Protocol: J1S-MC-JV02(g)

A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma

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1. Protocol Addendum J1S-MC-JV02(g) A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma

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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3. Study J1S-MC-JV02(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 Synovial Sarcoma

Rationale:

Study J1S-MC-JV02 (JV02) is designed to investigate the efficacy of ramucirumab in combination with gemcitabine and docetaxel for the treatment of pediatric and young adult patients with synovial sarcoma (SS).

Objectives and Endpoints:

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

Abbreviations: AE = adverse event; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DoR = duration of response; ORR = overall response; PFS = progression-free survival; PK = pharmacokinetics; SAE = serious adverse event; SS = synovial sarcoma.

Overall Design:

Study JV02 is a randomized, open-label Phase 1/2 study evaluating ramucirumab in combination with gemcitabine and docetaxel in pediatric and young adult patients with relapsed, recurrent, or refractory SS.

Number of Patients:

Approximately 30 patients will be enrolled.

The study must enroll a minimum of 5 patients ≤17 years old with SS.

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 21 days)				
Arm	**Ramucirumab IV, D1 and D8**	**Gemcitabine IV, D1 and D8**	**Docetaxel IV, D8**	**Number of Cycles**
1	9 mg/kg	900 mg/m^2	75 mg/m^2	Treatment will continue until a discontinuation criterion is met.
2	NA	900 mg/m^2	75 mg/m^2	

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

3.2. Schedule of Activities

Table JV02.1. 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		
AE collection	X		CTCAE, Version 5.0
Concomitant medication	X		

Radiologic imaging of known/primary lesions and measurement of palpable or visible lesions	X		• Preferred modalities:
			  ○ extremity/head/neck: MRI
			  ○ chest/abdomen/pelvis: CT
			• Perform according to RECIST 1.1 criteria.
			• See Section 3.9.1

Radiologic imaging for evaluation of metastatic disease: chest/abdomen/pelvis	X		• Preferred modality: CT • Required only if not performed as part of primary lesion evaluation. • 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 or 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 females 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; MRI = magnetic resonance imaging; MUGA = multigated acquisition; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); TSH = thyroid-stimulating hormone.

Table JV02.2. 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 maximum frequency every 21 days.

	Treatment Period 21-Day Cycle				
	Cycle 1		Cycle 2-n		
Day within Cycle	**1**	**8**	**1**	**8**	
Procedure					**Instructions**
Physical examination	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	Perform prior to administering study drug(s). • Including temperature, blood pressure, and pulse rate.
Concomitant medication	X	X	X	X	
AE collection	X	X	X	X	CTCAE, Version 5.0. To be performed before treatment.
ECOG/Lansky/ Karnofsky performance status	X		X		
Radiologic imaging of known lesions and chest CT, and measurement of palpable or visible lesions	Perform every 9 wk (±7 days)				• Preferred modalities: o extremity/head/neck: MRI o chest/abdomen/pelvis: CT • Perform according to RECIST 1.1 criteria, by the same method used at baseline, q 9 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 following surgical resection with clean margins, 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 21-Day Cycle				
	Cycle 1		Cycle 2-n		
Day within Cycle	**1**	**8**	**1**	**8**	
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	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.
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	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	See instructions				Serum or urine per institutional standard. Applies only to females of childbearing potential. Perform on Day 1 of each treatment cycle (at least once every 28 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 3.7.6.1.7.1).
Administer gemcitabine	X	X	X	X	Premedicate according to Section 3.7.1.1.

	Treatment Period 21-Day Cycle				
	Cycle 1		Cycle 2-n		
Day within Cycle	**1**	**8**	**1**	**8**	
Procedure					**Instructions**
Administer docetaxel		X		X	Premedicate according to Section 3.7.1.1.
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); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); IV = intravenous; MRI = magnetic resonance imaging; q = every; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); wk = week.

Table JV02.3. 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		Including weight, and vital signs (temperature, blood pressure, and pulse rate) Include height for patients with open growth plate. In the event of abnormal growth plate findings, continue to obtain height periodically at investigator's discretion.
Concomitant medication	X		
AE collection	X		CTCAE, Version 5.0
ECOG/Lansky/Karnofsky performance status	X		
Radiologic imaging of known lesions and chest CT, and measurement of palpable or visible lesions	See instructions		• Preferred modalities: o extremity/head/neck: MRI o chest/abdomen/pelvis: CT • Perform q 9 wk (±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. • See Section 3.9.1
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.

Visit	Short-Term Follow-Up[a] 801	Long-Term Follow-Up 802-8XX	
Procedure			**Instructions**
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 months (±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.
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; MRI = magnetic resonance imaging; 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 JV02.4. 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)			In the event of an IRR (including hypersensitivity reactions), blood samples will be collected as outlined in Section 3.7.6.1.7.1 and Attachment 3.
Administer ramucirumab (investigational arm)	X		Premedicate according to Section 3.7.1.1.
Administer gemcitabine	X		Premedicate according to Section 3.7.1.1.
Administer docetaxel	X		Premedicate according to Section 3.7.1.1.

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

[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.

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; Carmeliet and Jain 2011).

Similar to adult tumors, 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).

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-rhabdomyosarcima 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).

Consistent with the clinical data implicating the VEGF pathway in STS, preclinical data in SS patient-derived xenograft models treated with VEGF-targeted therapy, bevacizumab or

pazopanib, demonstrated markedly suppressed tumor growth and inhibition of host angiogenesis. The presence of VEGF led to SS tumor proliferation in an autocrine fashion and SS18-SSX, a translocation specific for SS, directs the VEGF signal from differentiation to cell growth implicating the VEGF pathway as a potential critical therapeutic target for SS (Wakamatsu et al. 2014). Furthermore, in preclinical patient-derived xenograft studies using desmoplastic small round cell tumor (DSRCT; Studies CTG-0926 and CTG-1458) and synovial sarcoma (SS; Studies CTG-0331 and 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 J1S-MC-JV01 (JV01) and 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 (JV02) describes the hypothesis and details of the SS investigation. When relevant to the discussion, references to the DSRCT investigation (JV01) will be included.

3.3.2. Background

3.3.2.1. Synovial Sarcoma

SS is the most common non-rhabdomyosarcoma STS in children and adolescents and makes up 10% of all STSs (Soole et al. 2014). SS is found in both pediatrics and adults and is classified as a malignant mesenchymal tumor, characterized by local invasiveness and a propensity to metastasize (Ferrari et al. 2015). These tumors arise in close proximity to tendon sheaths, joint cavities, and bursae and often metastasize to the lungs or lymph nodes (Stanelle et al. 2013).

Treatment strategies have been difficult to identify due to low incidence and unusual clinical behavior that does not follow typical patterns of local recurrence, metastasis, or response to treatment.

For both adult and pediatric patients with SS, the current standard approach for local disease is surgical resection; radiation therapy and/or chemotherapy may be given before or after surgery. As a chemosensitive malignancy, SS tumors have shown response to ifosfamide-based chemotherapy (typically in combination with doxorubicin, and generally with multimodal therapy). However, there is no defined standard treatment regimen in the relapsed setting. Despite initial treatment, approximately 25% to 40% of pediatric patients with SS who initially present with local tumors develop recurrent or refractory disease; in these patients the 5-year overall survival (OS) is just 30% to 42% after relapsing (Ferrari et al. 2015; Soole et al. 2014).

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 OS, in multiple indications as both a monotherapy and 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. Gemcitabine and Docetaxel

The combination of gemcitabine and docetaxel is an effective option for pediatric and young adult patients with metastatic STS and has been studied using a diverse range of doses and across subtypes (Maki et al. 2007). For patients with SS specifically, Abouharb et al. (2014) described their findings of activity in an institutional retrospective review of 42 pediatric and adult patients with metastatic SS treated with a gemcitabine/docetaxel regimen following initial treatment with doxorubicin and ifosfamide. Response rates were complete response (CR) 2.4% (1/41), partial response (PR) 7.1% (3/41), and stable disease (SD) 33.3% (14/41), with a median duration of response of 46 weeks, 42 weeks, and 16 weeks, respectively.

The combination of gemcitabine and docetaxel with the anti-VEGF pathway inhibitor, bevacizumab, has been evaluated in two prospective STS studies including young adults, with compelling outcomes. In a Phase 2 study investigating the combination in 35 patients with metastatic or locally recurrent STS who received no more than one prior line of chemotherapy, the overall response rate was 49% (17/35), in which 10 responding patients elected to stop treatment to undergo tumor resection (Dickson et al 2015). This response rate was a notable improvement from the historical control rate of 16% for gemcitabine and docetaxel alone, described by Maki et al. (2007). A Phase 1b dose-escalation study evaluated the combination in chemotherapy-naïve patients with advanced or recurrent STS. The 35 evaluable patients had an

overall response rate of 31.4% and a disease control rate of 82.8% (5 CR, 6 PR, and 18 SD), for which the median duration of response was 6 months (Verschraegen et al 2012). Of the two patients enrolled with SS, one had a PR and the other SD. Together, these data warrant further exploration of gemcitabine and docetaxel in combination with ramucirumab in patients with relapsed, recurrent, or refractory SS.

Infusion of gemcitabine at a fixed-dose rate refers to infusing gemcitabine at a continuous rate enabling the maintenance of the gemcitabine concentration at a level that will optimize the incorporation of gemcitabine triphosphate, which is the active gemcitabine metabolite, into deoxyribonucleic acid (DNA) (Hensley et al. 2008a). Studies have shown that gemcitabine may have greater activity when given as a fixed-dose rate infusion (10 mg/m^2/min) compared with the recommended schedule (a 30-minute infusion) (Tempero et al. 2003).

Fixed-dose rate gemcitabine (900 mg/m^2 over 90 minutes [fixed-dose rate of 10 mg/m^2/min], Days 1 and 8, plus docetaxel 100 mg/m^2 on Day 8) yielded high objective response rates among patients with advanced leiomyosarcoma in both the second-line and first-line settings (Hensley et al. 2008a, 2008b). However, to increase the tolerability of this chemotherapy regimen a docetaxel dose of 75 mg/m^2 has been selected for this study. Some of the toxicity seen in previous clinical experience (fatigue, asthenia, and fluid retention) was more typical of the docetaxel counterpart, suggesting that this docetaxel dose modification could improve the tolerability of this regimen. This is consistent with the 75-mg/m^2 docetaxel dose chosen in recent Phase 3 GeDDiS trial (Seddon et al. 2015). Therefore, this Phase 1/2 trial investigates the efficacy and safety of ramucirumab in combination with gemcitabine (900 mg/m^2 over 90 minutes [fixed-dose rate of 10 mg/m^2/min]) and docetaxel (75 mg/m^2) for the treatment of pediatric patients and young adults with relapsed, recurrent, or refractory SS.

3.3.3. Benefit/Risk Assessment

SS is the most common nonrhabdomyosarcoma soft tissue sarcoma (STS) in children and adolescents and makes up 10% of all STSs (Soole et al. 2014). Currently, there is no standard of care for treating pediatric and young adult patients with SS in the relapsed setting, and the outcomes are unsatisfactory, with 5-year survival rates as low as 30% (Ferrari et al. 2012). Thus, even with treatments such as gemcitabine and docetaxel, which are not approved for the treatment of SS but are among the agents currently used to treat the disease, there is still need for further improvement of this disease (Abouharb et al. 2014). As SS 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 gemcitabine and docetaxel chemotherapy is expected to enhance these effects within evolving tumors by impeding the VEGF pathway's maintenance of vascular endothelial cell survival and the 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 gemcitabine/docetaxel backbone in 2 prospective STS studies which included young adults (Verschraegen et al. 2012; Dickson et al. 2015), and in a retrospective review and a case series in pediatric and young adult patients with sarcoma (Hingorani et al. 2012; Kuo 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 JV02 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 gemcitabine and docetaxel 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 gemcitabine and docetaxel is 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 gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.	PFS
Secondary	
To evaluate the safety and tolerability of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.	SAEs, AEs, safety laboratory assessments, and vital signs
To evaluate the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.	• ORR • DoR • CR
To characterize the PK of ramucirumab when co-administered with gemcitabine and docetaxel in pediatric and young adult patients with SS.	C_{max} and C_{min}
To assess the immunogenicity of ramucirumab when co-administered with gemcitabine and docetaxel in pediatric and young adult patients with SS.	Incidence of immunogenicity
Exploratory	
To explore additional measures of the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.	• 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; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SS = synovial sarcoma.

3.5. Study Design

3.5.1. Overall Design

Study JV02, combined with Protocol J1S-MC-JVAA (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 SS not amendable to surgery evaluating ramucirumab in combination with gemcitabine and docetaxel. 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 on Study JV01. 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 SAP, Section 6.6.1.

The study design is illustrated in Figure JV02.1.

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 to the ramucirumab arm at the planned 9-mg/kg dose (on a D1, D8 every 21 day schedule), the ramucirumab dose will be de-escalated to 6 mg/kg (on a D1, D8 every 21 day schedule) for Study JV02 should any of the 'de-escalate' criteria (Table JV02.5) 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 JV02 will be immediately terminated for safety should any of the criteria for terminating the study be met due to DLTs observed at 6 mg/kg (Table JV02.6) based on the totality of the data. Otherwise, enrollment will continue with ramucirumab dosing at 6 mg/kg. Enrollment in Study JV02 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 JV02.5 and Table JV02.6). Patients who 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 JV02.5. Rolling Six Rules (Ramucirumab at 9 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 9 mg/kg
2	2	0	0	**De-Escalate to 6 mg/kg**
3	0	0,1,2	3,2,1	Continue Lead-In at 9 mg/kg
3	0	3	0	Lead-In Period Ends
3	1	Any	Any	Continue Lead-In at 9 mg/kg
3	≥2	Any	Any	**De-Escalate to 6 mg/kg**
4	0	0,1,2,3	4,3,2,1	Continue Lead-In at 9 mg/kg
4	0	4	0	Lead-In Period Ends
4	1	Any	Any	Continue Lead-In at 9 mg/kg
4	≥2	Any	Any	**De-Escalate to 6 mg/kg**
5	0	0,1,2,3,4	5,4,3,2,1	Continue Lead-In at 9 mg/kg
5	0	5	0	Lead-In Period Ends
5	1	Any	Any	Continue Lead-In at 9 mg/kg
5	≥2	Any	Any	**De-Escalate to 6 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 6 mg/kg**

Abbreviation: DLT = dose-limiting toxicity.

Table JV02.6. Rolling Six Rules (Ramucirumab at 6 mg/kg)

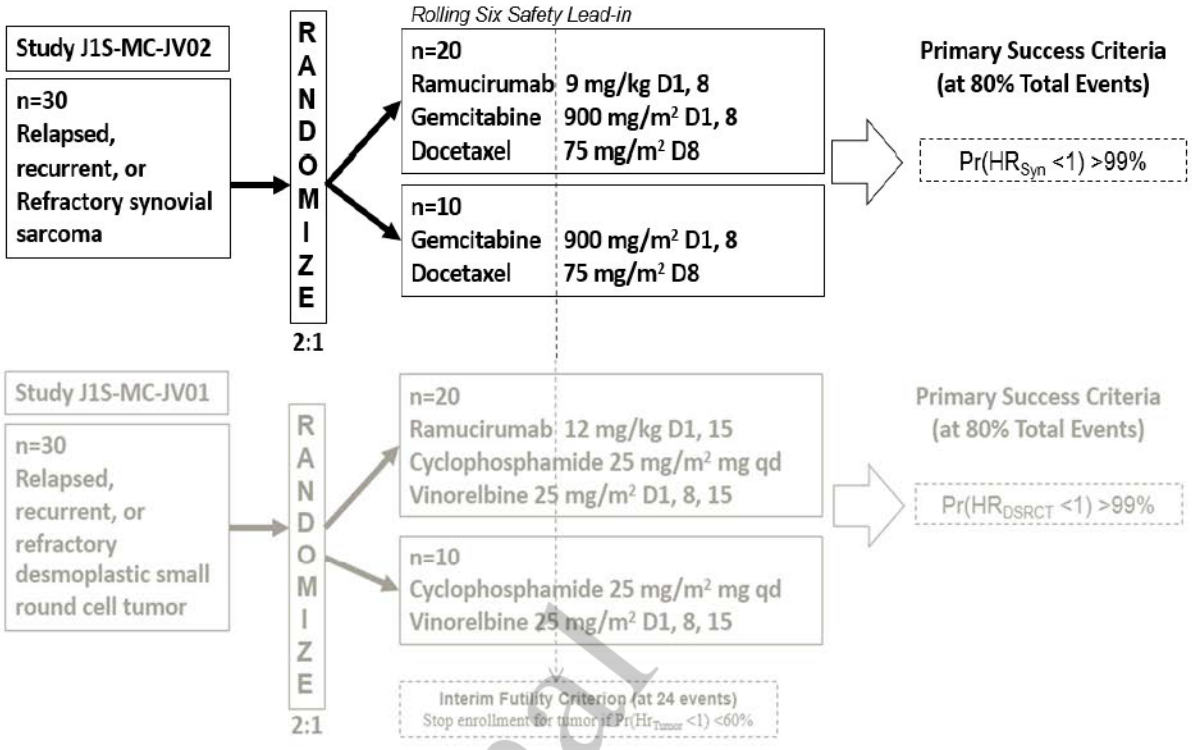
Number Enrolled	Number with DLT	Number without DLT	Number Pending DLT Data	Safety Lead-In Rules
2	0,1	Any	Any	Continue Lead-In at 6 mg/kg
2	2	0	0	**Terminate**
3	0	0,1,2	3,2,1	Continue Lead-In at 6 mg/kg
3	0	3	0	Lead-In Period Ends
3	1	Any	Any	Continue Lead-In at 6 mg/kg
3	≥2	Any	Any	**Terminate**
4	0	0,1,2,3	4,3,2,1	Continue Lead-In at 6 mg/kg
4	0	4	0	Lead-In Period Ends
4	1	Any	Any	Continue Lead-In at 6 mg/kg
4	≥2	Any	Any	**Terminate**
5	0	0,1,2,3,4	5,4,3,2,1	Continue Lead-In at 6 mg/kg
5	0	5	0	Lead-In Period Ends
5	1	Any	Any	Continue Lead-In at 6 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 will be triggered for Study JV02 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 SS patients) in order for enrollment on Study JV02 to continue. Otherwise, enrollment on Study JV02 will be stopped.

Primary Analysis: If Study JV02 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 JV01 passed its futility look). In order to conclude success for the investigation in SS, Study JV02 must carry a minimum of 99% confidence in treatment superiority (PFS HR<1 for SS patients) evaluated via the Bayesian analysis.

Study completion occurs following the final analysis of PFS, as determined by Lilly.



Abbreviations: n = approximate number of patients per group.
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 JV02.1. 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 JV02. The study must enroll a minimum of 5 patients ≤17 years old with SS.

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 SS in the pediatric setting. Superiority of any one regimen has not been determined for SS, 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. One such regimen that has demonstrated some activity in patients with relapsed SS is gemcitabine with docetaxel (Abouharb et al. 2014).

Given SS is a disease that straddles adolescence into early adulthood, with little to no expectation of difference in clinical presentation or outcome, Study JV02 will include children, adolescents, and young adult patients ≤29 years of age to ensure the study is feasible.

3.5.5. Justification for Dose

A ramucirumab dosing regimen of 9 mg/kg intravenously (IV) on Days 1 and 8 every 3 weeks (Q3W) in combination with gemcitabine (900 mg/m^2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m^2 IV on Day 8 of a 3-week cycle) will be evaluated in SS patients in Study JV02.

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 gemcitabine/docetaxel backbone being used.

To optimize the dosing regimen sought to treat pediatric and young adult patients, the RP2D in 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 JVDA.

Results of the dose-finding component of JVDA identified the RP2D for pediatric and young adult patients as 12 mg/kg when administered as monotherapy on an every-2-weeks (Q2W) schedule. The safety profile of this regimen in the pediatric population 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.

To verify the weight-based dosing approach for ramucirumab in the age range proposed for Study JV02, preliminary pharmacokinetic (PK) data from 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 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 JVDA (data on file), indicating the body weight-based dosing regimen is expected to produce comparable exposure levels for patients within the age range 3 to 21 years old. Pharmacokinetic 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 are not available for patients younger 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. The event was Grade 2 proteinuria, which resulted in the 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 dyspnea 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), anemia 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 JV02 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.

Due to the 3-week cycle of the gemcitabine/docetaxel backbone, a Q3W regimen for ramucirumab was also selected to ease patient participation and avoid additional clinical visits. Although the Q3W regimen was not studied in JVDA, results from the PK simulation indicate that ramucirumab 9 mg/kg on Day 1 and Day 8 of a Q3W regimen should achieve a total exposure similar to the RP2D of 12 mg/kg Q2W determined in JVDA (data on file). It is therefore expected that the chosen ramucirumab regimen for Study JV02 of 9 mg/kg on Days 1 and 8 will provide a comparable safety and efficacy profile relative to the 12 mg/kg Q2W regimen.

To mitigate potential safety risks and ensure the proposed regimen maintains an acceptable safety profile in SS patients, a safety lead-in will be conducted to assess the safety and tolerability of ramucirumab administered IV at a dose of 9 mg/kg on Days 1 and 8 Q3W in

combination with gemcitabine and docetaxel, since the selected ramucirumab dosing schedule and combination have 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 9 mg/kg IV on Days 1 and 8 Q3W in combination with gemcitabine (900 mg/m2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m2 IV on Day 8 of a 3-week cycle) was selected for this study to potentially maximize clinical benefit and is anticipated to produce a favorable benefit-risk profile in SS patients.

3.6. Study Population

3.6.1. Inclusion Criteria

Patients are eligible to be included in the Study JV02 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 and >11 kg at the time of study enrollment.

[15] Patients with either relapsed, recurrent, or refractory SS.

[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) that contains ifosfamide and/or doxorubicin, or any 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 years 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≤ the 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 BPs 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 any 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 JV02, the below inclusion criteria should be used in place of the CAMPFIRE Master Protocol inclusion criteria of the corresponding number.

[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	≥1000/µL 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	≥100,000/mm³ 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/m² (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 and for at least 3 months following the last dose of ramucirumab and 6 months following the last dose of docetaxel and gemcitabine 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, or 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 non pregnant 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) 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 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 JV02 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 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 or 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 gemcitabine or docetaxel. Patients who received combination as maintenance therapy, without progression, would be eligible.

[28] Patients with a known hypersensitivity to ramucirumab, gemcitabine, docetaxel, or agents formulated with Polysorbate 80.

[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 symptomatic interstitial pneumonia or pulmonary fibrosis (or consistent findings of interstitial pneumonia/pulmonary fibrosis on imaging).

[32] Patients with CNS involvement are ineligible.

3.6.1.2. Exceptions to the CAMPFIRE Master Protocol Exclusion Criteria

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

3.6.3. Lifestyle Restriction

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 docetaxel.

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 alternative antihistamine within 30 to 60 minutes prior to each infusion with ramucirumab.

3.7.1.1.2. Gemcitabine

Prophylactic antiemetics should be routinely administered. Additionally, premedication for gemcitabine may be administered according to institutional guidelines and/or clinical practice. All premedication administered must be adequately documented in the eCRF.

Sites should consult the manufacturer's instructions for gemcitabine for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of gemcitabine.

3.7.1.1.3. Docetaxel

Premedication for docetaxel should be administered according to institutional guidelines and/or clinical practice and should include a corticosteroid prior to initiation of each infusion to reduce the incidence and severity of fluid retention and hypersensitivity reactions (HSRs).

Recommended corticosteroids include dexamethasone starting the day prior to docetaxel and continuing for 3 days or at the discretion of the investigator. Patients who develop peripheral edema as a side effect of docetaxel may be treated with diuretics at the discretion of the investigator. Additional antiemetic premedication may be employed at the discretion of the investigator. All premedication administered must be adequately documented in the eCRF.

Sites should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel.

3.7.1.1.4. Granulocyte-Colony Stimulating Factors

Granulocyte-colony stimulating factor (G-CSF) use is required in all cycles for patients. The G-CSFs should be administered according to American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006) and European Society for Medical Oncology (Crawford et al. 2009) guidelines.

Prophylactic use of G-CSF should consist of at least 5 days of G-CSF (dose per institutional standard) or a single dose of peg-G-CSF (dose per institutional standard) beginning on Day 8 or 9 per institutional guidelines. If G-CSF is given daily, then continue until ANC ≥1000/µL post nadir and discontinue at least 24 hours prior to the next cycle of therapy per study.

3.7.1.2. Dosing Schedule

The following treatments will be administered in this study every 3-week (21-day) cycle:

Table JV02.7. JV02 Treatment Dosing Schedule (Synovial)

Study Drug	Arm	Dose	Route	Timing
Ramucirumab	1	9 mg/kg[b]	IV	Approximately 60-minute infusion on Days 1 and 8 of each 21-day cycle
Gemcitabine[a]	1 and 2	900 mg/m^2	IV	Approximately 90-minute infusion on Days 1 and 8 of each 21-day cycle
Docetaxel	1 and 2	75 mg/m^2	IV	Approximately 60-minute infusion on Day 8 of each 21-day cycle

Abbreviation: IV = intravenous.

[a] Patients must be closely monitored for a 1-hour observation period following the ramucirumab infusions for the first 2 infusions (see Section 3.7.6.1.7.1).

[b] The infusion time of gemcitabine after its dose reduction may be maintained at 90 minutes or may be shortened to keep a rate of approximately 10 mg/m^2/min according to discretion of the investigator. The infusion start and stop times must be recorded.

[c] During the rolling-six safety lead-in, de-escalation of ramucirumab to 6 mg/kg may be necessary per Table JV02.5.

A cycle is defined as an interval of 21 days.

Ramucirumab should be administered first, followed by gemcitabine, and then docetaxel on the days when it is given. For the first 2 ramucirumab infusions, patients must be closely monitored for a 1-hour observation period following the infusion before receiving gemcitabine or docetaxel (see Section 3.7.6.1.7.1). Thereafter, gemcitabine and docetaxel may be given without the post-ramucirumab observation period, unless an infusion-related reaction (IRR) has occurred. There

are no required waiting times between the administration of gemcitabine and docetaxel; however, appropriate respective premedications are given for each, as outlined Section 3.7.1.1.

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 1 week between ramucirumab administration is required.

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 study drugs that is greater than 1 treatment cycle (21 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 be done before resuming study drugs. In addition, all on-treatment SoA as in Table JV02.2 must resume.

If a dose de-escalation is deemed appropriate during the safety lead-in period due to DLTs (Table JV02.5), the dose of ramucirumab will de-escalate to 6 mg/kg. 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 post-surgery 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.' Docetaxel contains approximately 26 mg of polysorbate 80 for each 1 mg of medicinal product, which results in over 35 mg/kg of polysorbate 80 per dose. Hepatoxicity, hypotension, and hypersensitivity are reported as associated with polysorbate 80 use. The potential for torsades de pointes in humans due to polysorbate 80 is unknown.

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 AEs reported during Cycle 1 of the rolling six safety lead-in, if considered to be definitely, probably, or possibly related to ramucirumab by the

investigator; and fulfills any one of the following criteria using the National Cancer Institute Common Terminology Criteria for Adverse Events (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 a DLT:

   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
   - A 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, a 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 7 days; or ≥3g/24h 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 clinical research physician (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 and will be considered non-evaluable for DLT assessment. 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 drug will be allocated to patients using the IWRS.

Patients who meet all criteria for enrollment will be randomly assigned to receive gemcitabine and docetaxel 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/Clinical Research Scientist (CRS).

In general, dose adjustments of one study drug (ramucirumab, gemcitabine, or docetaxel) due to toxicity guidance outlined in Section 3.7.4.1 will not necessitate suspensions, reductions or discontinuations 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 with the exceptions specified in Table JV02.10. For ramucirumab, gemcitabine, or docetaxel, 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 all study agents are held beyond the duration of one cycle, when reinitiated deem that Day 1 of the subsequent cycle.

Table JV02.8 presents the dose reduction for ramucirumab, gemcitabine, and docetaxel. Dose adjustments required for hematologic and nonhematologic toxicity due to ramucirumab, gemcitabine, or docetaxel are presented in Table JV02.10 and Table JV02.11, respectively.

Table JV02.8. Dose Reductions for Ramucirumab, Gemcitabine, and Docetaxel-Related Toxicities

Study Drug	Starting Dose	Dose Reduction	
		First	Second
Ramucirumab	9 mg/kg	7 mg/kg	5 mg/kg
if de-escalated	6 mg/kg	5 mg/kg	4 mg/kg
Gemcitabine[a]	900 mg/m^2	675 mg/m^2	500 mg/m^2
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2

[a] The infusion time of gemcitabine after its dose reduction may be maintained at 90 minutes or may be shortened to keep a rate of approximately 10 mg/m^2/min according to discretion of the investigator. The infusion start and stop times must be recorded.

3.7.4.1. Guidelines for Hematological and Nonhematological Dose Modifications

In general, ramucirumab therapy does not need to be altered for either gemcitabine- or docetaxel-related toxicity. Similarly, gemcitabine or docetaxel 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. 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 chemotherapy agents and not the other is permissible. General guidelines for study treatment dose modifications due to toxicities are presented in Table JV02.9. Dose adjustment guidelines for specific hematologic and nonhematologic toxicity due to ramucirumab, gemcitabine, and/or docetaxel are presented in Table JV02.10 and Table JV02.11, respectively.

See Section 3.7.4.2 and Table JV02.12 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 JV02.9. General Guidelines for Study Treatment Dose Modification Due to Toxicities Related to Ramucirumab, Gemcitabine, or Docetaxel

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 JV02.10. Dosing Algorithm on Days 1 and 8 for Gemcitabine, Docetaxel, and Ramucirumab Based on Absolute Neutrophil Count and Platelet Count

Toxicity	Day 1[a]		Day 8[b]			
	Gem	Ramucirumab[c]	Gem	Doc	Ramucirumab[c]	NOTES
Absolute Neutrophil Count (cells/µL)						
≥1000	Administer	Administer	Administer	Administer	Administer	
500 to <1000	Omit	Administer	Delay until ANC ≥1000 only if Gem not administered on Day 1 due to ANC. Otherwise, reduce at investigator discretion[d]	Delay until ANC ≥1000 only if Gem not administered on Day 1 due to ANC. Otherwise, reduce at investigator discretion[d]	Administer	Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle if resolved.
<500	Delay and reduce at investigator discretion[d]	Delay at investigator discretion	Omit and reduce at subsequent cycles at investigator discretion[d]	Delay and reduce at subsequent cycles at investigator discretion[d]. See notes for further instruction.	Delay at investigator discretion	**Gemcitabine** In case of recurrence reduce dose of gemcitabine to the next dose level for subsequent cycles. **Docetaxel** At Day 8 withhold dose until ANC≥1000 or omit if the treatment is delayed >7 days.
Grade 4 neutropenia lasting ≥7 days or ≥Grade 3 neutropenic fever/infection	Delay and reduce[d]	Delay	Omit and reduce[d] at subsequent cycles	Delay and reduce[d] at subsequent cycles. See notes for further instruction.	Delay	**Docetaxel** At Day 8 withhold dose until ANC≥1000 and reduce (omit if the treatment is delayed >7 days).
Platelet Count (cells/µL)						
50,000 to <100,000	Omit	Administer	Reduce at investigator discretion[d]	Reduce at investigator discretion[d]	Administer	Day 8 dose reduction of gemcitabine or docetaxel because of Day 8 blood count parameters does not need to be continued on Day 1 of the subsequent cycle if resolved.
<50,000	Delay and reduce[d]	Delay at investigator discretion	Omit and reduce[d] at subsequent cycles	Omit and reduce[d] at subsequent cycles	Delay at investigator discretion	Omit gemcitabine or docetaxel at Day 8 and then reduce gemcitabine to the next appropriate dose level for subsequent cycles.

Note: For other hematologic toxicities not specified please refer to Table JV02.9.

[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 delays may be allowed after discussion with the Lilly CRP/CRS.

[b] Day 8 treatment may be delayed for up to 7 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). If Day 8 treatment is delayed >7 days, Day 8 should be omitted in order to maintain the 21-day cycle and treatment should be resumed with planned Day 1 treatment of the next cycle. A minimum of 7 days' interval between any ramucirumab dose must be maintained.

[c] Investigational arm.

[d] Reduction dose per Table JV02.8

Table JV02.11. Guidelines for Dose Modification Due to Study Drugs-Related Non-Hematologic Toxicities

Toxicity	Day 1[a]		Day 8[b]			NOTES
	Gem	Ramucirumab[c]	Gem	Doc	Ramucirumab[c]	
Grade 1 to 2 total bilirubin	Administer	Administer	Administer	Omit	Administer	Exception: Patients with Gilbert's Syndrome may have a total bilirubin <3 mg/dL before requiring a dose reduction in vinorelbine. Refer to Section 3.9.3.1.1 and Attachment 4 for hepatic safety monitoring.
AST and/or ALT > 1.5 x ULN concomitant with ALP >2.5 x ULN	Administer	Administer	Administer	Discontinue	Administer	
Grade ≥3 total bilirubin	Delay and reduce	Investigator Discretion	Reduce or omit at investigator discretion[d]	Discontinue	Investigator Discretion	Reduce[d] gemcitabine and discontinue docetaxel for all subsequent cycles. Permanently discontinue gemcitabine and docetaxel in case of severe hepatic toxicity. Refer to Section 3.9.3.1.1 and Attachment 4 for hepatic safety monitoring.
Grade ≥3 AST or ALT elevations						
Grade 2 neurologic toxicity	Administer	Administer	Administer	Reduce	Administer	
Grade 3 neurologic toxicity	Administer	Administer	Administer	Discontinue	Administer	
Cystoid macular edema (CME)	Administer	Administer	Administer	Discontinue	Administer	If vision becomes impaired, seek prompt ophthalmology evaluation to look for CME
Severe pulmonary toxicity	Discontinue	Investigator Discretion	Discontinue	Investigator Discretion	Investigator Discretion	Including unexplained new or worsening dyspnea.
Hemolytic Uremic Syndrome or severe renal impairment	Discontinue	Investigator Discretion	Discontinue	Discontinue	Investigator Discretion	
Capillary Leak Syndrome	Discontinue	Investigator Discretion	Discontinue	Discontinue	Investigator Discretion	

Toxicity	Day 1[a]		Day 8[b]			NOTES
	Gem	Ramucirumab[c]	Gem	Doc	Ramucirumab[c]	
Posterior reversible encephalopathy syndrome	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = clinical research physician; CRS = clinical research scientist; Doc = docetaxel; Gem = gemcitabine.

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 delays may be allowed after discussion with the Lilly CRP/CRS.

b Day 8 treatment may be delayed for up to 7 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). If Day 8 treatment is delayed >7 days, Day 8 should be omitted in order to maintain the 21-day cycle and treatment should be resumed with planned Day 1 treatment of the next cycle. A minimum of 7 days' interval between any ramucirumab dose must be maintained.

c Investigational arm.

d Reduction dose per Table JV02.8

3.7.4.2. Ramucirumab Dose Modifications 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 JV02.12). If administration of ramucirumab is delayed for more than 6 weeks (2 cycles) after Day 1 of the most recent treatment cycle, 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 5 mg/kg (4 mg/kg for patients treated on dose de-escalation) of ramucirumab will have ramucirumab discontinued. Such patients may continue with gemcitabine and/or docetaxel as per protocol.

Table JV02.8 presents the ramucirumab dose reductions.

Table JV02.12 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 JV02.12. 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 3.7.6.1.7.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV02.8*** *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 3.7.6.1.7.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV02.8*** *Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.*
3	**Hypertension for patients <18 years old:**		• 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 or >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 3.7.6.1.7.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV02.8*** *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 h (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 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.**

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	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 3.7.6.1.7.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV02.8*** *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. o If UPC ratio returns to <1, administer ramucirumab at current dose o 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 JV02.9.
	Bleeding/Hemorrhage	3 or 4	Immediately and permanently discontinue ramucirumab.
8.	**Gastrointestinal perforation**		Immediately and permanently discontinue ramucirumab.
9.	**Reversible posterior leukoencephalopathy syndrome**		Immediately and permanently discontinue ramucirumab.
10.	**Congestive heart failure**		
	Congestive heart failure	2	Continue with treatment unless investigator considered related. See Table JV02.9.
	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 Section 3.7.6.1.7.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Table JV02.8*** *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

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4. Avoid concurrent use of docetaxel with inhibitors and inducers of CYP3A4. Refer to Attachment 6 for a list of common CYP3A4 inducers and inhibitors. Use of a drug that is listed in Attachment 6 when there is no appropriate clinical substitute for that drug will not be considered a protocol violation. Close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

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 AESIs.

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. Growth Factors

See Section 3.7.1.1.4 for required use of G-CSF.

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. 2004) (Attachment 5).

3.7.6.1.3. Antiemetic Agents

Prophylactic antiemetics should be routinely administered per institutional standard for gemcitabine. The use of antiemetic agents is permitted at the discretion of the investigator for ramucirumab and docetaxel. Acceptable antiemetic agents include 5-hydroxytryptamine 3 (5-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 nonopiate 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. 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.

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

Refer to Table JV02.12 for AESI dose modification guidelines.

3.7.6.1.7.1. Infusion-Related Reactions (Including Hypersensitivity Reactions)

Administration of monoclonal antibodies such as ramucirumab can result in 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 will be collected for PK and immunogenicity analysis for ramucirumab, 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.

Infusion-related reactions 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 JV02.12 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.

3.7.6.1.7.2. 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 <upper limit of normal (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.

3.7.6.1.7.3. 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.

3.7.6.1.7.4. Thromboembolic Events

3.7.6.1.7.4.1. Arterial Thromboembolic Events

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

3.7.6.1.7.4.2. Venous Thromboembolic Events

Venous thromboembolic events 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. The 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.

3.7.6.1.7.5. 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 Investigator's Brochure (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.

3.7.6.1.7.6. 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.

3.7.6.1.7.7. 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 2008a; 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.

3.7.6.1.7.8. 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.

3.7.6.1.7.9. 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).

3.7.6.1.7.10. 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.

3.7.6.1.7.11. 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 SS, 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.
- The patient has had maximum dose reductions of ramucirumab, gemcitabine or docetaxel 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).

Magnetic resonance imaging (MRI) scans are the preferred methods of measurement for extremity, head, or neck; computed tomography (CT) is preferred for chest, abdomen, or pelvis.

Spiral CTs (CT scan thickness recommended to be ≤5 mm) are also acceptable in certain situations. Intravenous and oral contrast is required when abdominal and pelvic CTs are obtained unless medically contraindicated; no oral contrast is required when just chest CTs are being obtained.

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, as appropriate). 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 scan of the thorax is 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 information.

3.9.2.1. Adverse Events of Special Interest - Ramucirumab

Section 3.7.6.1.3 describes supportive care measures for each ramucirumab AESI. Table JV02.12 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, 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 the 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 SS.

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 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 JV02 and JV01, joint scenarios of truth in both SS and DSRCT must be considered when evaluating operating characteristics for JV02 (and likewise for JV01). 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 JV02 is met when, in reality, $HR_{SS} = 1$. Given the stringency of the Bayesian success criterion (i.e., 99% probability of superiority threshold), false positives are unlikely for Study JV02. In particular, when neither tumor cohort truly benefits from ramucirumab-based therapy (i.e., $HR_{SS} = HR_{DSRCT} = 1$), the Type I error rate for Study JV02 is approximately .003. Importantly, the Type I error rate remains low even under scenarios of strong heterogeneity in effect-size between Study JV01 and Study JV02. In particular, if $HR_{SS} = 1$, but $HR_{DSRCT} = .5$, the probability of Type I error for Study JV02 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, JV02 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 SS. For reference, a traditional log-rank analysis of SS at 24 PFS events (independently from DSRCT) 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 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, $\Pr(HR_{SS} < 1) > 99\%$, was calibrated to ensure that meeting the primary endpoint should imply both statistical significance and large estimated magnitude of patient benefit (3 months 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 JV02, observed data from JV01 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_{SS}) 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 $HR_{SS} = .51$ 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 post-baseline 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 detail 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 JV02.13).

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 HR_{SS}.

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 JV02 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 JV02. Second, the Bayesian model includes a mechanism for dynamic borrowing on effect-size (log PFS HR) between the two addenda, JV02 and JV01. 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 JV02.14 and Table JV02.15).

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 HR_{SS}. 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 JV02.13. 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 JV02.14 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 JV02.15 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 CR or 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 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 of PFS analysis must provide a minimum of 60% posterior probability of superiority (PFS HR<1 for SS patients) in order for enrollment on Study JV02 to continue. Otherwise, enrollment on Study JV02 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 JV02 Addendum Abbreviations and Definitions

The List of abbreviations and definitions found in the Study JV02 Addendum are 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	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
BP	blood pressure
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 where 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 3.5.3) 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 childbearing potential
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
GGT	gamma-glutamyl transferase
HR	hazard ratio
HSR	hypersensitivity reaction
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
Q3W	every three weeks
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.
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	MedDRA System Organ Class
SS	synovial sarcoma
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 JV02 Addendum 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 • C3a • C5a		**x**
Cytokine Panel • IL-6 • IL-1β • IL-10		**x**

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 JV02 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 samples 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 both 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 5		Cycle 9	Cycle 13	Short-Term Follow-Up
		Day 1	Day 8	Day 1	Day 1	Day 8	Day 1	Day 1	
		Week 0	Week 1	Week 3	Week 12	Week 13	Week 24	Week 36	
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 gemcitabine 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 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: C5D8 = Cycle 5 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 on Days 1 and 8 every 3 weeks. The infusion duration is 1 hr. Each cycle is a 21-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 8 and Cycle 2 to Cycle 13 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 C5D8 can be collected at any time 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 reactions; 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 JV02 Addendum 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 JV02 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 (eg, 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	
CYP3A4 strong inhibitors/inducers	No	No	See list in Attachment 6.
Erythroid growth factors	Yes	No	Follow local guidelines.
Experimental medicines or investigational agents	No	No	Other than ramucirumab, gentamicin, docetaxel
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.
Live vaccines	No	N/A	Prohibited as concomitant therapy during the study and for at least 3 months after last dose of study drug.
Radiation therapy	No	No	Localized radiation therapy to a symptomatic, solitary lesion or to the brain may be allowed after consultation with the Sponsor. Note: Gemcitabine must not be administered for at least 7 days before or after radiation treatment.

Abbreviations: BCRP = breast cancer-resistance protein; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drugs.

Attachment 6. Protocol JV02 List of Common CYP3A4 Inhibitors and Inducers of Docetaxel

The table below describes the drug class and associated medications that will be restricted during the study treatment period. Patients who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should discontinue docetaxel (see Section 3.7.6). This is not an all-inclusive list and due diligence should be followed.

CYP3A4 Inducers	Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Aminoglutethimide	Clarithromycin	Amiodarone
Bosentan	Chloramphenicol	Amprenavir
Carbamazepine	Cobicistat	Aprepitant[a]
Efavirenz (in liver only)	Conivaptan	Atazanavir
Fosphenytoin	Cremophor EL	Cimetidine
Nafcillin	Cyclosporine	Ciprofloxacin
Nevirapine	Delavirdine	Clotrimazole
Oxcarbazepine	Diclofenac	Darunavir
Pentobarbital	Diltiazem	Darunavir and ritonavir
Phenobarbital	Elvitegravir and ritonavir	Desipramine
Phenytoin	Enoxacin	Doxycycline
Primidone	Fosamprenavir	Dronedarone
Rifabutin	Grapefruit juice	Efavirenz
Rifampin	Indinavir	Erythromycin
Rifapentine	Indinavir and ritonavir	FK1706
St John's wort	Itraconazole	Fluconazole
	Ketoconazole	Fluvoxamine
	Lopinavir and ritonavir	Haloperidol
	Mibefradil	Imatinib
	Miconazole	Metronidazole
	Nefazodone	Norfloxacin
	Nelfinavir	Protease inhibitors
	Nicardipine	Quinidine
	Posaconazole	Schisandra sphenanthera extract
	Quinidine	Sertraline
	Ritonavir	Tetracycline
	Saquinavir	Tofisopam
	Telithromycin	Verapamil
	Theophylline	
	Troleandomycin	
	Voriconazole	

[a] Aprepitant is allowed when given according to local practice and institutional guidelines and if no alternative antiemetic is recommended.

Attachment 7. Protocol Addendum Amendment J1S-MC-JV02(g) Summary A Randomized, Open-Label Phase1/ 2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma

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 plain AP radiograph.	Regulatory requirement.
3.2 Schedule of Activities	Added Day 8 Urinalysis throughout the treatment period.	Align with monitoring table in protocol.
3.7.1.2 Dosing Schedule	Added text to indicate a minimum of 1 week 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	Added "footnote d" in Table JV02.10 and Table JV02.11 to clarify that Table JV02.8 should be used for dose reductions.	Site clarification.
3.7.4.1 Guidelines for Hematological and Nonhematological Dose Modifications	Split cell in Table JV02.11 for Grade ≥3 total bilirubin and Grade ≥3 AST or ALT elevations	Minor clarification.
Attachment 3 Protocol Addendum JV02 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.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized.

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