ramucirumab, Cyclophosphamide, or Vinorelbine

Reaction Grade	Required Dose Modification
Grade 1	No dose modification is required.
Grade 2	Persistent or recurrent Grade 2 not resolving with maximal supportive measures: at the investigator's discretion, the patient may continue to receive study drug per protocol, provided that the event does not pose a serious health risk or is easily treated.
Grade 3	For a Grade 3 toxicity not adequately controlled with appropriate supportive care and assessed as related to study drug, the dose must be withheld until toxicity is ≤Grade 1 or has returned to pretreatment baseline; then treatment may resume at a reduced dose level. An exception to this would be isolated lab-only increases in GGT or ALP. If toxicity recurs after therapy resumes, despite up to two dose reductions, then treatment should be discontinued. • **First occurrence:** Delay agent until resolved to Grades 0-1. o If resolved to Grades 0-1, reduce dose. o If NOT resolved to Grades 0-1 within a reasonable timeframe (i.e. within 28 days), discontinue agent at investigator's discretion. • **Second occurrence:** Delay agent until resolved to Grades 0-1. o If resolved to Grades 0-1, reduce dose. o If NOT resolved to Grades 0-1 within a reasonable timeframe (i.e. within 28 days), discontinue agent.
Grade 4	Permanent discontinuation should be considered for any patient experiencing Grade 4 toxicity assessed as related to study drug. An exception to this would be isolated lab-only increases in GGT or ALP. However, if resumption of dosing is deemed appropriate by the investigator, treatment may resume only after consultation with the Lilly CRP/CRS, with the dose reduced. If Grade 4 toxicity recurs after therapy resumes, study drug will be discontinued. Exceptions are Grade 4 fever or Grade 4 laboratory abnormality, in which case: • **First occurrence:** Delay agent until resolved to Grades 0-1. o If resolved to Grades 0-1, may resume agent at original dose at the discretion of the investigator. o If NOT resolved to Grades 0-1 within a reasonable timeframe (i.e. within 28 days), discontinue agent at investigator's discretion. • **Second occurrence:** Delay agent until resolved to Grades 0-1. o If resolved to Grades 0-1, reduce dose. o If NOT resolved to Grades 0-1 within a reasonable timeframe (i.e. within 28 days), discontinue agent at investigator's discretion.

Abbreviations: ALP = alkaline phosphatase; CRP = clinical research physician; CRS = clinical research scientist; GGT = gamma-glutamyl transferase.

Note: If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be considered for permanent discontinuation from study treatment. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS.

Table JV01.10. Dosing Algorithm on Days 1 ,8, and 15 for Cyclophosphamide, Vinorelbine, Ramucirumab, and G-CSF Use Based on Absolute Neutrophil Count and Platelet Count

Toxicity	Day 1[b]			Day 8			Day 15			
	Cyclo[c]	Vin	Ram[d]	Cyclo[c]	Vin	Ram[d]	Cyclo[c]	Vin	Ram[d]	NOTES and G-CSF Use[a]
Absolute Neutrophil Count (cells/µL)										
≥750	Administer	Administer	Administer	Administer	Administer	Not Applicable	Administer	Administer	Administer	G-CSF not required
<750	Omit until cell count parameters are met	Omit on Day 1	Administer	Omit until cell count parameters are met	Omit. See note for further instruction.	Not Applicable	Omit until cell count parameters are met	Omit. See note for further instruction.	Administer	If >7 days until counts recover: o 1st occurrence: administer G-CSF and resume cyclophosphamide once cell parameters are met at the next lower dose[e] for current and all subsequent cycles. Consider omitting D-15 of vinorelbine for current and all subsequent cycles and reducing dose of vinorelbine on D-1 and D-8 of all subsequent cycles[e]. o 2nd and subsequent occurrences: administer G-CSF and resume cyclophosphamide once cell parameters are met at next lower dose reduction[e] and/or reduce vinorelbine (D1 and D8[e]; omit D15 during that and all subsequent cycles.
Platelet Count (cells/µL)										
≥75,000	Administer	Administer	Administer	Administer	Administer	Not Applicable	Administer	Administer	Administer	
<75,000	Omit until cell count parameters	Omit on Day 1	Administer	Omit until cell count parameters	Omit only if not administered	Not Applicable	Omit until cell count parameters	Omit only if not administered	Administer	If >7 days until counts recover, on subsequent cycle(s): o 1st occurrence: reduce

Toxicity	Day 1[b]			Day 8			Day 15			
	Cyclo[c]	Vin	Ram[d]	Cyclo[c]	Vin	Ram[d]	Cyclo[c]	Vin	Ram[d]	NOTES and G-CSF Use[a]
	are met			are met	on Day 1. See note for further instruction.		are met	on Day 1. See note for further instruction.		cyclophosphamide and/or vinorelbine on D1, D8[e], and consider omitting D15 vinorelbine if thrombocytopenia recurs during that cycle. ○ 2nd and subsequent occurrences: reduce cyclophosphamide and/or reduce vinorelbine (D1 and D8[e]; omit D15 vinorelbine if thrombocytopenia recurs during that or subsequent cycles despite dose reductions).

Abbreviations: Cyclo = cyclophosphamide; G-CSF = granulocyte-colony stimulating factor; Ram = ramucirumab; Vin = vinorelbine.

Note: For other hematologic toxicities not specified, please refer to Table JV01.9.

[a] G-CSF use is recommended per the guidelines outlined in Section 3.7.6.1.6.

[b] Day 1 treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity or non-study-drug-related events at the investigator's discretion (eg, an automobile accident). In exceptional cases, longer suspensions may be allowed after discussion with the Lilly CRP/CRS.

[c] Cyclophosphamide can resume at any day once cell count parameters are met.

[d] Investigational arm.

[e] Reduction dose per Section 3.7.4 and Table JV01.8

Table JV01.11. Additional Guidelines for Dose Modification Due to Study Drugs-Related Non-Hematologic Toxicities

Toxicity	All Days[a]			Notes
	Cyclo	Vin	Ram[b]	
Total bilirubin >2 to 3× ULN or >2 to 3x baseline if baseline abnormal	Administer per Table JV01.9.[c]	Administer per Table JV01.9[d] but must reduce dose per Table JV01.8	Administer per Table JV01.9 [c]	Exception: Patients with Gilbert's Syndrome may have a total bilirubin <3 mg/dL before requiring a dose reduction in vinorelbine. Refer to Sections 3.9.3.1.1 and Attachment 4 for hepatic safety monitoring.
Total bilirubin >3x ULN or >3x baseline if baseline abnormal (Grade ≥3 bilirubin elevation)	Hold and follow guidelines per Table JV01.9[d]	Hold per Table JV01.9[d] and reduce dose for subsequent administration per Table JV01.8	Hold and follow guidelines Table JV01.9[d]	Refer to Sections 3.9.3.1.1 and Attachment 4 for hepatic safety monitoring.
Grade ≥3 elevations in AST or ALT	Hold and follow guidelines per Table JV01.9.[d]	Hold per Table JV01.9[d] and reduce dose for subsequent administration per Table JV01.8	Table JV01.9[d]	Refer to Section 3.9.3.1.1 and Attachment 4 for hepatic safety monitoring.
Grade ≥3 neurologic toxicity	Administer per Table JV01.9[d c]	Discontinue	Administer per Table JV01.9.[c]	
Severe pulmonary toxicity	Discontinue	Discontinue	Administer[c]	For vinorelbine, MUST discontinue for Grade ≥2 Interstitial Pneumonitis and ARDS, and HOLD for unexplained dyspnea (may restart if resolved/short-lived).
HUS, Gross Hemorrhagic Cystitis, or severe renal/bladder impairment	Discontinue	Administer[c]	Administer[c]	

Abbreviations: ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; Cyclo = cyclophosphamide; Ram = ramucirumab; ULN = upper limit of normal; Vin = vinorelbine.

[a] Day 1 treatment may be delayed for up to 14 days to allow a patient sufficient time for recovery from study drug-related toxicity or non-study-drug-related events at the investigator's discretion (eg, an automobile accident). In exceptional cases, longer suspensions may be allowed after discussion with the Lilly CRP/CRS.

[b] Investigational arm.

[c] Continue with treatment unless investigator considers possibly related.

[d] Hold treatment unless investigator considers not related.

3.7.4.2. Ramucirumab Dose Modifications for Adverse Events of Special Interest

The ramucirumab dose may need to be modified if the patient experiences an AE, including an AESI (Section 3.9.2.1). Doses may be delayed to allow time for the patient to recover from the event. Certain AEs require immediate and permanent discontinuation of study treatment (see Table JV01.12). If administration of ramucirumab is delayed for more than 4 weeks from last planned administration, the patient should be discontinued from ramucirumab treatment, unless a longer suspension has specifically been deemed appropriate for a given patient in discussion with the Lilly CRP/CRS. Any patient who requires a dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. Any patients requiring dose reduction to less than 8 mg/kg (5 mg/kg for patients treated on dose de-escalation) of ramucirumab will have ramucirumab discontinued. Such patients may continue with cyclophosphamide and/or vinorelbine as per protocol.

Table JV01.8 presents the ramucirumab dose reductions.

Table JV01.12 presents the criteria for dose modifications and dose discontinuations applicable if the patient experiences a ramucirumab AESI or other AEs at least possibly related to ramucirumab.

Table JV01.12. Dose-Modification Guidelines for Ramucirumab for Adverse Events at Least Possibly Related to Ramucirumab, including Adverse Events of Special Interest

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 3.7.6.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV01.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
1.	**Infusion-related reaction (including hypersensitivity reactions)**		
1.a.	Infusion-related reaction	2	Interrupt and reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab, premedicate with: • an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride • dexamethasone or equivalent • acetaminophen/paracetamol
1.b.	Infusion-related reaction	3-4	Immediately and permanently discontinue ramucirumab
2.	**Hypertension for patients ≥18 years old**		
2.a.	Hypertension (non-life-threatening and associated with symptoms) NOTE: Hypertension should be monitored prior to each ramucirumab infusion.	3	• Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grades 0-2. o If controlled with medication and resolved to Grades 0-2, then may resume ramucirumab at current dose. • If NOT controlled with medication and not resolved to Grades 0-2 within a reasonable timeframe (e.g. 28 days), discontinue ramucirumab at investigator's discretion.
2.b.	Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy	4	Immediately and permanently discontinue ramucirumab.

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 3.7.6.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV01.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
3	**Hypertension for patients <u><18 years old</u>**		• BP ULN in children: ≤95th percentile for age, height, and gender measured as described in NHBPEPWG on High Blood Pressure in Children and Adolescents (2004). • Baseline BP is the average of the serial BPs obtained at least 5 min apart on the same extremity, in the same position with an appropriate sized cuff. • Elevation in either systolic or diastolic BP is valid for dose modifications • Elevated BP should be re-evaluated on the same day for confirmation. If elevated, BP monitoring should occur at least twice weekly until BP ≤ULN Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. Highly recommended to consult pediatric cardiology or nephrology for evaluation and management of hypertension in the pediatric population
3.a.	BP: ≤10 mmHg above ULN for age		• Administer ramucirumab at the current dose. • Recheck BP within 3 days o If BP ≤ULN, then continue on current ramucirumab dose o If >ULN, start anti-hypertensive therapy and continue on current ramucirumab dose ▪ if BP ≤ULN within 14 days, continue on anti-hypertensive therapy and current ramucirumab dose If BP >ULN after 14 days on anti-hypertensive therapy; **see line 3.c.**
3.b.	BP: >10 mmHg to 25 mmHg above ULN for age <u>or</u> >35 mmHg above baseline		• Start anti-hypertensive therapy and continue on current ramucirumab dose ▪ if BP ≤ULN within 14 days, continue on anti-hypertensive therapy and current ramucirumab dose If BP >ULN after 14 days on anti-hypertensive therapy; **see line 3.c.**
3.c.	BP: >25 mmHg above ULN		• Hold ramucirumab and start or continue anti-hypertensive therapy ▪ if BP ≤ULN within 14 days, continue on anti-hypertensive therapy and resume ramucirumab at a reduced dose If BP >ULN after 14 days on anti-hypertensive therapy immediately and permanently discontinue ramucirumab.

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 3.7.6.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV01.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
3.d.	Hypertension, hypertensive crisis, or hypertensive encephalopathy	4	Immediately and permanently discontinue ramucirumab.
4.	**Proteinuria for patients ≥18 years old**		
4.a.	Proteinuria = 2+ (dipstick or routine urinalysis)[a]		• Administer ramucirumab at the current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 hr, administer ramucirumab at the patient's current dose. o If urine protein is ≥2 g/24 hr, modify the ramucirumab dose based on 24-hour collection. **See Proteinuria ≥2 g/24 hr (24-hour urine collection), line 4.c and 4.d.**
4.b.	Proteinuria >2+ (dipstick or routine urinalysis)[a]		• Omit ramucirumab and obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. • Delay ramucirumab until urine protein returns to <2 g/24 hr. o If urine protein is <2 g/24 hr, no further dose delay or dose reduction is required. o If urine protein remains ≥2 g/24 hr, **see line 4.c and 4.d.**
4.c.	Proteinuria ≥2 to 3 g/24 hr (24-hour urine collection)[a]		• **First or second occurrence:** delay ramucirumab until urine protein returns to <2 g/24 hr. o If urine protein returns to <2 g/24 hr, reduce ramucirumab dose. o If urine protein remains ≥2 g/24 hr and is not resolved within a reasonable timeframe, discontinue ramucirumab at investigator's discretion. • **Third occurrence:** discontinue ramucirumab.
4.d.	Proteinuria >3 g/24 hr **or** in the setting of nephrotic syndrome[a]		Immediately and permanently discontinue ramucirumab.
5.	**Proteinuria for patients <18 years old:**		
5.a.	Proteinuria ≥ trace (dipstick or routine urinalysis)[a]		Hold ramucirumab and obtain a random urine sample to calculate the UPC ratio. **See lines 5.b.to 5.d.**

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 3.7.6.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV01.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
5.b.	UPC ratio <1[a]		Administer ramucirumab at patient's current dose as scheduled.
5.c.	UPC ratio 1-1.9[a]		• Hold ramucirumab and repeat a second measurement within 72 hours of the next scheduled dose. ○ If UPC ratio returns to <1, administer ramucirumab at current dose. ○ If UPC ratio remains 1-1.9, omit ramucirumab until UPC ratio returns to <1. ▪ If UPC ratio returns to <1 within 14 days, resume ramucirumab with dose reduction. If UPC ratio remains ≥1 for 14 days or more, immediately and permanently discontinue ramucirumab.
5.d.	UPC ratio >1.9[a]		Immediately and permanently discontinue ramucirumab.
6.	**Arterial thromboembolic events, venous thromboembolic events**	3 or 4	Immediately and permanently discontinue ramucirumab.
7.	**Bleeding/Hemorrhage**		
	Bleeding/Hemorrhage	2	Continue with treatment unless investigator considered related. See Table JV01.9.
	Bleeding/Hemorrhage	3 or 4	Immediately and permanently discontinue ramucirumab.
8.	**Gastrointestinal perforation**		Immediately and permanently discontinue ramucirumab.
9.	**Posterior reversible encephalopathy syndrome**		Immediately and permanently discontinue ramucirumab.
10.	**Congestive heart failure**		
	Congestive heart failure	2	Continue with treatment unless investigator considered related. See Table JV01.9
	Congestive heart failure	3 or 4	Immediately and permanently discontinue ramucirumab.
11.	**Fistula formation**		Immediately and permanently discontinue ramucirumab.
12.	**Impaired wound healing**		
12.a.	Prior to planned surgery		Withhold ramucirumab.
12.b	After surgery		Resume ramucirumab based on clinical judgment.
12.c.	Wound-healing complications developed during study treatment		Delay ramucirumab dosing until the wound is fully healed.

	Adverse Event *NOTE: All specific adverse events listed are defined as AESIs in Section3.7.6.1.8.*	CTCAE Grade	Dose-Modification Guidelines *NOTES:* ***Dose reductions to occur as defined in Table JV01.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
13.	**Hypothyroidism**	2-4	Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted.
14.	**Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis**		Immediately and permanently discontinue ramucirumab,

Dose-Modification Guidelines for Ramucirumab for Adverse Events at least Possibly Related to Ramucirumab, including Adverse Events of Special Interest (concluded)

Abbreviations: AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; UPC = urine protein to creatinine.

[a] Perform urinalysis within 3 days prior to each infusion of ramucirumab. If 24-hour urine collection or UPC ratio (<18 years of age) is also performed, the results of these collections should be used for clinical decision-making.

3.7.5. Treatment Compliance

No additional requirements. Refer to the CAMPFIRE Master Protocol for treatment compliance.

3.7.6. Concomitant Therapy

A list of restricted and excluded concomitant therapies and exceptions is provided in Attachment 5. All premedication, supportive care, and concomitant medication must be reported on the CRF at each visit.

3.7.6.1. Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care as judged by the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult with the Lilly CRP/CRS. Use of any supportive care should be recorded on the eCRF. Investigators should consult the PI for additional precautions. Specific AEs have been identified based on past data for special monitoring and, when necessary, supportive care. For ramucirumab, these are referred to as AESI.

3.7.6.1.1. Transfusions

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion.

3.7.6.1.2. Supportive Management for Constipation and Bowel Obstruction

Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation can occur with vinorelbine administration. Supportive measures such as adequate dietary fiber intake, hydration, and routine use of stool softeners are recommended to mitigate potential constipation, bowel obstruction, and/or paralytic ileus. In the event of constipation, a prophylactic bowel regimen should be initiated.

3.7.6.1.3. Antiemetic Agents

The use of antiemetic agents is permitted at the discretion of the investigator. Acceptable antiemetic agents include 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonists (eg, ondansetron), dopamine receptor antagonists (eg, metoclopramide), corticosteroids (eg, dexamethasone), and others.

3.7.6.1.4. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. Opiate and non-opiate analgesic agents are permitted (including acetaminophen/paracetamol); however, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin is restricted (Attachment 5).

3.7.6.1.5. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator. Examples include megestrol acetate, dronabinol, and others.

3.7.6.1.6. Growth Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria.

The as-needed use of granulocyte-colony stimulating factor (G-CSF) is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO; Smith et al. 2006) and European Society for Medical Oncology (Crawford et al. 2009) guidelines.

In the event of Grade 3 or 4 neutropenia >7 days, initiate G-CSF as per Table JV01.10..

The as-needed use of erythroid-stimulating factors (eg, erythropoietin) is permitted at the discretion of the investigator based on ASCO guidelines (Rizzo et al. 2010) (Attachment 5).

3.7.6.1.7. Other Supportive Care Agents

The use of benzodiazepines, antidepressants, laxatives, and other agents that may be helpful in controlling disease-related symptoms are also permitted and encouraged, except as prohibited in Attachment 5.

3.7.6.1.8. Supportive Care by Adverse Event of Special Interest: Ramucirumab

Refer to Table JV01.12 for AESI dose modification guidelines.

3.7.6.1.8.1. Infusion-Related Reactions (Including Hypersensitivity Reactions)

Administration of monoclonal antibodies such as ramucirumab can result in hypersensitivity reactions (HSRs), including immediate reactions like anaphylactic reactions or IRRs, and delayed reactions such as those involving the mucocutaneous system. In the event of an IRR, every effort should be made to collect blood samples for PK and immunogenicity analysis for ramucirumab (see Attachment 3), at the following time points:

(i) as close as possible to the onset of the IRR,
(ii) at the resolution of the IRR, and
(iii) 30 days following the IRR.

In addition, in the case of generalized urticaria or anaphylaxis, blood and urine samples should be collected as described in Attachment 3 hypersensitivity labs):

(i) After the patient has been stabilized, obtain a sample within 1-2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
(ii) Obtain a follow-up sample 30 days following the IRR or at the next regularly scheduled visit following the IRR, whichever is later.

The IRRs may occur during or following ramucirumab administration. Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available.

Signs and symptoms usually develop during or shortly after infusion and generally resolve within 24 hours. Symptoms of IRRs include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension.

Table JV01.12 presents ramucirumab dose modification for patients who experience an IRR associated with ramucirumab.

Patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of each study drug, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

For the first 2 ramucirumab infusions, measure BP and pulse at the following time points: (i) within 15 minutes prior to the infusion, (ii) after completion of the infusion, and (iii) at the end of the 1-hour post-infusion observation period. For all subsequent infusions of ramucirumab, measure BP and pulse prior to the infusion. Measure other vital signs as clinically indicated.

Supportive care should be employed in accordance with the symptoms or signs. Participants should be treated appropriately by the investigator. If a significant HSR occurs (Grades 3 or 4), discontinue ramucirumab permanently.

3.7.6.1.8.2. Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab compared with placebo. In most cases, hypertension was controlled using standard antihypertensive treatment. Preexisting hypertension should be controlled before starting ramucirumab treatment.

Monitoring of BP is required during participation on trial, and must occur prior to ramucirumab therapy to ensure appropriate dosing and administration. Every attempt should be made to control BP prior to starting treatment with ramucirumab and throughout the study to systolic <140 mmHg and diastolic <90 mmHg for patients >18 years old, and < ULN for patients under 18 years of age. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

3.7.6.1.8.3. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGFR2 pathway, including ramucirumab. In ramucirumab clinical trials, the majority of events were Grade 1 or 2. Monitoring for the development or worsening of proteinuria during ramucirumab therapy is required. Discontinue ramucirumab if the patient experiences proteinuria >3 g/24 hours for patients >18 years old, UPC ratio >1.9 for patients under 18 years of age, or nephrotic syndrome.

3.7.6.1.8.4. Thromboembolic Events

3.7.6.1.8.4.1. Arterial Thromboembolic Events

Serious, sometimes fatal ATEs, including myocardial infarction, cardiac arrest, CVA, and cerebral ischemia, have been reported in clinical trials.

3.7.6.1.8.4.2. Venous Thromboembolic Events

Venous thromboembolic events (VTEs) are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the

incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. VTEs have been reported from clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices.

3.7.6.1.8.5. Bleeding/Hemorrhage

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Severe GI hemorrhages, including fatal events, have been reported in patients with gastric-GEJ cancer treated with ramucirumab in combination with paclitaxel.

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (ie, variceal bleeding from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma), although the rate of these complications varies considerably. As detailed in the ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases preclude any definitive association between bleeding and ramucirumab, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria.

3.7.6.1.8.6. Gastrointestinal Perforation

An infrequent incidence of GI perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of colorectal cancer (treated with combination regimens, including anti-VEGF antibodies and cytotoxic chemotherapy) and in advanced ovarian cancer. These events may be associated with extensive abdominal/peritoneal disease burden. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. The incidences of these events to date and presence of significant comorbidities and risk factors preclude any definitive association with ramucirumab, although ongoing surveillance remains essential. More information about GI perforation may be found in the IB.

3.7.6.1.8.7. Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome is an acute neurological disorder characterized by various neurological signs and symptoms in conjunction with distinctive neuroimaging findings reflecting vasogenic edema, often in association with elevated BP (Bartynski and Boardman 2007; Bartynski 2008; Fugate and Rabinstein 2015; Fischer and Schmutzhard 2017). Both clinical and imaging features are usually reversible (Hinchey et al. 1996; Lee et al. 2008; Fugate and Rabinstein 2015).

Cases of PRES, including fatal cases, have been rarely reported in patients receiving ramucirumab. Posterior reversible encephalopathy syndrome symptoms may include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.

Posterior reversible encephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. A diagnosis of PRES can be confirmed by brain imaging (e.g., magnetic resonance imaging [MRI]). Treatment encompasses

careful control of BP, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (Stott et al. 2005).

Permanently discontinue ramucirumab in patients who experience PRES.

3.7.6.1.8.8. Congestive Heart Failure

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

Patients with risk factors should be closely monitored for signs and symptoms of CHF.

Caution should be exercised when treating patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease or CHF. Ramucirumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

3.7.6.1.8.9. Fistula Formation

Because fistula formation has been associated with antiangiogenic agents, patients may be at increased risk for the development of fistula when treated with ramucirumab. Some fistulas can be resolved with surgical procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009).

3.7.6.1.8.10. Surgery and Impaired Wound Healing

Because ramucirumab is an antiangiogenic therapy, it may have the potential to adversely affect wound healing. Ramucirumab did not impair wound healing in a study conducted in animals; however, the impact of ramucirumab on serious or nonhealing wounds has not been evaluated in humans.

3.7.6.1.8.11. Liver Failure and Other Significant Liver Injury

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with 1) cirrhosis at a level of Child-Pugh Class B (or worse) or 2) cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis should not be enrolled in clinical trials with ramucirumab. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

3.8. Discontinuation Criteria

- Related to Investigator/Physician decisions
    - the investigator/physician decides that the patient should be discontinued from the study or study drug(s).
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of DSRCT, discontinuation from the study drug(s) occurs prior to introduction of the other agent.

- Related to patient, parent, or legal guardian
  - the patient or the patient's designee (for example, parents or legal guardian) requests to be discontinued from the study or study drug.
- Related to Sponsor
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- The patient becomes pregnant during the study.
- The patient has radiographic progressive disease or significant symptomatic disease deterioration characterized as progression of disease, in the opinion of investigator, in the absence of radiographic evidence of PD. In the event a patient is discontinued from treatment due to symptomatic deterioration, every effort should be made to document disease progression, unless it is not medically appropriate.
- The patient experiences unacceptable toxicity (for example, a persistent moderate toxicity that is intolerable to the patient).
- The patient is noncompliant with study procedures and/or treatment. Example, unable to take oral or liquid cyclophosphamide.
- The patient has had maximum dose reductions of ramucirumab, cyclophosphamide or vinorelbine allowed per protocol and experiences an AE that would cause an additional dose reduction.
- The patient is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

For additional treatment discontinuation criteria see Section 3.7.4.

3.9. Study Assessments and Procedures

Section 3.2 provides the Schedule of Activities for this study.

Attachment 2 provides a list of the laboratory tests that will be performed for this study.

Attachment 3 provides the schedule for collection of samples in this study.

3.9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 3.2).

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, MRI is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about

radiation exposure associated with CT. Intravenous and oral contrast is required, unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses, but cannot be used to assess response according to RECIST 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scans of the thorax, abdomen, and pelvis are required.

See Section 3.10.3.1 for definitions of the efficacy endpoints.

3.9.2. Adverse Events

Refer to the CAMPFIRE Master Protocol for Adverse Event general definitions, responsibilities, and reporting information.

3.9.2.1. Adverse Events of Special Interest: Ramucirumab

Section 3.7.6.1.8 describes supportive care measures for each ramucirumab AESI. Table JV01.12 presents the dose-modification guidelines for ramucirumab AESIs. Contact the Lilly CRP if questions arise concerning AESIs.

Any treatment-related IRRs are defined according to the CTCAE Version 5.0 definition (*General Disorders and Administration-Site Conditions*). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (*Immune System Disorders*). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

3.9.3. Safety

3.9.3.1. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

The study will be monitored for excessive toxicity experienced beyond the DLT assessment period. If excessive toxicity is observed, the study may be amended, or treatment with the combination halted to address the safety concern, as appropriate.

3.9.3.1.1. Special Hepatic Safety Data Collection

If, following the initiation of close hepatic monitoring as per master protocol Section 9.4.2, one or more of the following conditions are met, additional hepatic data should be collected as per Attachment 4:

- Patients enrolled with normal or near normal ALT or AST (<1.5× ULN):
    - elevation of serum ALT or AST ≥8× ULN; or

- elevated ALT or AST ≥5× ULN and total bilirubin ≥2× ULN

- Patients enrolled with elevated ALT or AST (≥1.5× ULN):
  - ALT or AST ≥4× baseline; or
  - ALT or AST ≥3× baseline and total bilirubin ≥2× ULN

- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests
- occurrence of a hepatic event considered to be an SAE.

3.9.3.1.2. Monitoring for Specific Toxicities: Growth Plate

In addition to monitoring height on trial, patients randomized to the ramucirumab arm and <18 years of age will have a plain anteroposterior (AP) radiograph of a single proximal tibial growth plate obtained prior to the first dose of protocol therapy.

- If patients randomized to the ramucirumab arm are found to have a closed tibial growth plate, no further radiographs will be required.
- If patients randomized to the ramucirumab arm are found to have an open tibial growth plate, then repeat plain AP radiographs of the same location every 4 months and at short-term follow-up, or until the growth plate has closed.

In some geographies, an MRI of the knee may be an alternate option instead of a plain AP radiograph.

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 months 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 Lilly CRP, 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.

- Monitoring in the Follow-up period for patients with open tibial growth plate on study and randomized to the ramucirumab arm:
  - Short term follow-up: All patients with an open growth plate while on study should repeat plain AP radiograph and obtain a height measurement.
  - In some geographies, an MRI of the knee may be an alternate option instead of a plain AP radiograph.
  - Long-term follow-up: Only for patients with an abnormal growth plate finding at short-term follow-up, continue to perform plain AP radiologic evaluations and obtain height measurements until resolution of growth plate abnormalities or

growth plate closure, whichever occurs first. Frequency of both the radiographs and height measurements are per the investigator's discretion/patient convenience during long-term follow-up.

- In some geographies, an MRI of the knee may be an alternate option instead of a plain AP radiograph.

3.9.4. Pharmacokinetics

Blood samples will be collected from study patients on the ramucirumab arm to assess ramucirumab concentrations in serum as specified in Attachment 3. Instructions and supplies for the collection, handling, and shipping of samples will be provided by Lilly or the central laboratory.

For all patients (whether in the ramucirumab arm or the control arm), in the event of an IRR, every attempt should be made to collect blood samples for anti-ramucirumab antibody and serum ramucirumab concentration determination at those given time points, as described in Attachment 3. Refer to Attachment 3 for the timing of blood sample collection during the continued-access period.

Serum concentrations of ramucirumab will be analyzed at a laboratory designated by the sponsor using a validated method.

Bioanalytical samples collected to measure ramucirumab concentration will be retained for a maximum of 1 year following the last patient visit for the study.

3.9.5. Pharmacodynamics

See Section 3.9.6 for Biomarkers

3.9.5.1. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected on all patients to determine antibody production against ramucirumab at specified time points and in the event of an IRR (Attachment 3). Refer to Attachment 3 for the timing of immunogenicity testing during the continued-access period.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab.

To interpret the results of immunogenicity in the ramucirumab arm, the concentration of ramucirumab in the blood will also be measured at the same time points (Attachment 3).

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by Lilly to enable further analysis of immune responses to ramucirumab. The duration allows Lilly to respond to regulatory requests related to ramucirumab.

3.9.6. Biomarkers

Biomarker research will address questions as described in Sections 9.7 and 9.8 of CAMPFIRE Master Protocol. This study will analyze biomarkers relevant to ramucirumab, mechanism of action of ramucirumab, the variable response to study drug(s), immune function, angiogenesis, and pathways associated with DSRCT.

Samples for biomarker research will be collected as specified in Attachment 3, where local regulations allow. Collection of samples for biomarker research will be optional.

3.9.6.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 3.9.6. The following samples for biomarker research will be collected according to the sampling schedule in Attachment 3, where local regulations allow.

Collection of the following tumor tissue sample(s) is **optional** for all patients participating in this study:

- an archived tumor sample
- a tumor tissue sample from a newly obtained biopsy specimen may be requested at a later time point (eg after a strong response or disease progression). Such additional biopsies are optional and should be performed only if clinically feasible. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms. If a biopsy is submitted, due diligence should be used to ensure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided and that the tumor sample contains tumor cells prior to shipment to the central laboratory. See the Laboratory Manual for details regarding sample collection and handling.

3.9.6.2. Other Samples for Biomarker Research

The following samples for biomarker research will be collected according to the sampling schedule in Attachment 3, where local regulations allow:

- whole blood for pharmacogenomic research (as described in Section 9.7 of the CAMPFIRE Master Protocol)
- serum
- plasma

A maximum of 4 samples may be collected at additional study time points, if warranted and agreed upon by the investigator and Lilly.

3.9.7. Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

3.10. Statistical Considerations

3.10.1. Sample Size Determination

Traditional operating characteristics associated with the proposed Bayesian design (SAP, Section 6.6.1) were evaluated via trial simulation. Note that due to the adaptive borrowing on PFS effect-size between Studies JV01 and JV02, joint scenarios of truth in both SS and DSRCT must be considered when evaluating operating characteristics for Study JV01 (and likewise for Study JV02). Under the proposed analysis framework, the sample size is considered adequate to support the primary objective:

- **Type I error:** Reported Type I errors are one-sided. Type I Error here refers to the event the 99% success criterion for Study JV01 is met when in reality $HR_{DSRCT} = 1$. Given the stringency of the Bayesian success criterion (ie, 99% probability of superiority threshold), false positives are unlikely for Study JV01. In particular, when neither tumor cohort truly benefits from ramucirumab-based therapy (ie, $HR_{SS} = HR_{DSRCT} = 1$), the Type I error rate for Study JV01 is approximately .003. Importantly, the Type I error rate remains low even under scenarios of strong heterogeneity in effect-size between JV01 and JV02. In particular, if $HR_{DSRCT} = 1$ but $H_{SS} = .5$, the probability of Type I error for Study JV01 is still less than 2%. This is due to both the adaptive nature of the hierarchical borrowing and the stringent primary success criterion.
- **Power:** Given the large magnitude of PFS benefit targeted in the young adult/pediatric setting, JV01 is unlikely to miss truly standard of care-changing improvements due to Type II error. Under the target scenario in which both tumors benefit substantially from ramucirumab-based therapy on the basis of PFS (ie, $HR_{SS} = HR_{DSRCT} = .33$), the Bayesian analysis of PFS yields statistical power of approximately 82% to conclude success in DSRCT. For reference, a traditional log-rank analysis of DSRCT at 24 PFS events (independently from SS) at $\alpha = .003$ (1-sided) carries approximately 43% power at $HR_{SS} = .33$ (note this calculation did not include a futility analysis such as that proposed in Studies JV01 and JV02, so a fairer assessment of power under the traditional approach would actually be lower than 43%).
- Simulation results over additional joint null/alternative and control scenarios (including scenarios of strong heterogeneity in effect-size between the two addenda and mismatch of historical/prospective controls) are tabulated and reviewed in the SAP, Section 6.6.1.

Trial simulations were implemented using the statistical software package R. Simulation results were independently replicated.

The stringent primary success criterion, $\Pr(HR_{DSRCT} < 1) > 99\%$, was calibrated to ensure that meeting the primary endpoint should imply both statistical significance and large estimated magnitude of patient benefit (3 months of additional PFS) for the pediatric/young adult population of interest. The interpretation of the stringent success criterion is that the posterior probability of the HR being less than 1 is greater than 99%, given the observed data from JV01, observed data from JV02 incorporated via dynamic borrowing, and prior distributions. Based on a large simulation study (SAP, Section 6.6.1), when the 99% posterior probability threshold is

reached, the associated estimate of the PFS HR (HR_{DSRCT}) is no larger than approximately .51. Under an example assumption of three months for control median PFS (and a further assumption of exponentially distributed PFS), the minimal effect size of $HR_{DSRCT} = .51$ would correspond to approximately 3 months of additional PFS in this population with high unmet medical need.

3.10.2. Populations for Analysis

The following analysis sets will be defined for this study:

Intention-to-treat (ITT) analysis set: will include all randomized patients. Should the ramucirumab dose be de-escalated during the safety lead-in period, all randomized patients will still be included in the ITT analysis set regardless of assigned dose. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This analysis set will be used for all baseline and efficacy assessments.

Safety analysis set: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which he or she was randomized. The safety analysis set will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic analysis set: will include all randomized patients who received at least 1 full dose of study treatment and have at least 1 postbaseline evaluable PK sample.

Biomarker analysis set: will include the subset of patients from the ITT analysis set from whom a valid assay result has been obtained.

3.10.3. Statistical Analysis

Statistical analysis of this study will be the responsibility of Lilly or its designee.

For Bayesian analyses, posterior medians and 80% (equal-tailed) Bayesian credible intervals will be provided for relevant quantities unless otherwise stated. Full details regarding specification of prior distributions will be outlined in the SAP.

All frequentist tests of treatment effect will be conducted at a 1-sided alpha level of .1, unless otherwise stated, and all confidence intervals (CIs) will be computed with (2-sided) coverage equal to 80%.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

3.10.3.1. Efficacy Analysis

This section discusses statistical analyses of primary and secondary efficacy endpoints. Exploratory efficacy analyses will be discussed in the SAP.

Progression-free survival is defined as the time from randomization until the first occurrence of documented disease progression per RECIST v1.1 criteria or death from any cause in the absence of progressive disease. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme is provided in the Table JV01.13).

Progression-free survival will be compared between treatment arms using the Bayesian hierarchical Weibull model outlined in the SAP, Section 6.6.1, with associated success/futility criteria based on the posterior distribution of the HR_{DSRCT}.

The Bayesian model involves two mechanisms of statistical borrowing to boost power in light of limited sample size via acknowledgement of relevant data exogenous to the JV01 enrolled population. First, a Bayesian augmented control (BAC) approach will incorporate historical PFS outcomes from propensity-matched real world historical control patients. The historical control data will be down-weighted using a fixed power prior (Ibrahim et al. 2015). The BAC approach reduces the required proportion of patients randomized to the prospective control arm in JV01. Second, the Bayesian model includes a mechanism for dynamic borrowing on effect-size (log PFS HR) between the two addenda, JV01 and JV02. This is accomplished via a simple random-effects meta-analytic framework within the Bayesian model. The dynamic borrowing on effect-size boosts power substantially under key scenarios in which both tumors (both JV01 and JV02 populations) truly benefit from the addition of ramucirumab to standard chemotherapy, while maintaining acceptable control of Type I error in scenarios of strong heterogeneity in effect-size (see Table JV01.14 and Table JV01.15).

Full mathematical detail (including prior specification) regarding the Bayesian model for PFS is elaborated in the SAP along with computer code in the JAGS language (Plummer et al. 2017) used for implementing Markov Chain Monte Carlo (MCMC) simulation from the approximate posterior distribution.

To correspond with the 99% superiority threshold for success, a 98% (equal-tailed) Bayesian credible interval will be provided to accompany the median of the posterior distribution of the HR_{DSRCT}. In addition, PFS curves, median PFS, and PFS rates at various time points will be estimated via corresponding posterior summaries and reported along with associated 80% Bayesian credible intervals, where appropriate. Per sensitivity, these quantities will also be estimated using the traditional method of Kaplan-Meier (Kaplan and Meier 1958). Additional details are available in SAP Section 6.6.

Table JV01.13. PFS Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (whichever is later)[b]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of randomization
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following randomization[b,c]	Censored	Date of randomization
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate tumor assessment, per RECIST 1.1 criteria, or date of randomization (whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

a Symptomatic deterioration (ie, symptomatic progression that is not confirmed per RECIST 1.1 criteria) will not be considered as tumor progression.

b Adequate tumor assessment per RECIST 1.1 criteria refers to an assessment with one of the following responses: CR, PR, SD, or PD.

c Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window.

Table JV01.14 Simulated Operating Characteristics

True Hazard Ratio		Pr(Pass Interim)		Pr(Pass Final)	
SS	DSRCT	SS	DSRCT	SS	DSRCT
1.00	1.00	0.44	0.44	0.003	0.003
0.50	0.50	0.96	0.96	0.37	0.37
0.33	0.33	0.99	0.99	0.82	0.82

Table JV01.15 Impact of Heterogeneous Effect-Size Between Tumors

True Hazard Ratio		Pr(Pass Interim)		Pr(Pass Final)	
SS	DSRCT	SS	DSRCT	SS	DSRCT
1	0.80	0.50	0.61	0.008	0.018
1	0.50	0.60	0.88	0.015	0.164

Overall response rate is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) divided by the total number of patients randomized to the corresponding treatment arm (ITT population). Confirmation of PR or CR is required. The ORR, with 80% CI based on the method of Clopper and Pearson (1934), will be summarized for each treatment arm and compared between treatment arms using Fisher's exact test at 1-sided level $\alpha = .1$.

Duration of response is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

3.10.3.2. Safety Analysis

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

Refer to the CAMPFIRE Master Protocol Section 10.3.1 for additional safety analysis.

3.10.3.3. Other Analysis

3.10.3.3.1. Pharmacokinetic/Immunogenicity Analyses

Serum concentrations of study drug (ramucirumab) prior to infusion (trough concentration) and at the end of the infusion (approximately peak concentration) will be summarized using descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored. Details will be described in the SAP.

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

3.10.3.3.2. Biomarker Analyses

Biomarkers relevant to ramucirumab, mechanism of action of ramucirumab, the variable response to study drug(s), immune function, angiogenesis, and pathways associated with cancer will be analyzed for association with disease state and clinical outcomes.

3.10.3.4. Subgroup Analysis

A prespecified list of subgroups will be identified in the SAP and will include (at a minimum) a comparison between adults and pediatrics with respect to certain safety and efficacy measures. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

3.10.3.5. Interim Analysis

Data will be reviewed on an ongoing basis during the safety lead-in period to inform the rolling-six decision rules.

An interim futility analysis will be triggered when minimum 24 total PFS events have been observed across Study JV01 and Study JV02 with a minimum of 8 events in each study. At the interim futility look, the Bayesian of PFS analysis must provide a minimum of 60% posterior probability of superiority (PFS HR<1 for DSRCT patients) in order for enrollment on Study JV01 to continue. Otherwise, enrollment on Study JV01 will be stopped.

In order to minimize the operational and statistical bias that result from performing an interim analysis, the interim analyses for this study will be conducted under the auspices of an Independent Data Monitoring Committee (IDMC). The purpose of the IDMC is to advise Lilly

regarding the continuing safety of study participants and the continuing validity and scientific merit of the trial. Details of the IDMC are provided in the IDMC charter.

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Attachment 1. Protocol Addendum JV01 Abbreviations and Definitions

The list of abbreviations and definitions found in the Study JV01 Addendum is included below.

Term	Definition
5-HT3	5 hydroxytryptamine 3
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore 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 related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	**a**bsolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
BP	blood pressure
BSA	body surface area
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
COG	Children's Oncology Group
collection database	A computer database in which clinical study data are entered and validated.
CR	complete response
CRF	case report form

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	Clinical Research Scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
CYP	cytochrome P450
DLT	dose-limiting toxicity
DSRCT	desmoplastic small round cell tumor
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
end of study	Date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 3.2) for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
EU	European Union
FOCBP	Females of child bearing potential
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
GGT	gamma-glutamyl transferase
HR	hazard ratio
HSR	hypersensitivity reactions
IB	Investigator's Brochure
ICF	informed consent form

interim analysis	An analysis of clinical study data conducted before the final reporting database is created/locked.
IRB	institutional review board
IRR	infusion-related reaction
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (ie, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed-up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive Web-response system
LLT	MedDRA Lower Level Term
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	MedDRA Preferred Term
Q2W	every two weeks
QD	once daily
randomize	The process of assigning patients to an experimental group on a random basis.
RECIST	Response Evaluation Criteria in Solid Tumors

reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
RMS	rhabdomyosarcoma
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	MedDRA System Organ Class
study completion	Occurs following the final analysis of progression-free survival, as determined by Lilly.
TIA	transient ischemic attack
ULN	upper limit of normal
UPC	urine protein to creatinine
VEGF	vascular endothelial growth factor
VHP	Voluntary Harmonization Procedure (participating countries include: Belgium, Germany PEI, Italy, Netherlands, and Spain)
VTE	venous thromboembolic event

Attachment 2. Protocol Addendum JV01 Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – laboratory[a]	**Local**	**Central**
Leukocytes (WBC)	x	
Neutrophils[b]	x	
Lymphocytes	x	
Monocytes	x	
Eosinophils	x	
Basophils	x	
Erythrocytes (RBC)	x	
Hemoglobin (HGB)	x	
Hematocrit (HCT)	x	
Mean corpuscular volume (MCV)	x	
Mean corpuscular hemoglobin concentration (MCHC)	x	
Platelets (PLT)	x	

Manual Differential – laboratory	**Local: x**	**Central**

Coagulation- laboratory	**Local**	**Central**
Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)	x	
International normalized ratio (INR) or Prothrombin time (PT)	x	

Clinical Chemistry – laboratory	**Local**	**Central**
Serum Concentrations of:		
Alanine aminotransferase (ALT)	x	
Albumin	x	
Alkaline phosphatase	x	
Aspartate aminotransferase (AST)	x	
Bilirubin, direct	x	
Bilirubin, total	x	
Blood urea nitrogen (BUN) or blood urea	**x**	
Calcium	**x**	
Creatinine	x	
Glucose nonfasting	x	
Magnesium	x	
Phosphate	x	
Potassium	x	
Protein	x	
Sodium	x	

Urinalysis – laboratory	**Local**	**Central**
Blood	X	
Glucose	X	
Ketones	X	
pH	X	
Protein	x	
Specific gravity	x	
Urine leukocyte esterase	x	

Pregnancy Test (for female patients of childbearing potential) - laboratory	**Local**	**Central**
Serum/urine pregnancy test	x	

TSH and FreeT4 – laboratory	**Local:** x	**Central**

Hypersensitivity Tests – laboratory	**Local**	**Central**
Tryptase[c]		**x**
Urine N-methylhistamine		**x**
Complements		**x**
• C3a		
• C5a		
Cytokine Panel		**x**
• IL-6		
• IL-1β		
• IL-10		

Abbreviations: CRF = case report form; EGFR = epidermal growth factor receptor; Free T4 = thyroxine; IL = interleukin; K-*ras* = Kirsten rat sarcoma; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.

a Treatment and enrollment decisions will be based on local laboratory results.

b Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

c If a tryptase sample is obtained more than 2 hours after the event (i.e. within 2-12 hours) or is not obtained because more than 12 hours have lapsed since the event, obtain urine for *N*-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

Attachment 3. Protocol Addendum JV01 Sampling Schedule for Genetics/ Biomarkers/Immunogenicity/Pharmacokinetics

Pharmacokinetic samples will be collected for ramucirumab in patients in the ramucirumab arm. Immunogenicity (IG) samples will be collected for patients in both the ramucirumab and control arms. Predose samples should be taken as close as possible to the start of first infusion, that is ramucirumab infusion, but can be drawn up to 1 hour (60 minutes) prior to start of infusion, and exact clock readings should be recorded. Postdose (post end of infusion) samples for PK should be drawn, preferably within 15 minutes after the end of the ramucirumab infusion, and an exact clock reading for the sample draw should be recorded.

Preferred time windows for each PK/IG sample collection are also provided in the tables in this section. While best efforts should be made to draw the blood sample for PK/IG within the time window provided, it is more important to ensure the predose sample is actually collected before the start of ramucirumab infusion and post-dose samples (post end of infusion samples) are collected after infusion is actually completed. It is also equally important to record the actual date and time of blood collection for the PK/IG sample on the Requisition Form after drawing the sample (ie, do not record planned time of collection). Sample collection for post-infusion PK/IG must be from the opposite arm to that used for study drug infusion. If the drug was administered via a central venous catheter, the sample collection should be from a different site.

In addition, if a patient in either the ramucirumab or control arm experiences an IRR, blood samples should be drawn for PK and IG. Samples will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.

Sampling Schedule for Genetics/Biomarkers/Immunogenicity/Pharmacokinetics

Procedure	Sample Time	Cycle 1		Cycle 2	Cycle 4		Cycle 7	Cycle 10	Short-Term Follow-Up
		Day 1	Day 15	Day 1	Day 1	Day 8	Day 1	Day 1	
		Week 0	Week 2	Week 4	Week 12	Week 13	Week 24	Week 30	
Pharmacokinetics[a] (for ramucirumab arm only)	Prior to ramucirumab infusion[b,c]	X	X	X	X		X	X	Any time during the short-term follow-up visit
	Within 0.5 hours after the end of the ramucirumab infusion and prior to vinorelbine infusion[c]	X							
Immunogenicity[a]	Prior to chemotherapy infusion[b,c]	X			X			X	Any time during the short-term follow-up visit
Tumor tissue[d,e]	Prior to chemotherapy infusion[b]	X							
Serum for biomarkers[d] (for both treatment arms).	Prior to chemotherapy b infusion[b]	X				X			
Plasma for biomarkers[d] (for both treatment arms).	Prior to chemotherapy infusion[b]	X				X			Any time during the short-term follow-up visit
Whole blood[d] (for both treatment arms).	Prior to chemotherapy infusion[b]	X[f]							

Abbreviations: C4D8 = Cycle 4 Day 8; eCRF = electronic case report form; hr = hour; IG = immunoglobulin; IRR = infusion-related reaction; PK = pharmacokinetic.

Note: For those patients on the ramucirumab arm, ramucirumab infusion is given every 2 weeks. The infusion duration is 1 hr. Each cycle is a 28-day cycle.

[a] In the event of an IRR (including hypersensitivity reactions), additional blood samples will be collected from all patients, whether in the ramucirumab arm or the control arm, for both PK and IG analysis at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR (see table below).

[b] Cycle 1 Day 1 samples can be collected within 7 days prior to ramucirumab infusion; Cycle 1 Day 15 and Cycle 2 to Cycle 9 Day 1 samples can be collected within 3 days prior to ramucirumab infusion, but predose samples should be preferably collected within 1 hour prior to start of ramucirumab infusion if possible. Serum and plasma biomarkers collected at C4D8 can be collected at anytime during the scheduled visit.

[c] While best efforts should be made to draw the blood sample for PK/IG within the time windows provided above, it is more important to ensure the predose sample is actually collected before the start of first infusion and postdose samples are collected after the infusion is actually completed. It is also equally important to record ACTUAL date and time of blood collection for the PK/IG sample on the Requisition Form AFTER drawing the sample and to accurately record the ACTUAL infusion start and end dates and times on the eCRF to be able to use the data for analyses. Sample collection for post-infusion PK/IG must be from the opposite arm to that used for study drug infusion. If the drug was administered via a central venous catheter, the sample collection should be from a different site.

[d] Collection of tumor tissue and biomarkers (serum, plasma, whole blood) is optional. Previously archived formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a whole block or unstained slides.

[e] Optional collection of an additional biopsy specimen after treatment start may be requested.

[f] A pretreatment blood sample is preferred; however, the whole blood sample for genetic analysis (as described in Section 9.7 of the main protocol) may be collected at a later time point if necessary.

Infusion-Related Reaction (Including Hypersensitivity Reactions) Immunogenicity/Pharmacokinetics Sampling for ALL Patients[a]

Procedure	Sample Time			
	Onset of the IRR	**Once Hemodynamically Stable[b]**	**Resolution of the IRR**	**30 days following the IRR**
PK	X		X	X
Immunogenicity	X		X	X
Hypersensitivity testing		X		X[c]

Abbreviations: IRR = infusion-related reaction; PK = pharmacokinetics.

[a] In the event of an IRR (including hypersensitivity reactions), additional blood samples will be collected from all patients, whether in the ramucirumab arm or the control arm, for both PK and IG analysis at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

[b] After the patient has been stabilized obtain a sample within 1-2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.

[c] Obtain a follow-up sample at the 30-day follow-up or at the next regularly scheduled visit following the IRR, whichever is later.

Attachment 4. Protocol Addendum JV01 Hepatic Monitoring Tests for Treatment Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti-actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 5. Protocol JV01 Restricted and Prohibited Concomitant Therapy

The table below describes medications, treatments, and drug classes restricted or prohibited, with exceptions and conditions for use during the study treatment period (there are no prohibited therapies during the follow-up period). Patients who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the trial. Patients may receive other supportive therapy or vaccinations that the investigator deems to be medically necessary.

Therapy	Allowed As Needed	Allowed for Chronic Use	Exceptions or Conditions for Use
Anti-platelet therapy and NSAIDs	Yes	Yes, with restrictions	Chronic use of aspirin up to 325 mg/day is permitted. Chronic use of NSAIDs is not permitted. However, in certain medical situations, NSAIDs may be the best treatment option (for example, for pain management) and are therefore permitted as needed. Increased risk of bleeding should be considered by the treating physician and the patient.
Anticoagulation therapy	No	Yes, with restrictions	At enrollment, patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin or similar agent. If on warfarin, the patient must have an INR≤3 and no active bleeding or pathological condition present that carries a high risk of bleeding (eg, tumor involving major vessels or known varices).
Anti-cancer biological therapy	No	No	
Chemotherapy	No	No	
CYP3A strong inhibitors	No	No	See list in table.
Erythroid growth factors	Yes	No	Follow local guidelines.
Experimental medicines or investigational agents	No	No	Other than ramucirumab, cyclophosphamide, vinorelbine.
Glucocorticoids	Yes	Yes, with restrictions	Systemic glucocorticoids are permitted to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Use in patients with contrast allergies is acceptable. A temporary course of corticosteroids will be allowed for other indications, at the discretion of the principal investigator (eg, chronic obstructive pulmonary disease, radiation, nausea, etc.). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Inhaled steroids are allowed for management of asthma.
Immunotherapy	No	No	Other than inhaled steroids and vaccinations.
Radiation therapy	No	No	Localized radiation therapy to a symptomatic, solitary lesion or to the brain may be allowed after consultation with the Sponsor.
Live Vaccines	No	N/A	Prohibited as concomitant therapy during the study and for at least 3 months after last dose of study drug.

Abbreviations: INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

Restricted Strong inhibitors of CYP3A[a]
All HIV protease inhibitors
Boceprevir
Clarithromycin
Conivaptan
Danoprevir and ritonavir
Diltiazem
Elvitegravir and ritonavir
Idelalisib
Itraconazole
Ketoconazole
Nefazodone
Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
Posaconazole
Telaprevir
Troleandomycin
Voriconazole

a This is not an all-inclusive list and due diligence should be followed.

Attachment 6. Protocol Addendum Amendment J1S-MC-JV01(g) A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor

DOCUMENT HISTORY	
Document	**Date**
Amendment f	9-Oct-2020
Amendment e	18-May-2020
Amendment d	17-Oct-2019
Amendment c	26-Sep-2019
Amendment b	2-Aug-2019
Amendment a	23-Jan-2019
Original Protocol	7-Dec-2018

Amendment g
This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:
This amendment is being updated to align urinalysis collection in the schedule of activities with monitoring table in later sections. Other changes and clarifications were made based on recent feedback from sites.

Section # and Name	Description of Change	Brief Rationale
3.2 Schedule of Activities; 3.9.3.1.2 Monitoring for Special Toxicities: Growth Plate	Added text to clarify "Plain anteroposterior radiograph of a single proximal tibial growth plate" are for participants randomized to the ramucirumab treatment arm only.	Update based on site and regulatory feedback.
3.2 Schedule of Activities	Added text to clarify timing of radiologic imaging begins at C1D1.	Minor clarification.

Section # and Name	Description of Change	Brief Rationale
3.2 Schedule of Activities; 3.9.3.1.2 Monitoring for Special Toxicities: Growth Plate	Added text to allow an alternate option of MRI of the knee in some geographies for growth-plate monitoring instead of a plain AP radiograph.	Regulatory requirement.
3.2 Schedule of Activities	Added Day 15 Urinalysis throughout the treatment period.	Align with monitoring table in protocol.
3.7.1.2 Dosing Schedule	Added text to indicate a minimum of 2 weeks be observed between ramucirumab administration if the ramucirumab dose is delayed.	Site clarification.
3.7.1.2 Dosing Schedule	Added information related to treatment delays due to unforeseeable circumstances.	Added to address instances of exceptional circumstances.
3.7.4.1 Guidelines for Hematological and Nonhematological Dose Modifications	Updated Table JV01.10 with new G-CSF use recommendations for cyclophosphamide and vinorelbine dose adjustments.	Updated based on emerging information.
3.7.4.1 Guidelines for Hematological and Nonhematological Dose Modifications	Added “footnote d” in Table JV01.10 to clarify that Table JV02.8 should be used for dose reductions.	Site clarification.
Attachment 3 Protocol Addendum JV01 Sampling Schedule for Genetics/ Biomarkers/ Immunogenicity/ Pharmacokinetics	Clarified “serum for biomarkers,” “plasma for biomarkers,” and “whole blood” are to be collected for both arms and are optional.	Site clarification.
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized.

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